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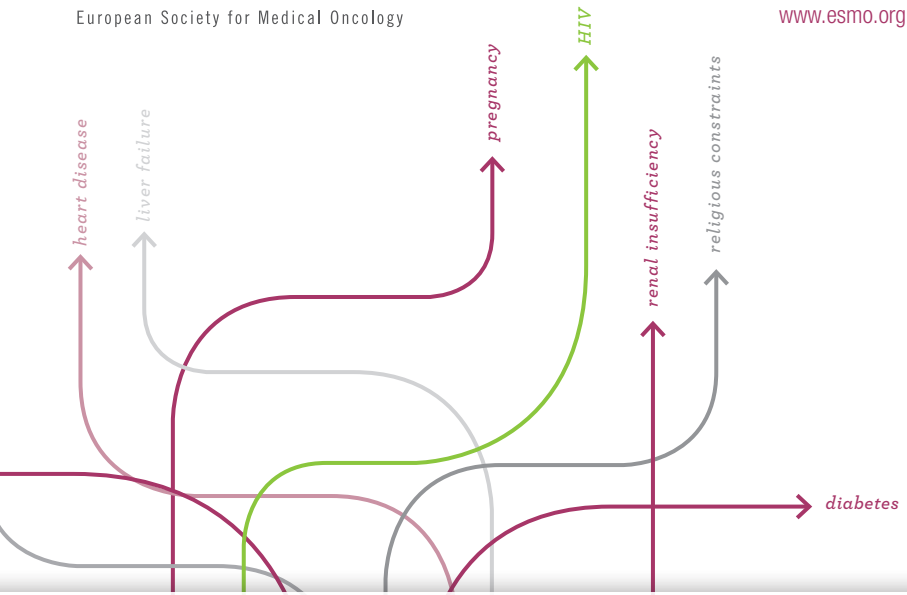

CANCER TREATMENTS IN SPECIAL CLINICAL SITUATIONS

Veronika Ballová and Mariano Provencio Pulla

ESMO Handbook Series

European Society for Medical Oncology

ESMO HANDBOOK OF **CANCER TREATMENTS IN SPECIAL CLINICAL SITUATIONS**

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Introduction

The recent ESMO publication strategy in the field of basic oncology relies on two book series: the "Essentials for Clinicians" series, covering the management of the most common tumours divided by organ of origin, and the general topics and treatment strategies covered by the annual "Handbooks" series.

The 2012 Handbook was devoted to the clinical pharmacology of anti-cancer agents and included tables describing the use of each anti-cancer drug in some specific situations. Nevertheless, many patients present with special situations which cannot be managed simply by consulting a table. These include clinical situations such as pregnant women, HIV-positive patients and people with organ insufficiencies, as well as those who present with other barriers to straightforward treatment decisions such as religious constraints or the inability to consent.

We thought it useful to provide European oncologists with a handbook containing practical guidelines for these cases, which could be consulted quickly and easily to answer the most common and urgent questions when having to treat such a patient.

I am very thankful to all the authors across Europe who devoted an important part of their time to the writing of the chapters. I am even more grateful to the two editors, Veronika Ballová and Mariano Provencio Pulla, who invested so much time and energy in reviewing, correcting, modifying and co-ordinating the production of this book. From the two extremes of Europe, South West to North East, they have brilliantly co-operated with Jennifer Lamarre and Claire Bramley of the ESMO Staff to achieve this final product.

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Professor Michele Ghielmini
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Cancer Treatment during Pregnancy

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Introduction

The diagnosis of cancer during pregnancy is relatively uncommon. However, with the rising trend of delaying childbearing, more cancer patients are expected to be diagnosed during the course of gestation. The exact incidence is unknown, although it is estimated that around 1 in 1000 pregnancies is complicated with cancer. Pregnant patients are often diagnosed with cancer at relatively late clinical stages, which makes delaying therapy until delivery not feasible in the majority of cases. Induction of abortion could be proposed, even if there is no evidence supporting a therapeutic role for this approach. In addition, it is considered ethically unacceptable by some individuals and cultural groups. In this chapter, we will provide key tips on managing pregnant cancer patients and discuss in greater detail the most common tumours diagnosed during pregnancy.

Diagnostic Radiology and Radiation Therapy

Radiation doses greater than 100 mGy may result in up to 1% risk of childhood cancer and foetal malformations. However, staging procedures that involve radiation exposure are usually below this dose. Nevertheless, it is preferred to strictly limit their use during pregnancy. Chest x-ray could be performed to rule out pleural or lung pathology, yet with adequate

abdominal shielding. Abdominal ultrasound is quite safe and can be used to evaluate the liver and abdominal organs. Computed tomography, bone and fluorodeoxyglucose–positron emission tomography (FDG-PET) scans should be strictly avoided during pregnancy. Magnetic resonance imaging (MRI) without gadolinium could serve as a better alternative in the event that an abdominal ultrasound or chest x-ray shows suspicious or inconclusive findings. Whole-body MRI may be an interesting approach for pregnant cancer patients, as it provides a fast and accurate evaluation of the whole body without exposure to radiation or contrast material. However, experience with this technique is rather limited to only a few centres worldwide.

Radiation therapy is better postponed following delivery. Patients with brain metastasis often require immediate palliative radiotherapy, and this can be performed during pregnancy, provided adequate shielding is established. Palliative radiotherapy to the cervical spine, upper thoracic vertebrae and shoulders is also possible as the radiation fields are rather far from the uterus. Radiation to the pelvis and lumbar area should be avoided during the course of gestation. In case there is an urgent need for such treatment, abortion should be considered.

Systemic Anti-cancer Therapies

Chemotherapy during Pregnancy

The administration of chemotherapy during the first trimester is associated with a considerably higher rate of spontaneous abortion and congenital malformations. Hence, chemotherapy should be avoided during this period, if at all possible. In cases in which it is urgent to start chemotherapy for maternal advanced disease during the first trimester, abortion should be considered.

Generally, exposure to chemotherapy following the first trimester does not appear to be associated with major foetal complications, particularly in the short term. However, preterm labour and pregnancy-related complications (e.g. gestational diabetes, premature rupture of membranes) appear to be higher in cancer patients treated with chemotherapy compared to those exposed only to surgery. Thus, administering standard therapy

during pregnancy might not be feasible in all cases, and in some situations customised strategies could be adopted. Among such strategies, weekly fractionation of the chemotherapy dose emerges as an attractive approach. It is associated with a lower peak plasma concentration of the drug, which lowers the chances of placental crossing. In addition, it allows close monitoring of the pregnancy and easy interruption of the drug administration, if needed.

Importantly, the safety of the different chemotherapeutic agents is not equivalent when administered during pregnancy (Table 1). Some agents should be avoided even during the second and third trimester. This will be covered in more detail in the subsequent sections.

The pharmacokinetics of most chemotherapeutic agents is altered during pregnancy. These drugs are partly metabolised by the placenta, resulting in a reduced maximum plasma concentration (C_{max}) and a higher renal clearance when administered during pregnancy. However, it is not clear whether this has any clinical implications on their efficacy during pregnancy. Using higher dosages of chemotherapy during pregnancy is not recommended, but the actual body weight should be used, without adapting for the pregnant state.

Table 1 *Estimated Risk of Pregnancy Complications with Systemic Anti-cancer Therapy When Administered during the Second and Third Trimester of Gestation*

High risk: "prohibited"	Medium risk: "use with caution"	Low risk: "allowed"
Idarubicin	Cisplatin	Vinblastine
Daunorubicin	Carboplatin	Vincristine
Methotrexate	Cyclophosphamide	Doxorubicin
Trastuzumab	Rituximab	Epirubicin
Bevacizumab	Imatinib	Paclitaxel
Tamoxifen	All-trans-retinoic acid (ATRA)	Docetaxel
Zoledronic acid	Ifosfamide	Interferon-alpha

Note: This classification is not based on the Food and Drug Administration classification, but rather on the interpretation made by the authors of the limited available preclinical and clinical data.

Hormonal Agents during Pregnancy

The use of tamoxifen during pregnancy has been shown to be associated with ambiguous genitalia in animals. Similar observations were also noted in sporadic case reports in humans. Thus tamoxifen should be avoided during pregnancy. Caution is advised in young breast cancer patients who are on tamoxifen as a part of their adjuvant therapy. These patients should be asked to use contraception during treatment. If pregnancy has occurred, patients should be informed that there is a potential risk of foetal malformations secondary to tamoxifen in order to make an informed decision on whether they would like to proceed with the pregnancy.

Monoclonal Antibodies during Pregnancy

Monoclonal antibodies are large molecules that require active transport to cross the placenta and reach the foetus. Such mechanism is activated only following the first trimester. Hence, unlike chemotherapy and hormonal agents, early exposure to monoclonal antibodies is unlikely to be associated with foetal defects. This could be relevant in patients who become accidentally pregnant during maintenance therapy (trastuzumab in breast cancer; rituximab in non-Hodgkin's lymphoma). In these cases, the drug should be stopped once pregnancy has been established, yet abortion does not need to be considered. In pregnant cancer patients, prolonged administration of monoclonal antibodies following the first trimester could be associated with major pregnancy and foetal complications. This is rather drug-dependent and will be discussed in more detail in the subsequent sections.

Supportive Care

Nausea and vomiting

Active or proactive treatment with metoclopramide, domperidone or ondansteron is possible throughout the pregnancy period. Prednisone could also be used, but preferably during the second trimester.

Pain

Paracetamol is the analgesic of choice. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, as they are associated with foetal

defects, risk of miscarriage and oligohydramnios. Opiates could be used in cases of severe pain, but they are better avoided close to delivery, as they can be associated with neonatal withdrawal effects.

Infections

Cephalosporins, metronidazole and clarithromycin could be used safely during pregnancy. Limited data are available on imipenem and meropenem. Quinolones and aminoglycosides should be avoided during the course of gestation, as they are associated with foetal congenital malformations.

Anaemia and leukopenia

Erythropoietin and granulocyte-colony stimulating factor (G-CSF) should not be used unless there is an urgent need for them, given the limited safety data on their use during pregnancy.

Osteoporosis and bone metastases

Bisphosphonates were shown to induce foetal skeletal defects in animal models. They can also cause maternal hypocalcaemia, which could affect uterine contractions and hence should be avoided.

Obstetrical Care and Pregnancy Monitoring

Whenever possible, pregnant patients with cancer should be treated within institutions with known expertise in managing such cases and within a multidisciplinary team including an oncologist, obstetrician, neonatologist and also a psychologist. These pregnancies should be considered at high obstetrical risk, and hence should be closely monitored. Monthly ultrasounds should be performed to monitor foetal growth, particularly in patients receiving chemotherapy or those with advanced disease. Prophylaxis of deep vein thrombosis with low molecular weight heparin could be considered, particularly in obese patients and in those older than 35 years of age, given the hypercoagulable state of pregnancy as well as the prothrombotic effect of cancer.

Every effort should be made to complete the pregnancy to term. Preterm delivery has been associated with short- and long-term adverse effects

on the newborn. In addition, it has no positive implications on maternal prognosis. In cases in which waiting until full term is not possible, later preterm delivery (i.e. starting week 35) could be an alternative.

Delivery should be avoided during nadir periods in patients receiving systemic chemotherapy. In patients treated with 3-weekly regimens, chemotherapy should be avoided after the 34th week of gestation, as these regimens have relatively long nadir periods. Weekly regimens have shorter nadir periods and hence could be administered closer to term, if needed. Regardless of the chosen regimen, blood counts, liver and kidney functions tests should be performed prior to each chemotherapy administration.

In patients who need chemotherapy shortly after giving birth, vaginal delivery should be preferred to caesarean section, as recovery following vaginal delivery is typically faster. Vital signs, weight, height, head circumference and Apgar score of all neonates should be checked. Long-term foetal follow-up is highly recommended and this would be better performed through any of the currently available registry programs (www.cancerinpregnancy.org or www.pregnantwithcancer.org).

Common Cancers during Pregnancy

Breast Cancer

Breast cancer is the most commonly diagnosed cancer during pregnancy. Once a patient is diagnosed, she should be approached in a similar way as young breast cancer patients, taking into consideration the gestational age at diagnosis. Patients with small locally-confined tumours should be considered for primary surgery. In general, surgery could be performed any time during pregnancy, but a careful monitoring of maternal and foetal conditions is advised, particularly after the 25th week of gestation. The choice of surgery is the same as in the non-pregnant setting. Patients subjected to conservative breast surgery should receive adjuvant radiation therapy, which in general should be postponed until after delivery. In patients requiring surgery early during the first trimester, the expected delay in receiving radiotherapy could favour performing mastectomy in some of these cases, particularly those who are at a high risk of devel-

oping local recurrence. No foetal defects secondary to sentinel lymph node biopsy (SLNB) have been observed, acknowledging the limited published data in this regard. Hence, it could be considered in centres in which SLNB is routine practice in the non-pregnant setting.

Chemotherapy should be considered in patients with (1) metastatic disease at presentation, (2) large tumours requiring neoadjuvant therapy and (3) adverse prognostic features at surgery necessitating adjuvant therapy. Anthracycline-based regimens remain the chemotherapy of choice during pregnancy. Both epirubicin and doxorubicin can be safely administered. As for taxanes, transplacental transfer is very low and emerging clinical data are rather reassuring regarding their safety. Weekly paclitaxel does not require high-dose steroid preparation and is less toxic compared to 3-weekly docetaxel, and hence is preferred in pregnant breast cancer patients. On the other hand, regimens such as cyclophosphamide, methotrexate and fluorouracil (5-FU) (CMF) should be completely avoided, given the high abortive properties of methotrexate and the lack of particular importance of such a regimen in current breast cancer management.

Patients with HER2-positive breast cancer are candidates for treatment with anti-HER2 targeted agents. Trastuzumab increases the risk of developing oligohydramnios, a condition that can lead to premature delivery, foetal morbidity and mortality. This is believed to be secondary to the effect of trastuzumab on the foetal kidney, which expresses HER2 and is responsible for the amniotic fluid production. Currently, we lack any data on the safety of other HER2-targeted agents. Hence, all anti-HER2 targeted agents should be avoided during pregnancy.

Occasionally, pregnant breast cancer patients are diagnosed with small (e.g. pT1), node-negative, low-grade endocrine-sensitive tumours (i.e. luminal-A breast cancer). Outside pregnancy, chemotherapy is often not offered to these patients. Given that hormonal agents are contraindicated during pregnancy, these patients could be offered only surgery during pregnancy, postponing hormonal therapy along with radiation therapy, if indicated, following delivery.

Haematological Tumours

Pregnant patients diagnosed with acute leukaemias or aggressive lymphomas often require the prompt initiation of chemotherapy. Hence, in the majority of cases diagnosed during the first few weeks of pregnancy, abortion should be considered, as a delay in the initiation of therapy could significantly hamper the patient's prognosis.

In lymphomas, the standard ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and CHOP (cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone) regimens can be safely administered following the first trimester in patients with Hodgkin's and non-Hodgkin's lymphoma, respectively, with no obvious increase in foetal or pregnancy-related complications. The use of rituximab in patients with B-cell lymphomas has been shown to be associated with foetal B-cell depletion at delivery, which is generally reversible. Hence, in patients in whom the use of rituximab during pregnancy is deemed necessary, the drug could be administered, acknowledging that this might have a transient effect on foetal immunity at delivery.

Managing acute leukaemias during pregnancy is very challenging. The use of anthracycline analogues, such as daunorubicin and idarubicin, is preferably avoided during pregnancy, even following the first trimester. They are highly lipophilic, resulting in high placental crossing and serious foetal complications irrespective of the timing of exposure. An alternative could be doxorubicin, which is safer during pregnancy and has considerable activity in acute leukaemia as well. Patients with promyelocytic leukaemia require treatment with all-trans-retinoic acid as well, which can be safely administered starting from the second trimester.

The use of imatinib in patients with chronic myeloid leukaemia has been shown to be safe following the first trimester. When treatment is required during the first trimester, interferon could be used as an alternative, as it is a large molecule and does not cross the placenta. In addition, clinical data clearly support its safety when administered during the first trimester.

Gynaecological Tumours

Cervical cancer is the second most common tumour diagnosed during pregnancy. Radiation therapy is the standard of care in early stages but this would compromise the continuation of pregnancy and hence should be avoided. Otherwise, abortion should be considered. Lymphadenectomy should be considered in patients with positive lymph nodes and neoadjuvant chemotherapy with a cisplatin-based regimen could be considered until delivery.

Patients with epithelial ovarian cancer are often diagnosed at an advanced stage and require systemic chemotherapy. The combination of weekly paclitaxel and carboplatin is the preferred option until delivery. Radical surgery could be considered at the time of delivery. No clinical data are available on the safety of bevacizumab during pregnancy. However, preclinical data have shown developmental anomalies and interference with embryonic development. Hence, bevacizumab presently should not be used during pregnancy.

The use of standard BEP (bleomycin, etoposide and cisplatin) or EP (etoposide and cisplatin) regimens during gestation seems feasible, although the use of etoposide during pregnancy has been shown to be associated with relatively high risk of pregnancy and foetal complications. An alternative could be paclitaxel and cisplatin. No apparent increases in foetal toxicities have been reported using these regimens.

Declaration of Interest:

Dr Azim Jr has reported no conflicts of interest.

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Further Reading

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Cancer Treatment in Patients with Renal Insufficiency

2

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Renal insufficiency is defined as a glomerular filtration rate (GFR) of consistently less than 60 ml/min/1.73 m^2. It is considered chronic when the condition persists for more than three months. Routinely, assessment of renal function is based on blood creatinine levels, yielding an imperfect picture of kidney activity. It is imperative to note that this criterion gives a poor reflection of GFR: 43.7% of patients with normal creatinine levels in the Renal Insufficiency and Anticancer Medications (IRMA) study exhibited a GFR of between 60 and 90 ml/min, and 16.4% between 30 and 59 ml/min.

In 2007, two publications addressed the question of how best to calculate GFR; both concluded that renal function could be assessed using the abbreviated Modification of Diet in Renal Disease (MDRD) method or the Cockcroft-Gault formula. For elderly patients, no GFR assessment method has been validated. More recently, several clinical trials have suggested that the MDRD could be more accurate than the Cockcroft-Gault formula in oncology patients and in the elderly. Finally, in January 2013, the MDRD became clearly recommended for the routine calculation of GFR. On average, GFR falls by 0.75 ml/min/year after the age of 40 years, but approximately one third of elderly patients maintain normal or subnormal renal function until death.

Recent progress in cancer management has yielded a marked increase in the overall survival of patients with multiple neoplasms in the colon, kidneys and head or neck and of those with haematological

malignancies. This is due in part to improved therapeutics, better management of complications and earlier detection of relapse. Although the overall therapeutic index of such approaches has continued to improve, they rely regularly on nephrotoxic molecules such as platinum salts, anti-vascular endothelial growth factor (anti-VEGF) therapies, aminoglycosides or iodinated contrast media (ICM). Simultaneously, increased longevity in ageing populations has led to increased cancer rates in Western countries, given that approximately 60% of cases involve patients over 65 years old, whose renal function is decreased by a mean of 40%. The IRMA study conducted on 4684 cancer patients showed that only 7% had creatinine >110 µmol/L. Based on Cockcroft-Gault and abbreviated MDRD calculations, 57.4% and 52.9% respectively displayed abnormal renal function. Of the 7181 cancer-related prescriptions recorded, 53.4% of patients would have required an adaptation to renal function; 80.1% of patients received a potentially nephrotoxic molecule. The IRMA 2 study also demonstrated that GFR <60 ml/min/1.73 m^2 was an independent risk factor in early death. For the entire study population, kidney failure was associated with an 8.6-month decrease in survival versus the reference group with maintained renal function. Similar observations were made in the subgroup of non-metastatic patients, though to a lesser extent.

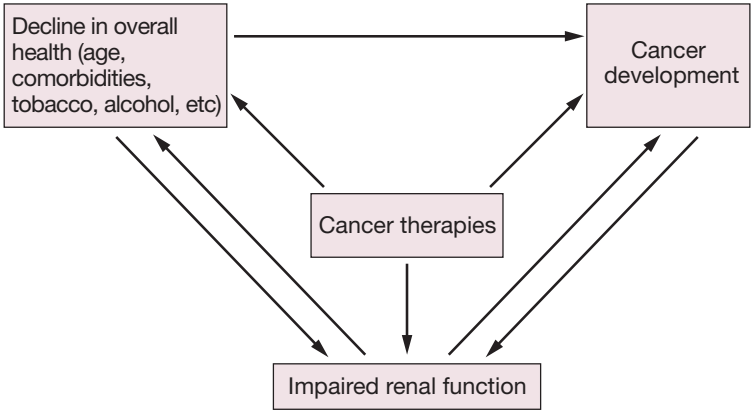

Figure 1 *Relationship between renal insufficiency and cancer.*

In summary, impaired renal function is a common condition in adults and in the elderly, and is a predictor of diminished survival. Its incidence is high in cancer patients who are treated regularly with nephrotoxic molecules, which are known to aggravate renal involvement and to feed this vicious cycle (Figure 1). Thus, the clinician's dilemma is how to prevent the deterioration of renal function and determine the adjusted dosage of a drug with regard to the patient's GFR without reducing the effectiveness of potentially nephrotoxic therapies. Changes should apply to the disease management strategy as a whole, from specific treatment (chemotherapy) to supportive care (pain relief) and complementary examinations (iodinated contrast).

Adapting Anti-cancer Drug Administration in Kidney Failure Patients

Chemotherapy

A degree of ignorance often surrounds the pharmacology of mitotic inhibitors in kidney failure patients. Delayed renal excretion may, in theory, increase the toxicity of molecules excreted by the kidneys (carboplatin, oxaliplatin, methotrexate, bleomycin) or of those with an active or eliminated toxic metabolite (high-dose cytarabine). Such situations require dose adjustments. Surprisingly, several studies have shown no link between kidney failure and increased toxicity from several of these molecules, even in very elderly patients. For instance, the pharmacokinetics of oxaliplatin have been assessed in kidney failure patients. Despite oxaliplatin being eliminated in the urine, the investigation concluded that no dose adjustment was required as long as the GFR was >20 ml/min and the impact of reduced GFR on oxaliplatin's pharmacokinetics remained unknown. On the other hand, a Cancer and Leukemia Group B (CALGB) study demonstrated increased fludarabine toxicity in chronic lymphocytic leukaemia patients with a creatinine clearance rate <80 ml/min. The authors concluded that a dose adjustment was warranted for this molecule, approximately 60% of which is renally excreted. Similarly, lowering the dose of cytarabine in kidney failure patients helped to reduce related neurotoxicity.

Table I *Summary of Dosage Adjustment Recommendations for Renally Cleared Anti-cancer Drugs*

Agent	Dose based on patient's creatinine clearance (CCr)			
	90–60 ml/min	60–30 ml/min	30–15 ml/min	<15 ml/min and/or haemodialysis
Ifosfamide	Intermittent dose/day: 1.5 to 3 g/m^2; dose/cycle: 5 to 10 g/m^2			Intermittent dose/day: 1.13 to 2.25 g/m^2 dose/cycle: 3.75 to 7.5 g/m^2
	Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 3.75 to 6 g/m^2
Melphalan	Oral 0.15 to 0.25 mg/kg/d	Oral 0.11 to 0.19 mg/kg/d per os for 4 to 7 days		Oral Multiple myeloma: 0.075 to 0.125 mg/kg/d per os for 4 to 7 days per os for 4 to 7 days
	IV 100 to 200 mg/m^2 or 2.5 to 5.0 mg/kg for 2 or 3 days	IV 75 to 150 mg/m^2 or 1.88 to 3.75 mg/kg for 2 or 3 days		IV 20 to 100 mg/m^2 or 1.25 to 2.5 mg/kg for 2 or 3 days
Carboplatin	Adjust according to patient using a formula such as the Calvert or Chatelut formula			
Cisplatin	50 to 120 mg/m^2 every 3 to 6 weeks	Not recommended. Carboplatin would be preferable despite a loss of activity (except for germinal tumour)		Not recommended. Carboplatin would be preferable despite a loss of activity (except for germinal tumour)
Oxaliplatin	85 or 100 mg/m^2 every 2 weeks or 130 mg/m^2 every 3 weeks			Contraindicated
Fludarabine	IV 25 mg/m^2/d	IV 20 mg/m^2/d	IV 15 mg/m^2/d	IV 15 mg/m^2/d
Methotrexate	IV Solid tumours: 30 to 50 mg/m^2	IV Solid tumours: 20 to 40 mg/m^2	IV Solid tumours: 15 to 25 mg/m^2	Contraindicated
		High-dose methotrexate contraindicated		

Agent	Dose based on patient's creatinine clearance (CCr)			
	90–60 ml/min	**60–30 ml/min**	**30–15 ml/min**	**<15 ml/min and/or haemodialysis**
Capecitabine	1250 mg/m^2 every 12 h	950 mg/m^2 every 12 h	Contraindicated	Contraindicated
Cytarabine	**Normal dose** An initial dose 100 mg/m^2/d for 7 to 10 days or 200 mg/m^2/d for 5 to 10 days followed by 20 mg/m^2/d for 5 to 10 days			
	High dose 2 to 3 g/m^2 every 12 h	**High dose** 1 to 2 g/m^2 every 12 h	**High dose** 1 g/m^2 every 12 h to 24 h	**High dose** 1 g/m^2 every 24 h
Hydroxyurea	2.5 to 25 mg/kg depending on the indication			
Raltitrexed	>65 ml/min: 3 mg/m^2 every 3 weeks; 65–55 ml/min: 2.25 mg/m^2 every 4 weeks; 54–25 ml/min: 1.5 mg/m^2 every 4 weeks; <25 ml/min and haemodialysis: contraindicated			
Pemetrexed	500 mg/m^2 by single IV infusion over 10 min	60–45 ml/min: 500 mg/m^2 by single IV infusion over 10 min <45 ml/min and haemodialysis: contraindicated		
Etoposide	**Oral** 80 to 300 mg/m^2/d for 3 to 5 days, followed by 50 to 100 mg/m^2/d	**Oral** 60 to 225 mg/m^2/d for 3 to 5 days, followed by 37.5 to 75 mg/m^2/d		**Oral** 40 to 150 mg/m^2/d for 3 to 5 days, followed by 25 to 50 mg/m^2/d
	IV 50 to 150 mg/m^2/d for 1 to 3 days	**IV** 37.5 to 112.5 mg/m^2/d for 1 to 3 days		**IV** 25 to 75 mg/m^2/d for 1 to 3 days
Topotecan	1.5 mg/m^2/d	60–40 ml/min: 1.5 mg/m^2/d; 39–20 ml/min: 0.75 mg/m^2/d; <20 ml/min and haemodialysis: not available		
Bleomycin	10 to 20 mg/m^2	7.5 to 15 mg/m^2	7.5 to 15 mg/m^2	5 to 10 mg/m^2
Lenalidomide	25 mg/d	10 mg/d	15 mg every other day	5 mg/d

*Adapted from Lichtman SM, et al. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Cancer 2007; 43:14–34.

In everyday practice, the overwhelming majority of cancer therapies require no dose modification for a creatinine clearance of between 60 and 90 ml/min. For clearance rates under 60 ml/min, there are few objective pharmacological data available on the use of mitotic inhibitors. A consensus conference of the International Society of Geriatric Oncology has nonetheless proposed dose modifications for the main mitotic inhibitors, which may serve as a reference despite the limitations of such a methodology. A simplified version is presented in Table 1.

Targeted Therapy (TT)

Monoclonal antibodies and tyrosine kinase inhibitors (TKIs) are the most commonly used TT. Despite frequently long-term prescription (maintenance therapy, chronic disease), renal toxicity is not the most relevant related adverse event in terms of frequency or severity. Nevertheless, some points have to be emphasised:

- Bevacizumab, an anti-VEGF monoclonal antibody, induces glomerulonephritis and proteinuria in 21% to 63% of cases. Proteinuria >3.5 g/24 h has been reported in only 2% of patients. Such toxicity is usually not associated with renal insufficiency and is reversible after bevacizumab discontinuation. Such toxicity is not specific to bevacizumab and can be observed with all anti-VEGF therapies.
- Cetuximab is a monoclonal antibody targeted against epidermal growth factor receptor. Some authors reported an increasing risk of grade III/IV hypomagnesaemia in patients treated with cetuximab monotherapy or associated with cisplatinum. This toxicity is reversible after magnesium supplementation, and anti-cancer treatment should not be discontinued.
- Several cases of interstitial nephritis have been reported with sunitinib. Imatinib induced tubular acidosis in 10% of patients, and mTOR inhibitor has been associated with acute renal insufficiency and acute tubular necrosis. Despite these cases, renal tolerance to TT is good in a large majority of cases.
- In very unusual situations, some TKIs require dose adaptation. For example, in chronic kidney disease, exposure to sunitinib is decreased,

suggesting that a higher dosage should be considered; however, no clear recommendations are available. Conversely, in this same context of low GFR, the dosage of vandetanib should be reduced.

Renal Toxicity of Contrast Media

Iodinated Contrast Media

Iodinated contrast-induced acute kidney injury (ICI-AKI) is the third leading cause of acute kidney failure during hospitalisation, after antibiotics and NSAIDs. The main risk factor for ICI-AKI is pre-existing renal insufficiency. The other risk factors are age >65 years, diabetes, dehydration, concomitant nephrotoxic drug intake, anaemia and hypoalbuminaemia. Thus, a patient designated to receive an ICM injection should first be screened for these risk factors. When clearance is between 60 and 90 ml/min, no special precautions are recommended. For clearance between 30 and 60 ml/min, the recommendation is to hydrate with isotonic saline (1 ml/kg/h, 4 hours before and 12 hours after ICM injection). Other strategies involving sodium bicarbonate, furosemide, mannitol or N-acetylcysteine have been proposed, but have been rejected by European or American drug agencies. Creatinine clearance <30 ml/min is considered a contraindication to ICM.

In all cases, preventing ICI-AKI requires the elimination of risk factors where possible, the smallest possible dose of ICM, and a strict 48-hour interval between injections. Requesting a specialist's opinion is also recommended if the initial GFR increases by more than 25%.

Gadolinium-based Contrast Media (GBCM)

Gadolinium is a ferromagnetic agent used as a contrast medium in magnetic resonance imaging (MRI). Intravenous GBCM are not nephrotoxic even in kidney failure patients, provided the dose does not exceed 0.2 mmol/kg. If, however, the GFR is <30 ml/min, GBCM may induce nephrogenic systemic fibrosis, a rare disease whose pathophysiology and treatment remain poorly understood. In such situations, the recommendation is to perform MRI without injection when it is clinically relevant or to use a low-risk GBCM such as gadoterate, which has never been associated with GFR impairment.

Renal Toxicity and Adapted Analgesia

Pain is a very common phenomenon in oncology, affecting approximately 40% of patients undergoing curative therapy and nearly 90% of those receiving palliative care. Strong opioids are used regularly to treat such pain, and require an initial titration phase to determine the effective tolerated dose. In kidney failure patients, it is best to perform titration slowly and in the hospital, where side effects and overdoses can be monitored, especially if creatinine clearance is <60 ml/min. If the patient is elderly, cognitively impaired, malnourished or experiencing liver and/or respiratory failure, titration should be initiated with fast-acting opioids on request, rather than with long-acting opioids. Extended-release opioids (orally, by fentanyl patch or as a continuous drip) may be prescribed once the background pain is under control. As for non-opioid analgesics, it should be stressed that NSAIDs are not recommended, and should be replaced by a short course of corticosteroids if possible. Bisphosphonate dosage in cases of bony secondaries should be adjusted accordingly. Detailed dose modifications have been provided by the Saint-Paul de Vence Consensus Conference.

Discussion

The IRMA study showed that renal insufficiency is common in cancer patients and associated with reduced life expectancy. A vicious cycle exists involving the various factors that contribute to a patient's overall decline in health (age, tobacco and alcohol use, chronic disease). These factors foster the development of cancer, which in turn requires stringent therapies that are then responsible for further damage to overall health and further cancer progression. Every component in this vicious cycle is a risk factor for kidney failure, which then worsens a patient's overall condition and limits his or her treatment choices (Figure 1).

The clinician's first concern should therefore be to prevent this cycle from starting, namely by initiating a rigorous assessment of renal risk factors in every cancer patient. Such assessments may be based on the recommendations of the Kidney Disease Outcome Quality Initiative™, which recommends stratifying patients into six stages of chronic renal disease according to creatinine clearance rate, risk factors (e.g. diabe-

tes, hypertension, family history, elderly age), and signs of direct renal involvement such as proteinuria and kidney size. For early-stage renal disease (high-risk and stage I), management should be based on patient education, lifestyle and nutrition guidelines, and by limiting the use of nephrotoxic products such as NSAIDs or ICM. For stages II and over, no consensus data are available. Two simple criteria can be applied: the possibility of a cure or at least prolonged survival, and whether the kidney disease is primary or secondary.

The decision-tree in Figure 2 takes into account both of these parameters as well as creatinine clearance in order to suggest cancer therapy modifications and appropriate-strength treatment for renal disease. We can thus see that, in a de-novo multiple myeloma patient with acute renal insufficiency, a reduction in serum free light chain levels will be associated with restored kidney function. In this case, where the acute renal insufficiency is only a symptom of the neoplasm and life expectancy is good, the disease should be managed aggressively, with close collaboration between nephrologist and oncologist. In the opposite case, that of an elderly patient with serious chronic kidney failure and multiple metastatic lung cancer, one might start by discussing purely palliative measures. Anywhere between these extremes, case-by-case decision-making will guide the clinical approach.

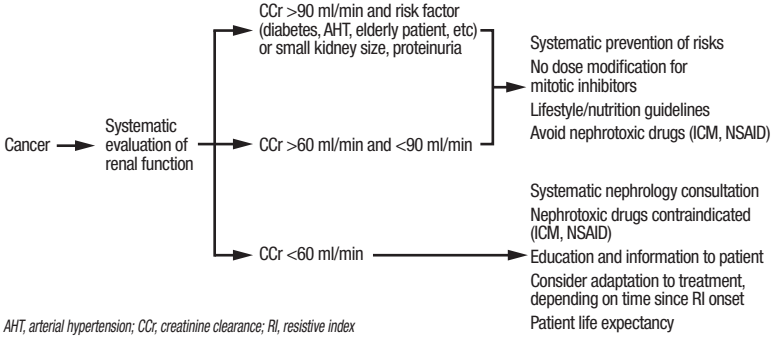

Figure 2 *The kidneys and cancer, a proposal for comprehensive management.*

In most cancer-related clinical trials, patients with creatinine clearance <50 ml/min are routinely excluded, which would explain the paucity of data available on such cases. It would be informative to try including such patients in new trials, providing them with a special therapeutic regimen so as to gain a better understanding of appropriate doses and the periodicity of administration in this common scenario.

Declaration of Interest:

Dr Peyrade has reported that he is on the board of Merck.

Dr Thyss has reported no conflicts of interest.

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Cancer Treatment in Patients with Hepatic Dysfunction

3

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Introduction

The liver is the primary organ for essential processes such as metabolism, excretion and protein production. Patients with hepatic dysfunction (HD) may experience reduced metabolic capacity and altered plasma protein-binding capacity, leading to differences in active drug concentrations. Dose adjustments may be required in order to prevent drug exposure outside the therapeutic window. This chapter will: (1) describe the current categorisation of HD; (2) discuss drug characteristics requiring HD studies and/or dose modifications; and (3) review anti-cancer agents for which dose adjustment recommendations have been developed.

Categorisation of Hepatic Dysfunction

Most surrogates for liver function are plasma-based and measure protein production (albumin, prothrombin time), hepatocellular damage (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), or cholestasis (alkaline phosphatase [AP], gamma-glutamyltransferase [GGT], total bilirubin [TB]).

The Child–Pugh classification was intended for alcoholic cirrhosis and portal hypertension, and categorises HD into groups A (“mild”), B (“moderate”), and C (“severe”), corresponding to scores of 5–6, 7–9

and 10–15, respectively. The laboratory parameters (albumin, TB, prothrombin time) in Child–Pugh are better related to drug-eliminating capacity than the clinical features (encephalopathy, ascites). A Food and Drug Administration (FDA) survey of 57 HD studies between 1995 and 1998 revealed that almost half used the Child–Pugh scale. The Cancer Therapy Evaluation Program at the National Cancer Institute (NCI-CTEP) categorises patients based on TB and AST as follows.

- Normal: AST ≤ULN; TB ≤ULN (ULN: upper limit of normal)
- Mild1: AST >ULN; TB ≤ULN
- Mild2: AST any; TB >1.0–1.5× ULN
- Moderate: AST any; TB >1.5–3× ULN
- Severe: AST any; TB >3× ULN

As opposed to creatinine clearance with renal function, none of the laboratory parameters is specific for HD, and they may be biased by inflammation, cholestasis, haemolysis, or Gilbert's syndrome. Conversely, some markers are not very sensitive for HD because of a large reserve capacity. Prothrombin time may be increased by, for example, vitamin K deficiency in cholestatic liver disease, and may be paradoxically decreased due to enzyme induction in early stages of cholestasis. Liver metastases may also cause increased AST/ALT, which may not be associated with organ dysfunction. The Child–Pugh classification is often used in HD studies, despite the fact that it offers the clinician only a rough guidance for dosage adjustment, because it lacks the sensitivity to quantitate the specific ability of the liver to metabolise individual drugs. In patients suffering from hyperbilirubinaemic syndromes caused by genetic defects in UGT1A1, such as Gilbert's syndrome, increased TB is a surrogate for impaired biliary clearance, and it should be accounted for when adapting the dose of chemotherapy.

Drug Characteristics and Altered Pharmacokinetics in the Context of HD

The primary goal of HD studies is to identify patients at risk for severe toxicity or decreased activity due to HD. Depending on the extent to which the pharmacokinetic (PK) parameters are affected, the next step

is to assess the quantitative association between HD, PK and clinical outcome. The FDA recommends an HD study if hepatic metabolism and/or excretion accounts for a substantial proportion (>20% of the absorbed drug) of the elimination of a parent drug or active metabolite. If the drug has a narrow therapeutic range or if the metabolism of the drug is unknown, a study is also recommended. Even though there is a clear emphasis on PK measures to explain differences in tolerability across HD categories, there may not always be such an HD–PK correlation.

Hepatic Dysfunction and Chemotherapy

Oncologists should understand the meaning and limitations of liver biochemical tests, be aware of liver toxicity from anti-cancer drugs, and oversee dosing strategies for patients with HD. The therapeutic index of anti-cancer drugs undergoing hepatic metabolism and biliary elimination is even narrower in the case of HD, increasing the risk of severe toxicity and/or impaired activity. Often patients present with several causes of HD, including liver metastases, paraneoplastic hepatotoxicity, pre-existing liver infections, concurrent medication, and complementary and illicit substances. The most appropriate measures in cases of HD include avoiding or discontinuing hepatotoxic drugs and searching for potential clots or extrahepatic cholestasis.

Individual Compounds (Table 1)

Docetaxel is metabolised by hepatic CYP3A4, followed by biliary excretion. Clearance is 50% of normal in patients with AST/ALT ≥2.5× ULN and 25% in patients with TB ≥1.5× ULN. The risk for febrile neutropenia increases with a higher docetaxel AUC (area under the curve). Docetaxel should be omitted in patients with TB >ULN according to the package insert. Individualised dosing using a prespecified docetaxel AUC (3.6 mg•h/L in Engels et al. 2011) may be of interest in patients with HD.

Doxorubicin undergoes hepatic metabolism and biliary excretion. A dose reduction by 25% of the normal dose is recommended in patients with AST >ULN, by 50% with TB >ULN, and by 75% with TB >3× ULN.

Table 1 *Dose Adjustments of Common Anti-cancer Drugs in Patients with Hepatic Dysfunction*

Drug	Dysfunction	Dose
Docetaxel	*Normal LF*	*75 mg/m²/3 w*
	Bilirubin >ULN or AST/ALT >1.5× ULN plus AP >2.5× ULN	Omit
Doxorubicin	*Normal LF*	*50–75 mg/m²/3 w*
	AST >ULN	Reduce by 25%
	Bilirubin 1.75–2.5× ULN	Reduce by up to 50%
	Bilirubin 2.5–5× ULN	Reduce by up to 75%
	Bilirubin >5× ULN	Omit
Epirubicin	*Normal LF*	*Fixed dose 125 mg/3 w* [a]
	AST 4–6× ULN	Reduce by 25%
	AST 6–12× ULN	Reduce by 50%
	AST >12× ULN	Reduce by 75%
Erlotinib	*Normal LF*	*150 mg/d*
	AST >3× ULN or TB >ULN	Reduce by 50%
Etoposide	*Normal LF*	*120 mg/m²/d1–3*
	Bilirubin 1.25–2.5× ULN	Reduce by up to 50%
	Bilirubin >2.5× ULN	Substantially reduce or omit
Everolimus	*Normal LF*	*10 mg/d*
	Bilirubin >2× ULN	Reduce by 50%
Gemcitabine	*Normal LF*	*1000 mg/m²/w*
	Mild to moderate LD	Consider 800 mg/m²/w, then increase
Imatinib	*Normal LF*	*Up to 800 mg/d*
	AST >ULN and bilirubin ≤1.5× ULN	500 mg/d is maximum recommended dose
	Bilirubin >1.5× ULN	Consider reduction to 300 mg/d
	Bilirubin >3× ULN or AST/ALT >5× ULN	Hold treatment until bilirubin >1.5× ULN
Irinotecan	*Normal LF*	*350 mg/m²/3 w*
	Bilirubin 1.5–3× ULN	200 mg/m²/3 w
	Bilirubin 3–5× ULN	Omit
Ixabepilone	*Normal LF*	*40 mg/m²/3 w*
	Bilirubin 1.5–3× ULN	Reduce by 25%

Table 1 *Dose Adjustments of Common Anti-cancer Drugs in Patients with Hepatic Dysfunction (Continued)*

Drug	Dysfunction	Dose
Paclitaxel	*Normal LF*	*175 mg/m²/3 w*
	AST/ALT >ULN	135 mg/m²/3 w
	Bilirubin 1.25–2× ULN	115 mg/m²/3 w
	Bilirubin 2–3.5× ULN	100 mg/m²/3 w
	Bilirubin >3.5× ULN	Omit
Sorafenib	*Normal LF*	*400 mg twice daily*
	Bilirubin 1.5–3× ULN	Reduce by 50%
	Bilirubin 3–10× ULN	Omit
Temsirolimus	*Normal LF*	*25 mg/w*
	Bilirubin >3× ULN	60% reduction to 10 mg/w
Vincristine, Vinblastine	*Normal LF*	2 mg absolute dose (vincristine) 3 mg/m² (vinblastine)
	Bilirubin 1.25–2.5× ULN	Reduce by 50%
	Bilirubin >2.5× ULN	Omit
Vinorelbine	*Normal LF*	*30 mg/m²/w*
	Bilirubin 1.75–2.5× ULN	Reduce by 50%
	Bilirubin >2.5× ULN	Reduce by 75%
Vorinostat	*Normal LF*	*400 mg/d*
	Bilirubin >ULN or AST/ALT >ULN	Reduce by 25%
	Bilirubin 1.5–3× ULN	Reduce by 50%
	Bilirubin >3× ULN	Reduce by 75%

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LF, liver function; ULN, upper limit of normal; w, week
[a] Similar dose reductions may also be used for the more conventional epirubicin dose of 90 mg/m²/3 w

Epirubicin undergoes hepatic metabolism and biliary excretion. Using a target AUC of 4 mg•h/L, the following dosing algorithm is recommended: epirubicin fixed dose of 125 mg with AST <150 U/L, 90 mg with AST 150–250 U/L, 60 mg with AST 250–500 U/L, and 50 mg with AST >500 U/L.

Erlotinib is metabolised by hepatic CYP3A4 and CYP1A2. The risk for dose-limiting toxicity increases with AST >3× ULN or TB >1.5× ULN, requiring a 50% dose reduction. This is confirmed by a large PK analysis, showing that patients with TB ≥20 µmol/L have a 30% lower clearance.

Etoposide is metabolised by CYP3A4 and 3A5, and excreted primarily in the bile. Impaired hepatic clearance is compensated by increased renal elimination. Still, patients with TB >20 µmol/L have higher plasma concentrations of the unbound drug, with an increasing risk of severe neutropenia. A 50% dose reduction should be considered in patients with TB 25–50 µmol/L.

Everolimus is an oral mammalian target of rapamycin (mTOR) inhibitor that is metabolised by hepatic CYP3A4, followed by biliary excretion. Patients with moderate HD have a 50% lower clearance, requiring a dose reduction to 5 mg/d in patients with TB >40 µmol/L.

Gemcitabine is metabolised by hepatic cytidine deaminase and excreted via the kidneys. Patients with AST >ULN tolerate gemcitabine without increased toxicity, but patients with TB >ULN may experience substantial liver toxicity from gemcitabine. A weekly dose of 800 mg/m^2 may be considered in patients with TB >ULN, escalating to 1000 mg/m^2 if tolerated. A more recent series of seven patients with TB ≥75 µmol/L receiving the 1000 mg/m^2 dose found dose-limiting thrombocytopenia in only one patient. Therefore, patients with a normal kidney function and TB of 20–70 µmol/L may tolerate conventional doses of gemcitabine.

Imatinib is an oral TKI. The recommended dose of imatinib in patients with AST >ULN and TB ≤1.5× ULN is 500 mg/d, while in patients with TB >1.5–10× ULN, the maximum evaluated dose was 300 mg/d, so no definite recommendation can be made.

Irinotecan is metabolised to the active SN-38 by hepatic carboxylesterase, followed by glucuronidation by hepatic UGT1A1 and biliary excretion. Patients with TB >1.5× ULN have an increased risk of febrile neutropenia and diarrhoea. For the 3-weekly irinotecan dose, a reduction from 350 mg/m^2 to 200 mg/m^2 is recommended with TB >1.5–3× ULN, and no irinotecan is recommended if TB is >3× ULN. For the weekly irinotecan dose, a reduction from 125 mg/m^2 to 60 mg/m^2 is recommended with TB 1.5–3.0× ULN, and to 50 mg/m^2 with TB 3.1–5.0× ULN.

Ixabepilone is metabolised by hepatic CYP3A4, followed by biliary excretion. Moderate-to-severe HD is associated with increased toxicity, requiring a 25% dose reduction in patients with TB 1.5–3× ULN.

Paclitaxel is metabolised by hepatic CYP3A4 and 2C8, followed by biliary excretion. Patients with TB >25 μmol/L or AST ≥2× ULN have more severe myelosuppression after receiving a 3- or 24-hour paclitaxel infusion. There is a direct relationship between HD, paclitaxel elimination, and neutropenia/thrombopenia. A 3-weekly paclitaxel dose of 135 mg/m^2 is recommended in patients with AST/ALT >ULN, 115 mg/m^2 with TB of 25–40 μmol/L, and 100 mg/m^2 with TB of 40–70 μmol/L. Paclitaxel should not be used in patients with TB >70 μmol/L.

Sorafenib is metabolised by hepatic CYP3A4, glucuronidated by UGT1A, and excreted in the bile. Although sorafenib clearance does not decrease with increasing TB, patients with mild HD tolerate sorafenib doses of 400 mg twice a day. However, patients with TB 1.5–3× ULN should receive a reduced dose of 200 mg twice a day, and patients with a serum albumin <25 g/L a once-daily dose of 200 mg. Sorafenib should not be given in patients with TB >3× ULN.

Temsirolimus is metabolised to the active metabolite, sirolimus, and inactivated by CYP3A4. Patients with severe HD (using the NCI Organ Dysfunction Working Group [ODWG] criteria) should be dose-reduced by 60% to a weekly IV dose of 10 mg.

Vincristine and ***vinblastine*** are metabolised by hepatic cytochromes, followed by biliary excretion. Both drugs should be dose-reduced by 50% in patients with TB 25–50 μmol/L, and withheld in case of TB >50 μmol/L.

Vinorelbine is metabolised and excreted similarly to the other vinca alkaloids. The vinorelbine dose should be reduced by 50% in patients with TB >35 μmol/L. Dose adjustments are not recommended in patients with moderate tumour involvement of the liver (≥25% remaining normal liver parenchyma).

Vorinostat undergoes beta-oxidation and glucuronidation followed by biliary excretion. The recommended daily vorinostat dose in mild, moderate, and severe HD is 300, 200, and 100 mg, respectively, compared to a daily dose of 400 mg in patients without HD.

Declaration of Interest:

Dr Joerger has reported no conflicts of interest.

Dr Beumer reported that he receives research funding from Spectrum, BMS and Novartis, and that his wife is an employee of GlaxoSmithKline.

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Cancer Treatment in Solid Organ Transplant Recipients

4

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Introduction

Solid organ transplantation (SOT) remains the cornerstone of treatment in patients with end organ failure. Recipients of organ transplants are at an increased risk of developing de-novo malignancies. With the increasing number of successful organ transplants, reduction of cardiovascular complications, and longevity of transplanted patients, the number of patients with post-transplant malignancies is expected to rise. Cancer remains the leading cause of death in SOT recipients. Oncologists are increasingly faced with the challenge of managing this group of patients, who have complex comorbidities and multiple concurrent medications, in a field where there is a paucity of robust evidence to guide decisions regarding treatment.

Incidence and Aetiology

The epidemiological data of malignancies in SOT recipients are derived from national transplant and cancer registries. The overall standardised incidence rate of cancers in SOT recipients is two- to four-fold higher compared with the general population, based on European and North American transplant registries, and the cumulative risk of malignancies in these patients increases with age. In the United States, cancer risk was elevated with 10 656 new cases of cancer per 175 732 SOT recipients, an incidence of 1375 cancers per 100 000 person-years. Similarly, in the

37 617 SOT recipients on the British transplant registry, 2856 patients developed de-novo solid cancers, excluding non-melanoma skin cancers (NMSC).The standardised incidence ratio for different cancers can be seen in Tables 1 and 2.

Table 1 *Infection-related Cancers in Solid Organ Transplant Recipients*

Cancer type	Causative agent	Standardised incidence ratio* (95% confidence intervals)
Liver – Hepatocellular carcinoma	Hepatitis B, C	11.56 (10.83 to 12.33)
Blood – Hodgkin's lymphoma	Epstein–Barr virus (EBV)	3.58 (2.86 to 4.43)
Blood – non-Hodgkin's lymphoma	EBV	7.54 (7.17 to 7.93)
Skin – Kaposi's sarcoma	Human herpes virus 8	61.46 (50.95 to 73.49)
Stomach – gastric cancer	*Helicobacter pylori*	1.67 (1.42 to 1.96)
Nasopharynx – nasopharyngeal cancer	EBV	0.96 (0.42 to 1.90)
Anus – anal cancer	Human papilloma virus (HPV)	5.84 (4.70 to 7.18)
Oropharynx – oropharyngeal carcinoma	HPV	2.01 (1.64 to 2.43)
Genital tract – vulvar cancer	HPV	7.60 (5.77 to 9.83)
Genital tract – cervical cancer	HPV	1.03 (0.75 to 1.38)
Genital tract – penile cancer	HPV	4.13 (2.59 to 6.26)
Genital tract – vaginal cancer	HPV	2.35 (0.94 to 4.84)

*Standardised incidence ratio data from Engels EA et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011; 306:1891–1901 with permission.

Table 2 *Cancers in Solid Organ Transplant Recipients That are not Infection-related*

Cancer site	Standardised incidence ratio* (95% confidence intervals)
Lung	1.97 (1.86 to 2.08)
Prostate	0.92 (0.87 to 0.98)
Kidney	4.65 (4.32 to 4.99)
Colorectal	1.24 (1.15 to 1.34)
Breast	0.85 (0.77 to 0.93)
Melanoma	2.38 (2.14 to 2.63)
Thyroid	2.95 (2.58 to 3.34)
Urinary bladder	1.52 (1.33 to 1.73)
Skin (non-melanoma, non-epithelial)	13.85 (11.92 to 16.00)

*Standardised incidence ratio data from Engels EA et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011; 306:1891–1901 with permission.

Of note, there is often an increased risk of malignancy in the transplanted organs, e.g. the incidence of renal cancer in kidney transplant recipients is nearly seven-fold higher compared with the general population.

The cause of the increased incidence of cancer in these patients is multifactorial. Immunosuppression and activation of oncogenic infectious agents are widely implicated in the increased incidence of malignancies in organ transplant recipients. In addition, immunosuppressants (e.g. ciclosporin) *per se* are carcinogenic, although newer agents, such as the mammalian target of rapamycin (mTOR) inhibitors, are thought to be less carcinogenic. Other factors include genetic predisposition, increasing age of SOT recipients and pre-existing conditions (both modifiable and genetic) for which transplantation was performed, e.g. smoking-related diseases and primary sclerosing cholangitis.

Clearly, oncologists will have to formulate their treatment recommendations in accordance with transplant/native organ reserves and toxicities associated with chemotherapy. In the following sections, we will discuss the management of solid malignancies in SOT recipients. Since post-transplant lymphoproliferative disorder (PTLD) is a well-defined, distinct entity, it is discussed separately. The management of NMSC is primarily localised (cryotherapy/surgery/topical 5-fluorouracil) in conjunction with modification/withdrawal of the immunosuppressants and will not be discussed further.

Post-transplant Lymphoproliferative Disorders

Any lymphoma occurring following an organ transplant is classified as a PTLD, with virtually all histopathological forms of lymphoma having been identified. There appear to be two distinct types of PTLD. The early form, usually occurring within a year of transplant, tends to be more common in patients who receive transplants at a young age and seems to be more closely associated with Epstein–Barr virus (EBV) seronegativity in the recipient. The late-onset form has characteristics more in common with the non-transplant population, in that the incidence is higher in men and more common in older recipients.

Particularly in early-onset PTLD with polymorphic histology, prompt reduction of immunosuppression (RIS) may allow complete resolution; however, this should be seen within 4–6 weeks. Any failure to respond to RIS requires more aggressive intervention, as discussed below. RIS should be discussed with the transplant team to determine the rate and depth of reduction. It should be noted that the poor risk factors for RIS response are older age, bulky disease and advanced stage. For those patients who fail to respond to RIS or have two or more risk factors (as detailed above), therapy is required and will depend on the type of lymphoma, disease site, etc. There are data to support the use of rituximab in CD20-positive lymphomas, in some cases as a single agent, but most require chemotherapy as well. Prophylactic antimicrobials (Table 3) will depend on the chemotherapy regimen, but should probably include varicella zoster virus (VZV), Candida and Pneumocystis pneumonia (PCP) prophylaxis. In regimens that may cause neutropenia, the use of granulocyte colony stimulating factor (G-CSF) is advised.

Surgery and radiotherapy may be appropriate in localised disease. In patients failing chemotherapy, removing the transplanted organ should be considered if appropriate, e.g. renal transplants. The use of EBV-specific cytotoxic lymphocytes has been effective in single-arm studies but remains experimental.

Management of Post-transplant Solid Malignancies

The management of malignancies in SOT recipients should be tailored to individual patients, depending on the site and stage of the tumour, transplanted organ(s), baseline residual/native organ reserves and type of immunosuppressant used, in addition to assessment of performance status. Surgery remains the mainstay of treatment whenever possible, particularly in NMSC and in cancers arising in transplanted organs. In advanced cases, radiotherapy and chemotherapy can be cautiously considered. Given the paucity of data, clear definitive guidelines are lacking. We, therefore, discuss the potential interactions of the immunosuppressants with chemotherapy, the relevant organ toxicities associated with chemotherapy, and how these may have an impact on transplanted organ function.

In addition to the routine evaluation of patients, general principles include reducing the dose and/or changing the immunosuppressants, tailoring the chemotherapy according to the organ reserves, and having a clear knowledge of the potential interactions between chemotherapeutic agents and immunosuppressants. In parallel, there should be a clear definition of the agreed treatment goal, regardless of whether it is curative or palliative. The risks of transplanted organ rejection and/or damage from therapy should also be discussed with both the patient and the transplant team.

Dose Modification of Immunosuppressants

Commonly used immunosuppressants in organ transplant recipients are ciclosporin, methotrexate, tacrolimus, mycophenolate mofetil (MMF) and sirolimus. Of these, the newer generation immunosuppressants, namely MMF and sirolimus, are less carcinogenic. Careful reduction in the dose of ciclosporin along with introduction of an mTOR inhibitor, such as sirolimus, is a suitable strategy in the treatment of de-novo cancers in renal transplant patients, while maintaining graft survival. The goal of treating malignancy by withdrawing or reducing the immunosuppressants should be balanced against the risk of graft rejection and varies depending on the type of organ transplanted. Treatment should be decided in close collaboration with the transplant team, but, in principle, the lowest dose of immunosuppression should be used. Many chemotherapeutic agents are themselves immunosuppressants and this should be taken into account. The use of immunotherapy (e.g. bacillus Calmette-Guérin [BCG] in bladder cancer) is not recommended in immunosuppressed SOT recipients.

Radiotherapy

Radiotherapy has a primary role in the management of urothelial cancers and HPV-related anogenital cancers, which are increased in renal transplant patients; however, the pelvic location of the donor kidney will require meticulous radiotherapy planning to avoid it, along with a reduction in radiotherapy dose per fraction. Although isolated case reports indicate the safety of radiotherapy for prostate cancer in renal transplant patients, it is vital to stress that careful planning is advisable when radiotherapy is considered for this group of patients.

We suggest that in SOT recipients with malignancies, concurrent chemo-radiation should be used cautiously because of potential toxicity issues. There are, however, exceptions when treating with curative intent, such as radical treatment of head and neck cancers, squamous cancers of the oesophagus and anal cancers, where concurrent treatment should be considered, but may require dose adjustments. Main concerns when treating an immunosuppressed patient with radiotherapy are bone marrow, liver, gastrointestinal mucosa and skin toxicity, which may be magnified particularly in terms of concurrent infections. Clinicians need to be vigilant, to educate patients to be aware of the risks of such toxicity and to seek advice promptly.

Interactions of Immunosuppressants with Chemotherapy

Immunosuppressants used in SOT recipients can potentiate the chemotherapy-induced myelosuppression by 3–10%. Primary prophylaxis with G-CSF should be considered in patients where regimens can cause neutropenia. The use of other prophylactic agents may be appropriate and will again require tailoring to each chemotherapy regimen, individual case and pathogen risk (Table 3). Each case should be discussed with the transplant team and local infectious diseases/microbiology teams to determine appropriate prophylaxis.

Invariably most of the immunosuppressants used in SOT recipients can adversely interact with chemotherapeutic agents (Table 4).

Ciclosporin is a potent inhibitor of cytochrome P450 and P-glycoprotein (drug efflux pump) and plays a key role in affecting the pharmacokinetics of a variety of drugs including taxanes, anthracyclines, etoposide and vinca alkaloids. Concomitant use could result in increased plasma levels of these cytotoxic drugs with attendant increase in toxicities. The concurrent use of cisplatin and ciclosporin is contraindicated due to increased nephrotoxicity.

Azathioprine increases sensitivity to ultraviolet-A rays, which should be taken into consideration in the concomitant use of radiotherapy or when using local treatment for precancerous skin lesions.

Table 3 *Anti-infective Prophylactic Agents to be Considered*

Drug	Infection
Acyclovir	Herpes simplex
Acyclovir	Herpes zoster
Co-trimoxazole	*Pneumocystis jiroveci*
Dapsone	*Pneumocystis jiroveci*
Fluconazole	Candida

Table 4 *Interactions of Immunosuppressive Drugs and Cancer Agents*

Immunosuppressant	Interaction	Outcome	Cancer agent
Azathioprine	Increased sensitivity to UVA	Increased skin toxicity	Radiotherapy
Ciclosporin	Inhibits CYP450 3A4 metabolism	Reduced metabolism – increased toxicity risk	Methotrexate, taxanes, platinum drugs, anthracyclines, etoposide, vinca alkaloids, mTOR inhibitors (e.g. tacrolimus, everolimus)
	Inhibits P-glycoprotein efflux transporter	Reduced clearance – increased toxicity risk	Taxanes, topoisomerase II inhibitors (etoposide and tenoposide), anthracyclines, mitoxantrone, topoisomerase I inhibitors (topotecan and irinotecan), vinca alkaloids
	Concomitant bone marrow suppression	Increased infection risk	Most immunosuppressants and cytotoxins, especially tumour necrosis factor (TNF) blockers
	Renal	Increased nephrotoxicity risk	Cisplatin, melphalan, tacrolimus/ sirolimus
	Peripheral nerves	Increased neurotoxicity risk	Anthracycline
Methotrexate	Lungs	Increased pulmonary toxicity	Cisplatin
	Liver	Increased hepatic toxicity	Retinoic acid

The newer mTOR inhibitors appear to be less carcinogenic and have fewer interactions, but have multiple metabolic side-effects including hyperglycaemia and hyperlipidaemia. These could be potentiated by corticosteroids used for chemotherapy-related emesis prophylaxis and hypersensitivity reactions.

Dose Modification of Cytotoxic Drugs in Organ Transplant Recipients

To date, there are multiple published reports of chemotherapy use in the treatment of malignancy in SOT recipients. Cisplatin, etoposide, paclitaxel, doxorubicin, vinblastine and methotrexate have all been used to treat breast, bladder and testicular cancers, although most authors recommend a reduction of dose and/or duration of the chemotherapeutic agents. In addition, the use of platinum-based cytotoxics, notably cisplatin, is limited by nephrotoxicity. Renal transplant recipients usually have a solitary functioning kidney; therefore, oncologists need to be vigilant in monitoring renal function when administering such agents. However, cisplatin has been used safely in a variety of cancers in renal transplant recipients who have adequate renal function, providing that a good diuresis can be maintained, although the dose was modified in most patients. Other commonly used chemotherapeutic agents that are nephrotoxic include cyclophosphamide, paclitaxel and 5-fluorouracil, although paclitaxel has been shown to be safely tolerated in haemodialysis and also in renal transplant recipients where cyclophosphamide was contraindicated.

Similarly, a majority of cytotoxic drugs are metabolised in the liver, which is also the most common site of metastasis for most solid tumours. In addition, liver transplant recipients are at increased risk of developing de-novo malignancy in the transplanted liver. In this instance, surgical resection may be appropriate. Successful outcomes have been reported with the adjuvant use of doxorubicin and sorafenib in liver transplant recipients for hepatocellular carcinoma. For drugs that are primarily metabolised in the liver (e.g. taxanes, anthracyclines, vinca alkaloids, irinotecan), there are clear guidelines regarding dose reduction and monitoring in non-SOT patients with liver impairment that could be followed in liver transplant recipients. If the clinician has significant

concerns about potential hepatotoxicity in liver transplant patients, preference should be given for using cytotoxics that are not metabolised in the liver, e.g. platinum-based regimens in breast cancer. However, the above are isolated case reports, and we recommend avoiding hepatotoxic agents whenever possible or, if such agents are necessary, considering dose modification based on liver function with concurrent rigorous monitoring.

Irrespective of the cancer being treated, chemotherapy doses should be modified in accordance with organ function and based on knowledge of the pharmacology of the drugs and their interactions. The use of targeted agents in the SOT patient group has not been widely reported, but we recommend that dose reduction be carried out according to hepatic and renal function, as for non-SOT cancer patients.

Removal of Transplanted Organs

SOT removal may need consideration if there is failure to respond to therapy. This is to allow cessation of immunosuppression, particularly in PTLD, but also in other circumstances such as transplanted organ involvement. This should be discussed with patients and physicians, balancing toxicity of therapy versus quality of life following SOT removal. Repeat organ transplantation may be considered, but only after a minimum relapse-free interval. In a cohort of 1297 renal transplant recipients, cancer recurrence was documented in 21% of patients, with a conclusion that there should be a minimum relapse-free interval of 2–5 years before proceeding with a second transplant.

Prognosis

The prognosis of SOT recipients with malignancies is generally poor, in part due to the comorbidities, but also due to restrictions in using the best available treatment at the optimal dose due to concerns regarding SOT function. In patients with breast cancers arising *de novo* in renal transplant recipients, the 5-year overall survival in all stages was 66%. For early stage breast cancer the overall survival was 80%, which is significantly poorer than in the non-SOT population. Similarly, in a

retrospective case series of 17 lung cancer patients with SOT, the median survival was less than one year despite the patients being diagnosed at stage I or II. The 5-year overall survival of stage I disease was 35%. In contrast, a single centre reported better than expected survival data for lung cancers, which were predominantly stage III/IV, indicating that survival outcomes can be improved when adequately managed. Conclusions cannot be drawn on these small numbers of patients, but these data will help facilitate open discussion between patients and their oncologists concerning the likelihood of survival and whether aggressive therapy should be considered.

Conclusions

The management of cancer in SOT recipients presents a unique challenge to oncologists. It is hoped that newer generation immunosuppressants, such as sirolimus, may reduce the incidence, but their influence on overall survival is not clear. In addition, rigorous screening for cancers in SOT patients should also facilitate early detection and, hopefully, improvement in outcome. For all patients it is essential that a multidisciplinary team approach with close liaison among primary physicians, oncologists and the transplant team is implemented promptly. SOT recipients will consult closely with their transplant team, and their input into the final treatment plan is needed with regard to immunosuppression reduction, the possibility of SOT removal and the potential tolerability of any toxicity and infection risk that the proposed therapy may incur.

As with all patients, a realistic and open discussion regarding treatment goals and associated potential toxicities is vital. There are increased risks of toxicities in this group and, since palliation will be the main goal for many, it is important to discuss these risks versus possible marginal benefits with treatment. In particular, careful attention should be given to offset preventable toxicities such as life-threatening myelosuppression. In patients with the potential for long-term disease control, while consideration for SOT should be given, whenever possible this should not compromise the management of the cancer. While some organs are irreplaceable, in situations in which artificial organ support is available,

therapies that could cause increased toxicity and/or SOT loss or damage should be considered in close discussion with the patient and transplant team if significant improvement in survival may ensue.

Ideally, data from randomised clinical trials should be sought, but conducting randomised trials in these groups of patients is not really practicable. Therefore, registry and local audit data detailing therapies, toxicities and response rates should be collected. This information should be coordinated by collaborative groups to formulate best treatment guidelines to improve clinical outcome for those SOT patients who are unfortunate enough to develop malignancies.

Declaration of Interest:

Dr Venugopal has reported no conflicts of interest.

Dr Wilson has reported no conflicts of interest.

Dr Parker has reported no conflicts of interest.

Further Reading

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Cancer Treatment in Patients with HIV

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Introduction

Since the advent of highly active combination antiretroviral therapy (HAART), patients with HIV infection have experienced a significant improvement in their morbidity, mortality and life expectancy. In the last decade, despite a significant decrease in the incidence of AIDS-defining malignancies (e.g. Kaposi's sarcoma, non-Hodgkin's lymphoma [NHL], invasive cervical cancer), there has been an increase in the number of deaths due to non-AIDS-defining illnesses. Moreover, a significant increase in the incidence of non-AIDS-defining cancers (NADCs) has been reported in all epidemiological studies. In fact, the overall standard incidence ratio (SIR) for all NADCs is 2.8 in comparison to the general population, and, for some specific sites, the SIR is significantly higher, i.e. anal cancer (SIR 33.4–42.9), Hodgkin's lymphoma (HL) (14.7–31.7), liver cancer (7.0–7.7) and lung cancer (2.2–6.6).

Although the types of cancer with which HIV patients are diagnosed may be changing, the need for treatment with concurrent antineoplastic agents and HAART is increasingly common. Special attention should be paid to the approach taken with HIV-positive cancer patients to prevent opportunistic infections during treatment, and to avoid overlapping toxicity among antineoplastic agents, including targeted agents and HAART. Tables 1 and 2 show the most significant interactions between HAART and antineoplastic agents and common side effects of HAART.

Table I *Antineoplastic Agents Modulating or Metabolised by Cytochrome P450 Enzymes and Interaction with Antiviral Drugs*

Anticancer therapy	Primary isoforms that mediate bio-transformation	Interaction with NNRTI drugs (CYP inducers)	Interaction with PI drugs (CYP inhibitors)
Alkylating agents			
Cyclophosphamide	3A4, 2B6, 2D6	↑	_
Ifosfamide	3A4	↑	↓
Lomustine	3A4	↑	↓
Oxaliplatin	3A4	_	_
Anthracyclines			
Doxorubicin	3A4	_	↓
Mitoxantrone	3A4	_	↓
Camptothecins			
Irinotecan	3A4	↓	↑*
Topotecan	3A4	↑	_
Epipodophyllotoxins			
Etoposide	3A4	↓	↑
Taxanes			
Docetaxel	3A4	↓	↑↑
Paclitaxel	3A4, 2C8	↓	↑
Vinca alkaloids			
Vincristine	3A4	↓	↑
Kinase inhibitors			
Imatinib	3A4	↓	↑
Erlotinib	3A4, 1A2	↓	↑
Proteasome inhibitors			
Bortezomib	3A4	↓	↑
Antimetabolites			
Capecitabine	2C9	_	↑
5-Fluorouracil	2C9	_	↑
Antitumour antibiotics			
Bleomycin	3A4	↑	↑

NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors. ↑, interaction increases concentration of active metabolite; ↓, interaction decreases concentration of active metabolite; _, potential for interaction appears minimal; ↑↑, effects may be more pronounced with ritonavir; *atazanavir in particular.

NNRTIs: Efavirenz, rilpivirine, etravirine, delavirdine, nevirapine, lersivirine. PIs: tipranavir, indinavir, saquinavir, lopinavir, ritonavir, fosamprenavir, darunavir, atazanavir, nelfinavir.

Modified from Mounier N et al. Drug interactions between antineoplastic and antiretroviral therapies: Implications and management for clinical practice. Crit Rev Oncol Hematol 2009; 72:10–20 with permission.

Table 2 *Common Side Effects of HAART*

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)	
Zidovudine	**Stavudine**
a) Headache	a) Peripheral neuropathy
b) Fatigue	b) Nausea
c) Neutropenia	c) Vomiting
d) Nausea	d) Diarrhoea
e) Anaemia	e) Headache
f) Vomiting	f) Liver toxicity
g) Insomnia	g) Abdominal pain
h) Myalgia/myopathy	h) Lipodystrophy
i) Abdominal pain	i) Fatigue
Didanosine	j) Insomnia
a) Pancreatitis	k) Malaise
b) Diarrhoea	l) Mood swings
c) Peripheral neuropathy	m) Somnolence
d) Nausea	n) Rash
e) Gas/bloating	o) Itching
Lamivudine	**Emtricitabine**
a) Headache	a) Headache
b) Nausea	b) Diarrhoea
c) Vomiting	c) Nausea
d) Fatigue	d) Elevated creatine phosphokinase
e) Insomnia	e) Lipodystrophy
f) Diarrhoea	f) Osteonecrosis
g) Rash	**Abacavir**
h) Myalgia/myopathy	a) Fatal hypersensitivity reactions (strongly associated with HLA-B57:01; pre-therapy screening mandatory)
Tenofovir	b) Stevens–Johnson syndrome
a) Nausea	c) Erythema
b) Vomiting	d) Lactic acidosis
c) Diarrhoea	e) Hepatomegaly and steatosis
d) Lipodystrophy	f) Pancreatitis
e) Fatigue	g) Immune reconstitution syndrome
f) Dizziness	h) Autoimmune disorders
g) Headache	i) Nausea
h) Gas/bloating	j) Vomiting
i) Liver steatosis	k) Headache
j) Acute renal failure	l) Fatigue
k) Fanconi syndrome	m) Diarrhoea
Zalcitabine	n) Fever/chills
a) Peripheral neuropathy	o) Depression
b) Oral and oesophageal ulcers	p) Anxiety
c) Pancreatitis	q) Hypertriglyceridaemia
d) Rash	r) Lipodystrophy

Table 2 *Common Side Effects of HAART (Continued)*

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)	
Efavirenz	**Nevirapine**
a) Insomnia	a) Mild or moderate rash
b) Nightmares	b) Stevens–Johnson syndrome
c) Confusion	c) Toxic epidermal necrolysis
d) Memory loss	d) Hypersensitivity
e) Depression	e) Life-threatening liver toxicity
f) Psychosis	**Etravirine**
g) Nausea	a) Stevens–Johnson syndrome
h) Rash	b) Toxic epidermal necrolysis
i) Dizziness	c) Erythema multiforme
j) Headache	d) Rash
k) Birth defects	e) Liver failure
l) Liver steatosis	f) Diarrhoea
Delavirdine	g) Headache
a) Mild or moderate rash	h) Nausea
b) Fatigue	
c) Headache	
d) Nausea	

PROTEASE INHIBITORS (PIs)	
Saquinavir	**Darunavir**
a) Appetite loss	a) Rash
b) Headache	b) Diarrhoea
c) Feeling ill	c) Headache
d) Diarrhoea	d) Abdominal pain
e) Nausea	e) Constipation
f) Vomiting	f) Vomiting
g) Hypercholesterolaemia/hypertriglyceridaemia	**Atazanavir**
h) Mitochondrial toxicity	a) Raised bilirubin level
i) Diabetes mellitus	**Lopinavir/ritonavir**
Ritonavir	a) Diarrhoea
a) Nausea	b) Nausea and vomiting
b) Vomiting	c) Abdominal pain
c) Diarrhoea	d) Fatigue
d) Fatigue	e) Headache
e) Headache	f) Rash
f) Liver toxicity	g) Hypercholesterolaemia/hypertriglyceridaemia
Tipranavir	h) Lipodystrophy
a) Hypercholesterolaemia/hypertriglyceridaemia	i) Liver toxicity
b) Hyperglycaemia and diabetes mellitus	j) Cardiomyopathies
c) Intracranial haemorrhage	k) Ischaemic heart disease
d) Hepatitis	

PROTEASE INHIBITORS (PIs) *(Continued)*	
Fosamprenavir	**Nelfinavir**
a) Moderate or severe rash	a) Flatulence
b) Nausea and vomiting	b) Diarrhoea
c) Headache	c) Abdominal pain
Indinavir	d) Fatigue
a) General malaise	e) Kidney stones
b) Kidney stones	f) Mouth ulcers
c) Kidney failure	g) Rash
d) Fatigue	h) Arthralgia
e) Hypercholesterolaemia/hypertriglyceridaemia	i) Pancreatitis
f) Diabetes mellitus	j) Leukopenia
g) Lipodystrophy	k) Liver toxicity

ENTRY/FUSION INHIBITORS	
Maraviroc	**Enfuvirtide**
a) Nausea	a) Injection site reaction
b) Diarrhoea	b) Insomnia
c) Fatigue	c) Depression
d) Headache	d) Peripheral neuropathy
e) Anaemia	e) Cough
f) Liver toxicity	f) Anorexia
g) Rash	g) Arthralgia
	h) Dyspnoea
	i) Infection (bacterial pneumonia)
	j) Eosinophilia
	k) Liver toxicity
	l) Respiratory distress
	m) Glomerulonephritis
	n) Anaphylaxis

INTEGRASE INHIBITORS	
Raltegravir	
a) Depression	d) Kidney damage
b) Anaemia	e) Lypodystrophy
c) Suicidal thoughts or behaviour	f) Allergic reaction

Kaposi's Sarcoma (KS)

Treatment of KS has changed substantially in the HAART era. The degree of immunocompetence, the extent of tumour burden (T) and its rate of progression, HIV comorbidity and the patient's performance status (PS) dictate the choice of treatment. However, optimal antiretroviral therapy is a key component of KS management. Regression of KS with HAART has been documented in many studies, and HAART has been associated with prolonged time-to-treatment failure and longer survival among KS patients who have received chemotherapy. The available evidence suggests that HAART leads to regression of limited KS. Thus, HAART may be the only antineoplastic therapy used in the early stage of disease (T_0) and/or for slowly proliferating disease, when tumour growth is consistent with the long time interval to the development of HAART anti-KS activity (median 8–12 months). KS may progress during the first 2–3 months of HAART because of immune reconstitution inflammatory syndrome (IRIS). The potential additive effects of IRIS and steroids (which stimulate replication of human herpes virus 8, with progression of KS lesions) mean that steroids are contraindicated as an anti-inflammatory therapy in KS. There are several mechanisms by which HAART may be active in KS, including an increase of CD4 cell count, suppression of HIV replication and induction of an anti-angiogenic effect, which is mediated by protease inhibitors (PIs).

In patients with T_1 and/or rapidly proliferating disease, the first-line treatment is chemotherapy plus HAART, followed by maintenance therapy with HAART. Although in the past several chemotherapeutic agents (i.e. bleomycin, vinblastine, vincristine, vinorelbine, doxorubicin and etoposide) have demonstrated efficacy against KS, current systemic cytotoxic therapy comprises liposomal anthracyclines (pegylated liposomal doxorubicin [PLD] and liposomal daunorubicin) and taxanes. Liposomal encapsulation alters drug kinetics, resulting in a prolonged half-life. In two pre-HAART randomised studies, PLD (20 mg/m^2 i.v., every two weeks) had an activity superior to the combination of ABV (doxorubicin, bleomycin and vincristine) or BV (bleomycin and vincristine), with an overall response rate ranging from 46% to 59%, and a better safety profile. Liposomal daunorubicin at a dose of 40 mg/m^2 i.v. every two weeks in patients with pulmonary KS

resulted in clinical benefit and objective response in 59% and 32% of cases, respectively. Myelosuppression remains the most important dose-limiting toxicity of these drugs. Peripheral neuropathy and palmar–plantar erythrodysesthesia occur infrequently, and cardiotoxicity is rare. The combination of liposomal anthracyclines and HAART is safe and effective and is not associated with a detrimental immunosuppressive effect. Currently, these liposomal drugs are considered the best first-line chemotherapy for advanced KS patients.

Paclitaxel, a microtubule-stabilising drug known to inhibit Bcl-2 anti-apoptotic activity, is effective even in patients with anthracycline-resistant KS. The drug (100 mg/m^2 i.v., every two weeks) results in an overall response rate of 56–59%, with a median response duration of 10.4 months. The major side effects include myalgias, arthralgias and myelosuppression. Based on these data, paclitaxel is now used after failure of first-line systemic chemotherapy. Since the metabolism of paclitaxel involves the cytochrome P450 pathway, as do PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs), caution is necessary when the drug is co-administered with HAART.

The growing knowledge of KS biology provides multiple opportunities for rational targeted therapies. However, preliminary results of these clinical trials and the complexity of KS pathogenesis suggest that effective treatment strategies will require a combination of agents targeting multiple pathogenetic pathways.

Although in some patients KS has a rapid course with extensive visceral organ involvement, in other patients it is an indolent disease spanning many years. In the pre-HAART era, the ACTG TIS classification predicted survival in KS patients; CD4 count (I stage) and T (tumour) stage provided the most predictive information. In the HAART era, only the T and S (systemic illness) stages maintained a correlation with survival. Two different risk categories are identified: a poor risk (T_1S_1) and a good risk (T_0S_0, T_1S_0, T_0S_1), with a three-year survival rate of 53% versus 80–88%, respectively. Furthermore, pulmonary involvement predicts survival better than tumour extension, independent of the S stage, and identifies the poorest category.

Non-Hodgkin's Lymphoma (NHL)

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 45–50% of all NHL and frequently occurs at extranodal sites. Burkitt's lymphoma (BL) constitutes 30–40% of malignant lymphomas. It occurs in younger persons and early in the disease course, with still higher CD4+ cell counts, and it presents in advanced stages, sometimes with extensive bone marrow infiltration. Other subtypes such as plasmablastic lymphoma or primary effusion lymphoma (PEL) represent around 5–10% of cases. The treatment of HIV-associated lymphomas has evolved over the last 30 years in line with improved control of HIV replication and preservation of immune function. The introduction of HAART has dramatically improved the outcome of patients with HIV-NHL because of a significant reduction of infectious complications, better administration of chemotherapy and more favourable tumour biology.

Diffuse large B-cell lymphoma (DLBCL)

Several phase II studies have demonstrated that the addition of rituximab to standard chemotherapy, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), or infusional chemotherapy, i.e. CDE (cyclophosphamide, doxorubicin and etoposide) or EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone), is feasible, safe and very active as a first-line treatment of patients with DLBCL. However, concerns have been reported regarding an increased risk of infections due to the use of rituximab, based on the results of the first randomised study of CHOP ± rituximab (R-CHOP), which demonstrated that the use of rituximab significantly increased the number of infectious deaths, without better tumour control. However, the increased infectious deaths occurred primarily in patients with very low CD4 counts. In addition, many patients received 'maintenance' rituximab after chemotherapy, which has not been shown to be useful in HIV-negative DLBCL.

To further evaluate the effect of rituximab, the same group recently performed a randomised phase II study comparing concurrent versus sequential rituximab with EPOCH; they failed to find a significant increase in infectious deaths, and reported a 75% complete response rate in the concomitant arm. In order to evaluate whether infusional

chemotherapy is better than classical chemotherapy, a pooled analysis of AIDS malignancy consortium trials was performed. Results showed that patients who received concurrent R-EPOCH had improved event-free survival (hazard ratio [HR] 0.40; 95% confidence intervals [CI], 0.23, 0.69; p <0.001) and overall survival (HR, 0.38; 95% CI, 0.21, 0.69; p <0.01), in comparison with patients in the R-CHOP arm. However, these results should be confirmed in a randomised multicentre phase III study.

In conclusion, patients with DLBCL and HIV infection should receive rituximab plus chemotherapy (CHOP, EPOCH or CDE). HAART should be continued during chemotherapy in order to reduce the risk of infectious complications.

Burkitt's Lymphoma (BL)

Although HAART has significantly improved the outcome of patients with DLBCL, a lack of improvement has been observed in patients with BL, probably related to the use of less effective chemotherapy regimens. In recent years, several studies have demonstrated the efficacy of aggressive regimens commonly used in HIV-negative patients, i.e. CODOX-M/IVAC or hyper-CVAD or LMB86. However, because of the toxicity of these regimens, a randomised study of R-CODOX-M versus R-EPOCH has been initiated.

In conclusion, the treatment of BL in HIV patients is an example of the need to achieve balance between treatment efficacy and toxicity by optimising the therapeutic index. Up-to-date, aggressive regimens should be employed.

Hodgkin's Lymphoma (HL)

As with HIV-NHL, one of the most notable features of HIV-HL is the widespread extent of disease at presentation and the presence of B symptoms. The optimal therapy for HIV-HL has not been defined. Since most patients present with advanced stage disease, they are treated with combined chemotherapy regimens; however, the outcome remains worse than for HL in HIV-negative patients. There is a low incidence of the disease, and no randomised controlled trials have been conducted in this setting,

although several phase II studies have evaluated the feasibility and activity of different regimens. In the HAART era, both ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and Stanford V (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide and prednisone) have demonstrated significant activity in this setting with an acceptable toxicity. ABVD should be considered the standard regimen in HIV-HL patients.

Salvage Treatment

Because a large proportion of patients with HIV-related lymphomas progress or relapse, the use of high-dose chemotherapy and autologous stem cell transplantation (ASCT) has been investigated in this setting. Data from several different groups including the GICAT have demonstrated the feasibility of this approach, which can be considered standard salvage treatment. Patients who are able to undergo ASCT have comparable survival to HIV-negative patients; therefore, ASCT is recommended as salvage treatment for patients with HIV-positive relapsed or refractory lymphomas.

Anal Carcinoma

The longer life expectancy of HIV-human papillomavirus (HPV) co-infected patients in the HAART era provides an opportunity for invasive anal squamous cell carcinoma (ASCC) to develop from its dysplastic precursor. The prognosis of ASCC is poor in HIV-positive patients, who often present with advanced tumours. Concomitant radiation therapy and chemotherapy (fluorouracil and mitomycin C) is the current standard of care for HIV-negative patients with invasive ASCC. This approach has been applied successfully in HIV-positive patients with similar ASCC, particularly those with a CD4+ cell count >200 cells/μl. HIV-positive patients with ASCC treated with HAART tend to fare better than those patients who do not receive HAART. Anal cancer screening with anal cytology, high-resolution anoscopy and digital rectal examination should be offered to HIV patients, despite the fact that the efficacy and cost effectiveness of this screening programme have not been evaluated in large-scale studies.

Hepatocellular Carcinoma (HCC)

HCC is the most common primary cancer of the liver and the fourth most common cause of death due to cancer. The risk of HCC is seven-fold higher in HIV-infected than in HIV-negative patients. Since the introduction of HAART, no decrease in the incidence of HCC has been observed, unlike with other HIV-associated cancers. Recent data have demonstrated that, in the majority of cases, HCC was diagnosed in patients with well-controlled HIV disease and good PS.

Considering the key role of early diagnosis of HCC with regard to survival and re-treatment in the case of recurrence, extending regular screening programmes for HCC (according to proposed guidelines) to include HIV-infected patients, together with a greater proclivity for treatment and re-treatment options in the case of HCC diagnosis or recurrence, may represent an important and urgent breakthrough in facing this emerging problem. Currently, the same therapeutic approach as for HIV-negative patients is recommended.

Lung Cancer

Lung cancer is the primary cause of mortality by NADCs in the HIV-infected population, even after adjusting for age, sex and smoking history. Several reports showed that lung cancer in HIV is not associated with immunodeficiency, suggesting that the activity of the immune system plays a less important role in the pathogenesis of lung cancer than in KS or NHL.

There are no specific recommendations for the management of lung cancers in the HIV-infected population versus HIV-negative patients. In the general population, patients with advanced or metastatic non-small cell lung cancer (NSCLC) are treated with a histology-driven, platinum-based chemotherapy; the addition of the humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab is recommended in selected patients. In recent years, targeted agents such as epidermal growth factor receptor (EGFR)-targeting tyrosine kinase inhibitors and EML4-ALK-targeting tyrosine kinase inhibitors are recommended in patients harbouring EGFR-mutated tumours and EML4-ALK translocations, respectively.

Treatment of HIV-infected patients with lung cancer has been problematic because of frequent drug–drug interactions caused by HAART drugs. Enzyme-mediated metabolic reactions can cause either activation of prodrugs or inactivation of active drugs. Concomitant use of anti-cancer drugs and HAART is associated with overlapping toxicities due to elimination using CYP450 routes of metabolism. All protease inhibitors inhibit CYP450, and ritonavir is the most potent in the class. Therefore a dose reduction of EGFR inhibitors is recommended when administered together with CYP450 inhibitors. More information about specific drug–drug interactions between HAART and chemotherapy or targeted agents is required to optimise the treatment of lung cancer in HIV-positive patients.

Infectious Complications and Recommended Prophylaxis

The burden of experience in the HIV-positive setting comes from the treatment of patients with haematological malignancies. Haematological toxicity represents the most important complication in these patients. The use of prophylactic filgrastim is strongly recommended from days 6–10 following chemotherapy. During the neutropenic period, several bacterial infections (including *Pneumocystis carinii* pneumonia) have been reported, and both fungal (i.e. *Candida albicans*) and viral infections (i.e. cytomegalovirus [CMV] and/or herpes zoster virus [HZV]) may represent a significant clinical problem. Therefore, all patients should receive oral sulfamethoxazole/trimethoprim (960 mg daily or three times a week) and oral fluconazole (50 mg daily). Moreover, in patients with severe immunodeficiency (i.e. CD4 cell count <50 cells/dL), mucosa-associated lymphoid tissue prophylaxis is recommended with azithromycin (1250 mg weekly).

However, the most severe, life-threatening complication in the HAART era is IRIS. IRIS is frequently observed in patients with initially low CD4 cell counts (lower than 50 cells/dL) who started HAART concomitantly with chemotherapy, as a result of a rapid CD4 increase and a sudden increase in the inflammatory response. Typically, patients

develop non-specific symptoms such as fever and other complications. Infections most commonly associated with IRIS include Mycobacterium tuberculosis and cryptococcal meningitis, and CMV reactivation, progressive multifocal leukoencephalopathy and KS progression have been described frequently. Treatment of IRIS includes specific antibiotics or antivirals; in some severe cases, treatment with corticosteroids can be useful to reduce inflammation until the infection has been eliminated.

Conclusion

The introduction of HAART and the widespread use of prophylaxis have significantly improved the survival of HIV-positive cancer patients. To date, the majority of patients with HIV infection and a cancer diagnosis should receive the same treatment as HIV-negative cancer patients.

Declaration of Interest:

Dr Spina has reported no conflicts of interest.

Dr Bearz has reported no conflicts of interest.

Dr Berretta has reported no conflicts of interest.

Dr Vaccher has reported no conflicts of interest.

Dr Tirelli has reported no conflicts of interest.

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Cancer Treatment in Patients with Hepatitis

6

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Introduction

Liver injury is a frequent complication of chemotherapy. The main sources of this injury are drug hepatotoxicity and viral infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus and herpes simplex virus. Liver dysfunction may be a common finding in patients after haematopoietic stem cell transplantation (HSCT). Liver infections, particularly HBV and HCV, have been reported as causes of severe liver disease, including fulminant hepatitis, either by reactivation or by enhanced replication of the virus in the context of induced immunosuppression by chemotherapy. In this chapter we will discuss the mechanism of viral reactivation, clinical manifestations and recommendations for management in this population, to minimise morbidity.

Hepatitis B Infection

Natural History of Hepatitis B

HBV infection affects a large part of the world's population with close to two billion people having evidence of HBV exposure and 300–400 million with chronic infection. The prevalence of HBV surface antigen positivity (HBsAg) ranges from 8–25% in high endemic areas to less than 2% in Western countries. This prevalence is increased in individuals with onco-haematological malignancies, probably as a result of frequent

transfusions. The frequency of anti-core antibody (anti-HBc) seropositivity is even higher, reaching 62% of the population in some countries.

The natural history of HBV infection goes through several phases. The first relevant event is the loss of HBVe antigen (HBeAg) and seroconversion to HBVe antibody (anti-HBe). These patients maintain low level or even undetectable HBV DNA, persistently normal alanine transaminase (ALT) and minimal liver injury. This phase is known as *inactive HBV carrier* and usually has a good prognosis. Thereafter, HBsAg levels may decrease to below the level of detection as HBV surface antibody (anti-HBs) titres increase. An individual is defined as having had a *resolved HBV infection* when he/she tests seropositive for anti-HBc and/or anti-HBs. Patients in either situation (HBsAg carrier or HBsAg-negative/anti-HBc-positive patients) are at risk of viral reactivation following systemic chemotherapy.

Immune Responses and Pathogenesis of Reactivation

Following entry into the host cell, the HBV DNA genomes are converted to a covalently closed circular (ccc) DNA form. HBV cccDNA is a stable form of viral DNA that is the most resistant to antiviral therapy and to the host´s immunological response. Thus, cccDNA can persist in the liver, even in patients with anti-HBs, and result in replication when the host immune responses are impaired.

Definitions and Diagnosis of Reactivation

Most scientists define reactivation as the development of *hepatitis* in association with an *increase in serum HBV DNA* level. Reactivation can be divided into different categories, based on virological characteristics.

HBV carriers (HBsAg-positive patients) may be identified as: *active carriers*, in the presence of HBeAg or antibody to HBeAg and a viral load >20 000 IU/ml; or *inactive carriers*, in the case of HBeAg-negative and anti-HBe-positive status with HBV DNA below 20 000 IU/ml. In HBV carriers, reactivation is considered as the increase in at least one logarithm of HBV DNA compared to its nadir, reconfirmed in two consecutive serum tests during monitoring.

Occult HBV carriers have been defined as having HBV DNA present in the liver (with detectable or undetectable HBV DNA in serum) and testing HBsAg negative by currently available assays. When detectable, the amount of HBV DNA in the serum is usually very low (<200 IU/ml). In occult HBV infection, the conversion of serum HBV DNA test results from negative to positive or the re-emergence of HBsAg (reverse seroconversion or sero-reversion) are signs of HBV reactivation. Acute exacerbation of chronic hepatitis has been defined as: at least a threefold increase in serum levels of ALT between two consecutive controls made at least five days apart.

Pathogenesis and Clinical Manifestations

HBV reactivation can be separated into three phases (see Figure 1):

Increase in viral replication. Reactivation typically starts with the abrupt increase in HBV replication soon after initiating chemotherapy. The degree of increase in viral replication is measured by the rise in HBV DNA in serum. This rise can precede an elevation of ALT levels by up to three weeks. The first phase of reactivation can also feature reappearance of HBeAg and HBsAg (seroreversion). Suppression of a normal immunological response against HBV, due to chemotherapy, leads to enhanced viral replication and widespread infection of hepatocytes.

Appearance of disease activity. The second phase starts when immunosuppression is withdrawn or decreased and hepatocellular injury or hepatitis arises. On discontinuation of chemotherapy, immunocompetence is gradually restored, leading to an immunoclearance-like response, resulting in widespread cytotoxic T cell-mediated lysis of infected hepatocytes. This cell destruction can involve an increase in ALT levels and, in more severe instances, symptoms and jaundice. During this phase, HBV DNA levels may start to fall.

Recovery. In this phase, liver injury resolves and HBV markers return to baseline levels.

The clinical picture of HBV reactivation is quite variable. Some patients may experience mild hepatitis, but progression may occur to more severe and even fatal liver damage. Only 10% of HBV carriers will become

jaundiced. The fatality rate in patients with icteric hepatitis is up to 40%. The patients most at risk of complications from reactivation are those with evidence of advanced hepatic fibrosis, since they have a higher likelihood of developing hepatic decompensation.

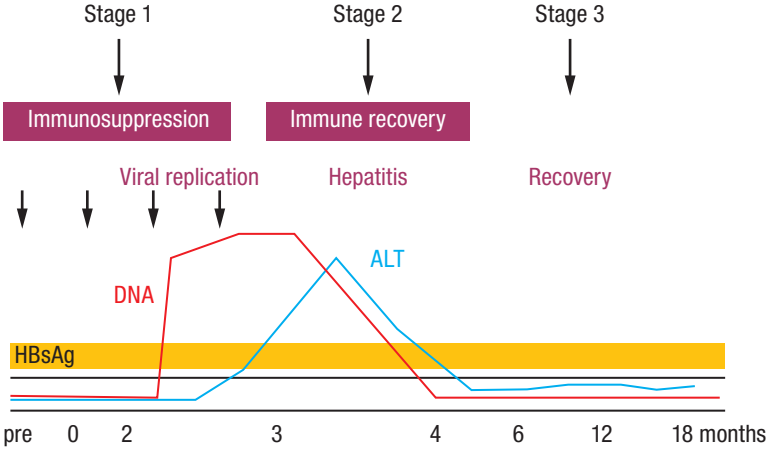


Figure 1 *The three phases of HBV reactivation. Immunosuppression induced by chemotherapy promotes an increase in viral replication (stage 1). After chemotherapy is withdrawn, immune recovery leads to destruction of infected hepatocytes and, in some cases, clinical hepatitis (stage 2). In the recovery stage, hepatitis resolves and HBV markers return to baseline levels (stage 3).*

Risk Factors

Risk of HBV reactivation depends on the balance between replication of the virus and the host's immune response. Thus, the risk of reactivation differs according to the patient´s HBV infection status prior to chemotherapy as well as to the degree of immunosuppression due to systemic chemotherapy. Factors predisposing to HBV reactivation in individuals with onco-haematological malignancies who receive chemotherapy are shown in Table 1.

Table 1 *Risk Factors for HBV Reactivation in HBV-positive Individuals with Cancer Who Receive Chemotherapy and Cytotoxic Agents*

Viral factors
■ HBsAg positivity
■ HBeAg positivity
■ High baseline HBV DNA levels (>10^5 copies/ml)
■ HBV genotype (B genotype)
■ Precore–core promoter HBV mutation
Host factors
■ Male gender
■ Young age
■ High basal serum ALT levels
■ Absence or decrease of anti-HBs titres during chemotherapy
■ Type of malignancy (haematological malignancies: lymphoma)
Treatment factors
■ Chemotherapeutic agents: anthracyclines, cyclophosphamide, fludarabine, vinca alkaloids
■ Steroid-containing regimens
■ Monoclonal antibodies: rituximab, alemtuzumab
■ Haematopoietic stem cell transplantation (HSCT)

Frequency of HBV Reactivation

Most cases of HBV reactivation occur in HBsAg-positive patients. Before the rituximab era, 24–53% of HBsAg-positive patients on cancer chemotherapy experienced reactivation, most of them during lymphoma therapy. Nonetheless, an increasing number of cases have been described among patients with solid tumours. Breast cancer has the highest rates of reactivation, reaching 41–56%. More recently, the reported incidence of HBV reactivation in patients receiving rituximab-containing chemotherapy has been very high (80%). Following HSCT, more than 50% of HBV carriers develop HBV exacerbation.

Until recently, HBsAg-negative patients were not recognised as being at risk for reactivation, based on the results of a study that reported HBV reactivation in only 2.7% of HBsAg-negative patients. However, the incidence of reactivation in this population increased after the use of rituximab, reaching 12.2–45%. Multivariate analysis demonstrated that

rituximab plus steroid combination chemotherapy was the most relevant risk factor for HBV reactivation.

In the HSCT scenario, the actuarial risk of reactivation in HBsAg-negative patients is 20.5%. This risk could increase cumulatively over time following HSCT, with a probability of 9% to 42.9% one to four years after the procedure. The severity of reactivation is higher in HBsAg-negative patients, with an incidence of fulminant hepatitis and mortality of 40% and 50%, respectively.

Management of Reactivation

There are two main trends regarding management of reactivation: to employ a prophylactic strategy for at-risk patients; or to start antiviral therapy when reactivation is detected. Prophylaxis can be *universal*, when pre-emptive antiviral therapy is applied to the whole population potentially at risk, or *targeted*, if it is secondary to the appearance of infection markers (HBV DNA or HBsAg), starting antiviral medications to suppress HBV replication in the absence of hepatitis.

Treatment of hepatitis

When reactivation is detected by the presence of clinical hepatitis, it has been managed by the discontinuation of chemotherapy and the addition of supportive care. However, this strategy does not usually stop liver damage and interferes with the patient's chemotherapy schedule.

Antiviral agents have been shown to interfere with HBV replication in these patients. Interferon use is limited because of its haematopoietic toxicity, the slow onset of action and its immunostimulatory effect, which may aggravate immune-mediated liver damage. Lamivudine has been widely used to manage hepatitis due to HBV reactivation. However, the use of lamivudine when hepatitis has developed does not guarantee patient survival, with a reported mortality rate of 20–30%. These detrimental results could be explained by the delayed start of lamivudine when the viral load is already elevated and massive immune-mediated hepatic damage is occurring. Antiviral treatment should continue until HBV DNA negativity is obtained, and should be stopped only when seroconversion to anti-HBs is stable and no further risk of immunosuppression is

foreseen. However, the prolonged use of lamivudine has been related to the emergence of resistant HBV mutants, with a cumulative rate of 24% after one year of treatment and 65–70% after five years.

Newer nucleoside/nucleotide analogues (NUCs) have been shown to be effective in the management of HBV reactivation, especially the third generation NUCs, entecavir or tenofovir, which have a higher potency and a higher genetic barrier compared to lamivudine. These characteristics may prevent the development of drug-resistant mutations in those patients who will probably require a long period of therapy. The published experience with third-generation NUCs is summarised in Table 2. Even with the newest NUCs, short-term mortality does not seem to be improved when severe HBV reactivation is established.

Table 2 Features and Outcome of HBV-positive Patients with HBV Reactivation Treated with Third-generation NUCs

Author	Patients (n)	Immunosuppressive agent (n)	NUC	Baseline serology (n)	Virological outcome (HBV DNA negative)
Colson	1	Rituximab	Entecavir	HBsAg–/anti-HBc+	1
Sanchez	1	Rituximab	Entecavir	HBsAg–/anti-HBc+	1
Ueda	1	Rituximab + HSCT	Entecavir	HBsAg–/anti-HBc+	1
Brost	4	HSCT (2), steroids (1), bendamustine (1)	Entecavir	HBsAg–/anti-HBc+ (1)	3
Rago	1	Rituximab	ENT + TDF	HBsAg–/anti-HBc+	1
Milazzo	1	HSCT	ENT + TDF	HBsAg–/anti-HBc+	1
Montineri	5	Rituximab	LAM (1), LdT (2), TDF (2)	HBsAg–/anti-HBc+ (4), HBsAg+ (1)	5

NUC: Nucleoside/nucleotide analogue; HSCT: haematopoietic stem cell transplantation; ENT: entecavir; TDF: tenofovir; LAM: lamivudine; LdT: telbivudine

Prophylactic approach

Screening. Preventing HBV reactivation is preferred to intervention after reactivation has already occurred. The first step in prevention should be screening for HBV markers in individuals at risk of viral reactivation.

The United States Centers for Disease Control and Prevention (CDC) and the European Association for the Study of the Liver (EASL) guidelines recommend universal screening of *all* candidates for chemotherapy. If screening is undertaken, it should include testing for the presence of HBsAg and anti-HBc.

Targeted prophylaxis. The aim of this strategy is to start antiviral therapy when the first signs of reactivation appear, before the onset of severe hepatitis. Although initial reports suggested that targeted prophylaxis could be a satisfactory strategy, other studies have demonstrated that universal prophylaxis is more effective than monitoring and targeted therapy in terms of prevention of HBV reactivation, severity of clinical hepatitis and chemotherapy schedule interruptions.

Universal prophylaxis. The efficacy of prophylactic lamivudine prior to chemotherapy versus no action with respect to reducing the incidence and severity of HBV reactivation in HBsAg-positive patients with solid cancer (breast cancer and hepatocellular carcinoma) has been confirmed in retrospective and prospective studies. Early pre-emptive therapy is superior to deferred therapy in preventing HBV reactivation of HBsAg-positive lymphoma patients undergoing chemotherapy.

The efficacy of preventive lamivudine in HBsAg-positive patients has been addressed in one meta-analysis and one systematic review. The investigators found that preventive treatment with lamivudine was associated with a reduction of clinical and virological HBV reactivation, overall mortality, HBV-related mortality and interruptions or discontinuations of immunosuppressive therapy.

The optimal duration of antiviral treatment for prevention of HBV reactivation has not been defined. Disease exacerbation can occur after withdrawal of lamivudine. In one study, the prophylactic group continued lamivudine for two months after completion of chemotherapy. HBV reactivation and hepatitis occurred in similar proportions of prophylactic (19%) and therapeutic (14%) groups after suspension of lamivudine. In addition, cases of reactivation after prophylactic therapy tended to be clinically apparent and more severe. In another study, prophylaxis was continued for three months after chemotherapy. After 26 months of

follow-up, HBV was reactivated in 24% of patients, and reached 40% at 40 months. Experts recommend extending prophylaxis from six to 12 months post-cytotoxic therapy. Close follow-up of patients with serial serum ALT and even HBV DNA level monitoring is advised after discontinuation of lamivudine prophylaxis.

Until 2010, published studies on the prevention of HBV reactivation were mostly limited to lamivudine. However, in some studies lamivudine could not prevent reactivation (12% of cases) or even hepatitis (8%), attributable to the development of tyrosine-methionine-aspartate-aspartate (YMDD)-resistant mutations. The risk of lamivudine resistance was related to high baseline HBV DNA levels.

There is scarce evidence available regarding prevention of HBV reactivation with other NUCs. The first report was published in 2010 describing entecavir as an optional agent to prevent HBV reactivation. Sixteen HBsAg-positive patients who required chemotherapy for different solid and haematological cancers were treated once daily with 0.5 mg of entecavir, before the initiation of treatment. HBV reactivation did not occur in any of these patients and the treatment of their underlying diseases could be continued. One year later, a comparison study of entecavir and lamivudine in preventing HBV reactivation in HBsAg-positive lymphoma patients was completed. Eighty-nine patients received lamivudine and 34 received entecavir. In the lamivudine group, 12.4% of the patients suffered a hepatitis B reactivation versus none of the patients treated with entecavir. The conclusion was that entecavir is more effective than lamivudine in preventing HBV reactivation in these patients.

No standard management to prevent HBV reactivation has been established for HBsAg-negative patients seropositive for anti-HBc and/or anti-HBs. Given the reported low reactivation rates in these patients, universal prophylaxis could result in over-treatment of a substantial number of patients. A possible strategy could be that all HBsAg-negative/anti-HBc-positive patients scheduled to receive chemotherapy should be analysed for HBV DNA to stratify the risk of reactivation. Those with HBV DNA negativity and treated with low immunosuppressive potential drugs should undergo HBsAg and HBV DNA monitoring every one to three

months, with *targeted prophylaxis* in case of seroreversion or hepatitis reactivation. Since the onset of reactivation has been reported to be four to 36 months after chemotherapy, it is reasonable to extend surveillance for HBV reactivation for at least 12 months after discontinuation of treatment, especially in patients treated with rituximab, or even longer after HSCT.

Universal prophylaxis has been proposed for anti-HBc-positive/HBsAg-negative patients treated with intense, highly immunosuppressive chemotherapy (Table 3). This approach was also indicated in patients with signs of advanced liver damage (chronic hepatitis or cirrhosis, either HBV-related or not) or in cases of positive serum HBV DNA and/or positivity for anti-HBe at baseline.

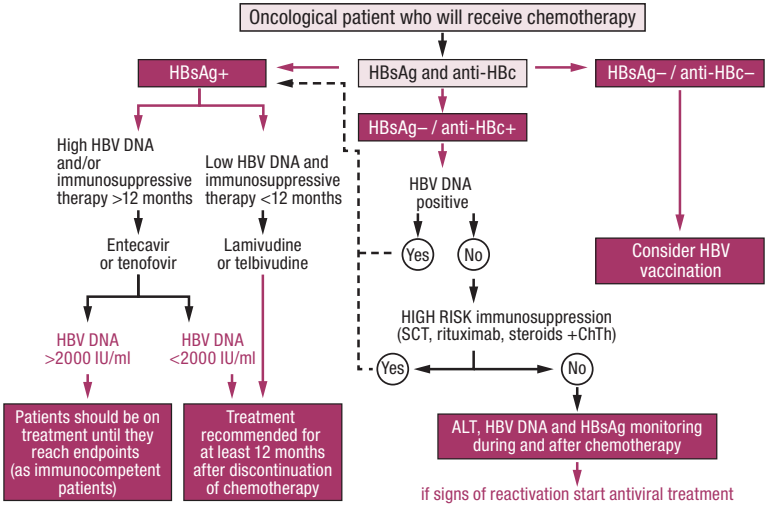
Some authors suggest a different approach for anti-HBc patients with HBs antibodies, given the reduced risk of reactivation in this group. Patients with anti-HBs positivity treated with highly immunosuppressive treatments (Table 3) could be at risk of reactivation if anti-HBs titres dropped below a protective level (<100 mIU/ml). HBV DNA surveillance should only be initiated if anti-HBs titres decrease below that level.

Table 3 *Highly Immunosuppressive Treatments*

■ Chemotherapeutic agents: anthracyclines, cyclophosphamide, fludarabine, vinca alkaloids
■ Dose-dense chemotherapeutic regimen
■ Induction in acute leukaemia
■ Steroid-containing regimens
■ Monoclonal antibodies: rituximab, alemtuzumab
■ Haematopoietic stem cell transplantation (HSCT)

General Recommendations

Based on the published evidence, and according to the main scientific associations (EASL, American Association for the Study of Liver Diseases [AASLD]), the proposed algorithm for the screening and management of HBV reactivation in patients with onco-haematological cancer receiving chemotherapy is summarised in Figure 2.



SCT, haematopoietic stem cell transplantation; ChTh, chemotherapy.

Figure 2 *Algorithm for the screening and management of HBV reactivation in patients with onco-haematological cancer receiving chemotherapy. Patients with cancer should be screened for HBV infection with HBsAg and anti-HBc. Patients who test positive for any of these markers should have HBV DNA levels measured to guide treatment. All HBsAg-positive patients should receive prophylactic therapy. Monitoring of ALT and HBV DNA levels is recommended in HBsAg-negative, anti-HBc-positive patients without active viral replication.*

Key points are the following:

- All candidates for chemotherapy should be screened for HBsAg and anti-HBc before initiation of therapy. This recommendation is especially relevant for geographical areas of high or intermediate prevalence rates for HBV. For people living in areas of low prevalence, it may be sufficient to screen only those patients who belong to high-risk groups for HBV infection: patients born in regions of intermediate and high HBV endemicity (HBsAg prevalence >2%); children of individuals who were born in regions of high endemicity (HBsAg prevalence >8%); patients with a history of intravenous drug use; patients undergoing haemodialysis; HIV-positive patients; and men who have sex with men. Vaccination against HBV in seronegative patients is highly recommended.

- HBsAg-positive patients should be tested for high HBV DNA levels. Those with HBV DNA levels >2000 IU/ml should be treated from one week before initiating chemotherapy until they reach treatment endpoints as in immunocompetent patients (seroconversion of HBeAg in HBeAg-positive patients or seroconversion of HBsAg in HBeAg-negative patients). Those with undetectable HBV DNA or levels <2000 IU/ml should continue treatment for 12 months after cessation of chemotherapy.
- Lamivudine (100 mg once daily) or telbivudine (600 mg once daily) can be used if the anticipated duration of treatment is short (≤12 months) and the baseline HBV DNA level is low (<2000 IU/ml).
- Entecavir (0.5 mg once daily) or tenofovir (300 mg once daily) is preferred if longer duration of treatment is anticipated or in patients with high baseline HBV DNA levels (>2000 IU/ml).
- HBsAg-negative and anti-HBc-positive patients should undergo testing for HBV DNA to rule out an occult blood infection. Patients who are HBV DNA-positive should receive antiviral prophylactic therapy according to HBV DNA levels, as indicated for HBsAg-positive patients. If HBV DNA testing is negative, close monitoring of HBsAg and HBV DNA levels every one to three months with targeted antiviral therapy as soon as seroreversion or reactivation appears is a reasonable strategy. HBsAg-negative and anti-HBc-positive patients scheduled for aggressive immunosuppressive treatments (Table 3) should be considered for antiviral prophylaxis even with negative basal HBV DNA levels.
- HBsAg-negative, anti-HBc-positive and anti-HBs-positive patients do not need monitoring or treatment. Only patients at high risk of reactivation (Table 3) should undergo monitoring of anti-HBs titres and HBV DNA levels when anti-HBs titres decrease below 100 mIU/ml.

Hepatitis C Infection

The prevalence of HCV infection is reported to be higher in haematological cancers, especially in patients with B-cell non-Hodgkin´s lymphoma (NHL), and is an estimated 9–15% compared to 1.5–3% in the general population. This is particularly the case in areas with a high incidence of

HCV infection, suggesting a role of HCV in the aetiology of B-cell NHL.

In patients with cancer, the incidence of HCV-related liver dysfunction is unclear. Most of the relevant studies were retrospective and the number of hepatic toxicities linked to HCV is not clear, as pre- and post-chemotherapy HCV RNA levels were not evaluated. The reported frequency of severe hepatic toxicity in HCV-positive patients with aggressive B-cell NHL is between 15% and 45%.

There is scant information available for solid cancers. In a retrospective study of patients with invasive breast cancer and HCV infection who were treated with anthracycline and taxane-based therapies, only 25% of patients showed an increase in ALT/aspartate aminotransferase (AST) during chemotherapy and 93% were able to complete the initial chemotherapy treatment plan, although 44% required dose reductions or dose delays during chemotherapy.

Pathogenesis, Clinical Implications and Diagnosis of HCV Reactivation

Chemotherapy-induced immunosuppression facilitates HCV replication. When cytotoxic chemotherapy is suspended, the period of depressed cellular immunity can be followed by an immunological rebound. This phenomenon is characterised by the restoration of immune function and increased inflammatory activity in the liver, resulting in the destruction of HCV-infected hepatocytes and liver injury. Some subgroups of cancer patients that seem to have an elevated risk for HCV reactivation include patients with lymphoma (mainly B-cell NHL) or those treated with certain drugs, such as corticosteroids or rituximab, and patients who undergo HSCT.

HCV reactivation can be defined as: at least a threefold increase in serum ALT level in a patient in whom the tumour does not affect the liver, who did not receive hepatotoxic drugs and had no other systemic infections besides HCV. Changes in liver enzymes should be accompanied by a reappearance or sudden increase in HCV RNA levels of more than 1 $\log_{10}$ IU/ml. In immunocompetent patients, HCV infection is diagnosed using serological assays (anti-HCV antibodies) and molecular tests (HCV RNA). However, patients with cancer, especially those with haematological

malignancies, can have false-negative antibody results. HCV RNA levels should be measured to confirm potential HCV reactivation if suspected during chemotherapy.

In the light of the published studies, 7–30% of lymphoma patients infected by HCV seem to be at risk of experiencing hepatotoxicity associated with chemotherapy. Acute exacerbation of HCV infection (ALT increase) can occur during chemotherapy but is usually observed weeks or months after chemotherapy has been withdrawn. In most patients, acute elevation of ALT or HCV RNA levels causes no symptoms. Once hepatotoxicity develops, mortality in HCV-positive patients may be as high as 20–45%. Evidence of active hepatitis or cirrhosis has been associated with more frequent hepatic failure and reduced survival. HCV-related hepatotoxicity can lead to modifications or interruptions of chemotherapy that may translate into poorer overall survival and shorter median progression-free survival.

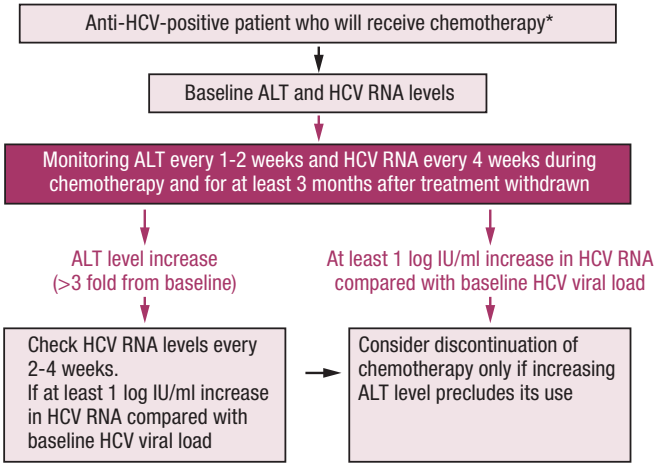
Treatment of HCV Reactivation

At present, treatment of HCV reactivation is mainly supportive. The use of protease inhibitors, such as telaprevir or boceprevir, has not been evaluated in patients with cancer. Both drugs inhibit hepatic cytochrome P450 and can potentially interact with drugs that are co-administered in patients with cancer. Anti-HCV therapy has traditionally been avoided during chemotherapy because the haematological adverse effects of antiviral drugs can exacerbate the toxicity of chemotherapy. The only data on the combined use of chemotherapy and antiviral treatment come from an abstract. The concomitant use of R-CHOP plus pegylated interferon and ribavirin to four patients with HCV and diffuse large B-cell lymphoma resulted in excessive haematological toxicity. Antiviral therapy was given after chemotherapy to the remaining patients and resulted in a better tolerance and effectiveness overall; however, currently there is not enough information to recommend administering anti-HCV therapy concomitantly with standard chemotherapy.

Prevention of HCV Reactivation

No drugs are currently approved for the prevention of HCV reactivation in patients who undergo chemotherapy. The risk of HCV reactivation may be reduced by using lower doses of immunosuppressive drugs or giving

less aggressive chemotherapy to prevent hepatotoxicity. However, this approach is not feasible since fatal hepatitis has been described even in patients treated with only one immunosuppressive agent. Hence, baseline screening for HCV infection is crucial in patients undergoing chemotherapy, especially in those with lymphoma. Patients with HCV infection (anti-HCV-positive and/or HCV RNA-positive) should be closely monitored for serum transaminase, especially after chemotherapy is reduced or withdrawn, and by measuring HCV RNA levels early during episodes of potential viral reactivation. The algorithm to manage HCV-positive patients with cancer who undergo chemotherapy is shown in Figure 3.



*In anti-HCV-negative patients with high-risk situations (haematological malignancy and unexplained liver disease) check for HCV RNA.

Figure 3 *Algorithm for the management of HCV-positive patients with cancer who receive chemotherapy. Patients with cancer, especially non-Hodgkin´s lymphoma, should be screened for HCV infection with serological assays (anti-HCV antibodies) and/or molecular tests to detect HCV RNA. Baseline ALT and HCV RNA levels should be measured and careful monitoring of these parameters is recommended during chemotherapy and after treatment is withdrawn. Modified from Torres et al. Nat Rev Clin Oncol 2012; 9:156–166.*

Conclusions

Reactivation of HBV or HCV can occur after immunosuppression in patients with cancer who receive chemotherapy. This complication can be clinically severe and result in progressive liver disease or death due to liver dysfunction. Patients needing cytotoxic agents should be screened for HBV and HCV infection before initiating chemotherapy. Periodic monitoring of ALT and HBV or HCV viral load levels should be performed during chemotherapy and after treatment is withdrawn. In high-risk patients, HBV reactivation can be preventable with the pre-emptive use of NUCs. As current treatment of HCV may not be used concomitantly with chemotherapy, management of HCV reactivation is mainly supportive.

Declaration of Interest:

Dr de la Revilla has reported no conflicts of interest.

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Cancer Treatment in Patients with Diabetes

7

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Introduction

Diabetes mellitus (DM) is a clinical syndrome associated with deficient insulin secretion (DM type 1) or peripheral resistance to insulin action (DM type 2). It is considered one of the largest emerging health threats in the 21st century. Worldwide, cancer is the second leading cause of death and diabetes is the 12th, but diabetes is commonly underreported both as a cause of death and as comorbidity. DM is associated with a wide range of vascular complications but also with non-vascular events such as infections, due to its overall effect on the immune system.

Diabetes and cancer are therefore both common diseases that have a great impact on health worldwide. Approximately 8–18% of people with cancer have diabetes as well, and both are diagnosed in the same individual more frequently than would be expected by chance. This increased frequency of concurrent cancer and diabetes has been described in epidemiological studies for many types of cancer such as liver, endometrial, colorectal and breast cancer, and it occurs predominantly in patients with type 2 diabetes. In view of the epidemiological links between the two diseases, a 2010 joint consensus report from the American Cancer Society and the American Diabetes Association (ADA) recommended regular cancer screening in diabetic patients.

The association between these two diseases may be direct (e.g. due to hyperglycaemia or underlying biological factors which modify the risk of developing cancer), or indirect (for example, when related to common risk factors such as age, obesity, physical activity, diet, alcohol consumption or smoking). Although several mechanisms are known to link cancer and diabetes, there is yet a limited understanding of the biological associations between cancer and DM.

The role of hyperglycaemia as a direct cause of cancer is controversial. Essentially, hyperglycaemia could be simply a surrogate biomarker of peripheral resistance to insulin and secondary hyperinsulinaemia, which are the main features of the metabolic syndrome associated with obesity and type 2 diabetes. Hyperinsulinaemia enhances synthesis of insulin-like growth factor 1 (IGF-1 or somatomedin C) and reduces the production of IGF-binding proteins, increasing free IGF-1, which is the form able to bind insulin-like growth factor receptor type 1 (IGF-1R). Functional activation of IGF-1R results in stimulation of signalling pathways downstream of the mitogen-activated protein (MAP) kinase and the phosphoinositide-3 kinase (PI3K)-Akt-mTOR pathways, which are relevant signalling cascades observed to be deregulated in many cancers.

In addition to IGF-1, hyperinsulinaemia also impacts other hormones, such as reducing the hepatic production of oestrogen-binding globulin and so indirectly increasing the exposure to oestrogens, which may increase breast cancer risk. Another alternative mechanism by which diabetes and cancer have been linked is based on the role of chronic inflammation in carcinogenesis, because an increase of inflammatory cytokines and an alteration of the normal inflammatory response are other common features of DM.

Impact of Diabetes on Cancer

In addition to an increased risk of cancer in DM, several studies have suggested that cancer in diabetic patients is associated with worse outcomes. It remains unclear whether the impact of DM on cancer mortality is due to the diabetes itself or to more aggressive cancer behaviour. In any case, DM may significantly increase both overall and specific mortality in patients with both conditions. This association between

diabetes and worse cancer outcomes differs among cancer sites and for different types of anti-diabetic treatment.

In this chapter, we review the impact of diabetic complications in cancer management, as well as the current evidence on the selection of anti-diabetic treatments in cancer patients.

Complications of Diabetes and their Impact on Cancer Management (Table 1)

Several complications associated with diabetes may make clinical decision-making in patients with cancer more challenging. These complications should be considered when selecting anti-cancer therapies, as sometimes treatment intensity may be hampered.

Table 1 *Summary of Recommendations*

General statements regarding diabetes and cancer
■ Despite higher risks of toxicities, "a priori" dose adjustments or specific anti-cancer treatment selection are not recommended on the basis of having concomitant diabetes, but close monitoring of side effects is necessary
■ Diabetes mellitus (DM) increases the risk of cardiovascular events and the susceptibility to infections, both relevant for cancer patients
■ Healing may be impaired in patients with DM, resulting in higher rates of postoperative complications
Practical hints in cancer patients with diabetes
■ Hypertension is a common problem. Target blood pressure for patients with DM is <130/80 mmHg
■ Monitor dyslipidaemia, especially in patients receiving hormonal treatments
■ Chemotherapy-related neuropathy tends to appear at lower cumulative doses in patients with DM
■ Risk of renal toxicity when receiving platinum-based therapies is higher for diabetic patients
■ Local infections like paronychia, folliculitis or gingivitis are commonly associated with some anti-cancer agents, and these infections may be more difficult to resolve in diabetic patients, leading to systemic infections
■ Use lower doses of steroids throughout the day when possible, instead of a high-dose daily bolus
■ Remember to adjust anti-diabetic treatment when starting steroids. Postprandial glycaemia should be monitored in addition to fasting values

Vascular Complications of Diabetes

The major causes of morbidity and mortality in type 1 and type 2 diabetes are the direct and indirect effects of hyperglycaemia on the vascular system. These include macrovascular (coronary artery disease, peripheral arterial disease and stroke) and microvascular (diabetic nephropathy, neuropathy, and retinopathy) complications, which are discussed later in this chapter.

Macrovascular complications of diabetes

Cardiovascular disease (CVD) is the primary cause of death in patients with either type 1 or type 2 diabetes. In fact, almost 70% of deaths in diabetic patients aged ≥65 years are from coronariopathy and another 16% of deaths are from stroke. Some studies have shown that the risk of myocardial infarction (MI) in patients with DM is equivalent to that in non-diabetics with a history of previous MI. Overall, DM increases the risk of CVD two- to four-fold compared to the non-diabetic population.

The pathophysiology of this increased CVD risk in diabetes is complex and multifactorial. The development of vascular atherosclerosis in the context of DM-related dyslipidaemia and deficient low-density lipoprotein (LDL) function appears to be a key factor in the pathogenesis of CVD disease in these patients.

Strict dietary control may benefit diabetic patients by decreasing the incidence of CVD; nonetheless, intensive hyperglycaemic control has recently been related to a lower incidence of CVD in DM type 1 patients. Current DM guidelines recommend that patients with DM have a lipid test at least once a year. The guidelines recommend lipid control targets for adults with DM: LDL <100 mg/dL, high-density lipoprotein (HDL) >50 mg/dL and fasting triglycerides <150 mg/dL. Statin therapy to lower LDL by 30–40%, regardless of baseline level, is recommended to decrease the risk of CVD in patients aged >40 years. To date, there are no specific recommendations for diabetic cancer patients; nonetheless, physicians should assess individual patient risk and consider more frequent monitoring in those patients receiving anti-cancer treatments which induce dyslipidaemia (e.g. luteinising hormone-releasing hormone [LHRH] analogues or anti-androgens) over long periods.

Recently, mTOR inhibitors (mTORi) have been approved for different cancer indications. Certain mTORi such as everolimus are associated with elevations in total cholesterol, LDL cholesterol and triglyceride levels. The PI3K-Akt-mTOR (PAM) Task Force of the National Cancer Institute recently established guidelines for managing hyperlipidaemia in cancer patients. In general, these metabolic effects may be more pronounced in patients with insulin resistance or who are at higher risk due to family history. The PAM Task Force recommends obtaining a complete fasting lipid panel at baseline and then at least at every cycle or event, and more frequently in the setting of clinical trials. Thresholds for intervention with drug therapy vary depending on patient estimated life expectancy. In general, for patients without any cardiac risk factors, the goal should be to keep fasting triglycerides <300 mg/dL and LDL <190 mg/dL. If the patient's life expectancy is estimated to be less than one year, drug therapy to lower triglyceride levels is needed for levels >500 mg/dL, primarily to prevent complications of hypertriglyceridaemia such as pancreatitis.

Endothelial dysfunction in diabetic patients is another factor associated with CVD and atherosclerosis. This dysfunction leads to a state of hypercoagulability with increased platelet activation and leukocyte adhesion, which contribute to thrombogenesis and inflammation. This association between DM and hypercoagulability is particularly relevant in cancer patients, and should be taken into consideration when assessing risk of thromboembolic events. Although the effect of aspirin for primary prevention of CVD in adults with DM is currently unclear, the ADA and the American Heart Association (AHA) jointly recommended that aspirin be used as a primary prevention strategy in DM in all men aged >50 years and in women >60 years who have one or more of the additional major risk factors: smoking, hypertension, dyslipidaemia, family history of premature CVD or albuminuria. Aspirin may also be beneficial in younger patients with risk factors for CVD, although more evidence is needed. No formal recommendation to use aspirin for primary prophylaxis of CVD events has been made for patients with both DM and cancer. Nevertheless, in those diabetic cancer patients treated with chemotherapy drugs associated with an increased risk of cardiac

ischaemia (e.g. 5-fluorouracil, paclitaxel or docetaxel) or thromboembolism (e.g. lenalidomide, thalidomide, cisplatin or erlotinib), the addition of anti-aggregants or even anticoagulants must be considered.

Arterial hypertension (HTN) is a very common problem in diabetic patients, but it is also the most frequent comorbid condition in cancer patients overall. In addition, novel cancer therapies targeted to disrupt angiogenesis (e.g. bevacizumab, sorafenib and sunitinib) affect the control of blood pressure in HTN patients and also cause *"de novo"* HTN in as many as 45% of cancer patients without a prior history. Although there are guidelines and recommendations for the control and secondary prophylaxis of drug-induced HTN, currently there are no specific guidelines for the primary prophylaxis of patients undergoing cancer treatments affecting blood pressure control. Nonetheless, the ADA has recommended that blood pressure in diabetic patients should be measured routinely, aiming for blood pressure readings of <130 mmHg and <80 mmHg for systolic and diastolic pressure, respectively. In patients with systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg, antihypertensive treatment should be initiated along with diet and lifestyle modifications.

Diabetic neuropathy

The term "diabetic neuropathy" includes a range of disorders related to injury to the microvasculature of the peripheral nerves. The most common subtype of neuropathy in diabetic patients is distal symmetric polyneuropathy. Mononeuropathies are also common (e.g. third cranial nerve palsy) and may cause significant morbidity. Autonomic neuropathies, although less common, may be potentially life-threatening in certain cases. The only effective treatment for neuropathies is to prevent them by good glycaemic control, especially in patients with type 1 diabetes, since patients with type 2 diabetes may already have some degree of neural injury at the time of diagnosis. Some diabetic patients with cancer may suffer neuropathic pain, which can be managed with antidepressants and anticonvulsants.

Several neurological symptoms are also known to be potential side effects of commonly used chemotherapies. There are two major groups of neurological side effects of chemotherapies: central and peripheral neuropa-

thies. Central neuropathies are associated with high doses of methotrexate, cytarabine or ifosfamide. Peripheral neuropathies are mostly sensory neuropathies, which are usually related to dose accumulation of platinum salts, taxanes or vinca alkaloids.

One example is the commonly observed oxaliplatin-related peripheral neuropathy, which is associated with the accumulated dose and may be dose-limiting in a significant proportion of cancer patients. A small retrospective study evaluating 85 colorectal cancer patients suggested an earlier onset of peripheral neuropathy in diabetic patients compared with non-diabetic patients (388 mg/m^2 versus 610 mg/m^2 of oxaliplatin). The presence of other common risk factors for neuropathy, such as smoking or HTN, hinders an accurate evaluation of the diabetes-related risk of platinum salt-induced neuropathy in this population.

It is advisable to personalise treatment and closely monitor diabetic patients receiving chemotherapy regimens containing drugs which induce peripheral neuropathy, especially in the adjuvant setting. Due to the lack of consistent data, treatment modifications should be based on established toxicities and not on the predisposition of diabetic patients, if such changes significantly compromise the potential benefits of treatment.

Diabetic nephropathy

Renal impairment is a common consequence of long-standing diabetes, characterised by a progressive decrease of glomerular filtration rate due to haemodynamic changes in the renal microvasculature. The pathogenesis of diabetic nephropathy usually starts with a phase of glomerular hyperperfusion that leads to structural changes in the glomerulus (mesangial expansion, thickening of the glomerular basement membrane and finally glomerular sclerosis due to glomerular HTN). The presence of microalbuminuria is a biomarker of renal damage in diabetic nephropathy and is prognostic of morbidity and mortality. Microalbuminuria is usually the first detectable sign of renal impairment, occurring even years before a decrease in glomerular filtration rate is observed. Prevention and treatment are based on control of the underlying conditions of hyperglycaemia and HTN, which are often associated, and the avoidance of nephrotoxic agents.

Patients with cancer are at risk of developing renal impairment secondary to several causes: the cancer itself (if the tumour is in the genitourinary tract), exposure to nephrotoxic anti-cancer therapies or concomitant medications that may be nephrotoxic (such as non-steroidal anti-inflammatory drugs [NSAIDs]) and other less common causes such as paraneoplastic syndromes or acute tumour lysis syndrome. In cancer patients, DM may also facilitate the development of chemotherapy-related renal impairment. For example, a retrospective analysis of 242 lung cancer patients, with or without DM and with normal baseline creatinine, estimated a three-fold higher risk of cisplatin-related nephrotoxicity among the diabetic patients.

The management of cancer patients with renal impairment, including the recommendation for chemotherapy dose adjustments, is discussed in another chapter in this book (Chapter 2). In general, there are no consensus guidelines for prophylactic dose adjustments in diabetic patients if kidney function is normal, but closely monitoring albuminuria and creatinine clearance is highly recommended when using nephrotoxic drugs or chemotherapies with predominantly renal excretion.

Immunosuppression and Infectious Diseases

Diabetic patients have an increased susceptibility to infectious diseases due to an attenuated immune response caused by the hyperglycaemic environment. Essentially, the excess of glucose results in a non-enzymatic glycosylation of proteins and lipids, also known as glycation. This process impairs the functioning of molecules and affects the production of interleukins, interferon gamma (IFN-γ) and tumour necrosis factor (TNF)-α, thereby interfering with the inflammatory response. It has been suggested that the non-enzymatic glycosylation of immunoglobulins in diabetic patients occurs in proportion to the level of glycated haemoglobin (HbA1c). Glycation does not seem to affect the antibody response after vaccination or the response to common infections in diabetic patients; therefore, its clinical relevance remains unclear. Glycation also reduces class I major histocompatibility complex (MHC) expression on the surface of myeloid cells, impairing cellular immunity. Glycation is also related to a decline in neutrophil function due to diverse mechanisms

such as reduction in adhesive capacity, chemotaxis, phagocytic activity and bactericidal capacity. Finally, a number of other factors contribute to a higher incidence of infections in diabetic patients, including the presence of micro- and macroangiopathies, neuropathy, gastrointestinal and urinary dysmotility, a decrease in the antibacterial activity of urine, and the greater number of medical interventions required for these patients.

From an epidemiological point of view, diabetic patients have a higher incidence of both nosocomial and community-acquired infections. At the same time, infections in these patients are precipitating factors for other serious complications inherently related to diabetes, such as hyperosmolar ketotic and non-ketotic decompensation.

The most frequent respiratory infections associated with DM are those caused by *Streptococcus pneumoniae* and influenza virus. Diabetic patients are six times more likely than non-diabetic patients to be hospitalised during influenza epidemics; therefore, immunisation with antipneumococcal and influenza vaccines is recommended for all diabetic patients. The current guidelines recommend vaccinations for all cancer patients aged >65 years for pneumococcus and >50 years for influenza (which is given annually). In the case of cancer patients with DM, we should extend these vaccinations to all age groups.

Patients with DM are at higher risk of contracting mycobacterial infections, especially tuberculosis, which can present as a multi-resistant disease. The management of tuberculosis in diabetic patients is challenging, as both the infection and the therapy complicate glycaemic control. An example of the latter is rifampicin, which induces the activity of certain hepatic cytochrome P450 enzymes, such as CYP2C9 and CYP3A4, accelerating the metabolism of multiple drugs including oral anti-diabetic drugs.

Urinary tract infections are also more prevalent in DM and have a higher complication risk due to multiple factors, including urinary dysmotility and alterations in the antibacterial properties of urine. Emphysematous pyelonephritis and cystitis are examples of severe complications of urinary tract infections, which are more commonly observed in diabetic patients. Despite this increased risk of infections and other severe complications,

urinary tract infection prophylaxis is not recommended in diabetic patients. Furthermore, the indication for antibiotic treatment of asymptomatic bacteriuria in diabetic women is controversial, as it is not clear whether bacteriuria can progress to serious complications such as pyelonephritis.

Regularity of gastrointestinal motility is another important mechanism of defence against infections that may be altered in diabetic patients, facilitating infections in the digestive tract. Chronic hyperglycaemia also contributes to an increased risk of gastrointestinal infections. Mucocutaneous candidiasis (usually due to *C. albicans*) is associated with DM and other hyperglycaemic states and very often affects cancer patients. Poor glycaemic control has also been associated with a greater incidence of gingivitis and later progression to periodontitis, which is four times more frequent than in non-diabetics. In fact, periodontitis is considered one of the most common complications of DM. Periodontal infections may worsen during cancer therapy (e.g. head and neck cancer patients treated with radiotherapy; neutropenia during the course of chemotherapy), causing oral pain, abscesses or even bacteraemia and sepsis. Therefore, periodontal disease should be assessed and treated prior to radiotherapy of oropharyngeal cancer and in patients in whom neutropenia may develop as a side effect of systemic chemotherapy. Although there is not a specific recommendation for diabetic patients, pre-treatment assessment and management of oral hygiene and periodontal care have been shown to be effective in preventing oral and systemic complications during cancer treatment.

DM patients are also more predisposed to skin and soft tissue infections such as folliculitis, furunculosis and subcutaneous abscesses. Foot infections are the most significant chronic complications of DM and, if not correctly treated, may progress to osteomyelitis. Paronychia is another frequent infection in diabetic patients which is also a common side effect of many cancer treatments.

Febrile neutropenia is a common acute side effect of cytotoxic chemotherapy, and it has been described as occurring more often among diabetic patients. Diabetes is a risk factor that should be considered when evaluating the indication for primary prophylaxis of febrile neutropenia. Diabetic patients with lymphoma who receive myeloablative

chemotherapy followed by autologous stem cell transplantation support seem to be more prone to infections during the neutropenic period following high-dose chemotherapy and transplantation.

Finally, there are also rare infectious complications that occur almost exclusively in diabetic patients. Examples are rhinocerebral mucormycosis, malignant external otitis and gangrenous cholecystitis. These infections can be lethal if not correctly treated.

In conclusion, DM increases the risk and the severity of infectious diseases in cancer patients. Again, there are no specific guidelines for the prevention or management of these infections in cancer patients that differ from the general recommendations for all diabetic patients. However, it is always advisable to take them into consideration when monitoring cancer treatment in diabetic patients.

Other Situations to Consider in Clinical Practice

Diabetic Patients Undergoing Surgery

Patients with cancer may require surgery either as primary treatment for the disease or with palliative intent. Those who also suffer from DM will have a higher risk of postoperative complications such as infections or healing problems. Studies of postoperative wound infections in diabetic patients have correlated the risk of wound infection with the hyperglycaemic control during the first 48 hours after surgery, but have not found an association with HbA1 or preoperative glycaemic levels. Therefore, the control of glucose levels during the postoperative setting is considered crucial to diminish the risk of wound infections, although its management can be challenging due to changes in the nutritional patterns and other concomitant perioperative stress factors.

Subcutaneous insulin is the preferred treatment option to control hyperglycaemia in the immediate postoperative period in all diabetic patients, especially those who have oral intake restriction, and independently of whether or not they required regular medical treatment for hyperglycaemia prior to surgery. Intravenous insulin requires intensive glucose monitoring (usually hourly) and should be employed for patients in the intensive care unit or with severe complications. The use of oral

anti-diabetic drugs in the postoperative phase should be reserved for those patients who were already taking them before surgery and who are able to receive oral alimentation. In patients who were previously taking oral anti-diabetics, renal and hepatic function should be monitored before restarting these drugs. In the case of patients using sulphonylureas, the risk of hypoglycaemia should be considered.

Hyperglycaemia in Patients Treated with Glucocorticoids

A proportion of cancer patients will be exposed to short or long courses of steroids with glucocorticoid activity. These steroids are commonly used as a component of anti-cancer treatment, as premedication for certain therapies or for symptom control, as they are effective for treating pain, nausea, asthenia and anorexia.

Steroid use is associated with hyperglycaemia in both diabetic and non-diabetic patients. When non-diabetic patients develop persistent high glucose levels after steroid use, this problem is known as new-onset steroid-induced diabetes (NOSID). Glucocorticoids interfere with the glucose regulation system at different levels. They favour gluconeogenesis and glycogenolysis, increasing the release of glucose in the circulation. In addition, they interfere with insulin action by decreasing its production as well as increasing the peripheral resistance to insulin.

The association of traditional risk factors such as obesity and family history with the development of NOSID remains unclear, as contradictory data have been reported. The dose level seems to be major predictor of the risk of steroid-related hyperglycaemia. The effect of steroids on glucose level deregulation is greater in the postprandial phase than in the fasting state, resulting in an underdiagnosis of NOSID in patients who were not previously known to have DM. It is also advisable to add a 2-hour postprandial capillary glucose test to the regular fasting glucose monitoring for diabetic patients receiving steroids.

In patients with baseline diabetes or in those who develop NOSID, it is preferable to fractionate the daily dose of steroids when feasible, instead of using a large single daily bolus. For patients with diabetes treated with

insulin, dose adjustment can be done in anticipation of starting glucocorticoids or on the basis of close glucose monitoring. For non-diabetic or untreated patients, treatment should be considered on an individual basis; the effects on glucose metabolism abate within 1–2 days of steroid discontinuation. Mild hyperglycaemia may be managed with oral drugs, particularly thiazolidinediones, due to their rapid onset of action. Marked hyperglycaemia may require insulin, especially in untreated diabetic patients or in patients with concomitant renal or hepatic impairment. A combination of basal long-acting and preprandial fasting insulin may be required, and dosage should be titrated daily.

Other Therapies Which may Affect Blood Glucose

Apart from corticosteroids, anti-androgens may also adversely affect glucose metabolism. This therapy causes a variety of metabolic abnormalities that include decreased insulin sensitivity and altered lipid profile (as discussed previously). Anti-androgens therefore increase the risk of diabetes. Diet and lifestyle interventions with a target 5–10% weight loss are the main strategies for preventing or treating the metabolic complications of androgen deprivation therapy.

An increasing number of compounds which alter the IGF-1 system and its downstream intracellular pathways are being tested for therapeutic use. Since IGF-1 signalling plays a key role in both tumour progression and glucose homeostasis, therapies targeting the IGF system for its pro-cancer effect may cause hyperglycaemia at the same time. Downstream of the receptor, IGF-1 signalling occurs via the activation of enzymes and substrates like PI3K, Akt and mTOR. Inhibitors against these three enzymes have been associated with hyperglycaemia. The PAM Task Force has recently published a guideline for managing hyperglycaemia in cancer patients. Hyperglycaemia screening for patients on PAM pathway inhibitors with a random glucose test is recommended at every visit for non-diabetics, and at least once per day of the first cycle for high-risk patients. If hyperglycaemia is sustained or high grade, treatment with metformin as first-line therapy, even in asymptomatic patients, is recommended.

Management of Diabetes During End-of-life Care of a Cancer Patient

During the end-of-life care of diabetic cancer patients, we can consider reducing the glycaemic control targets, but we should not ignore them. Insulin and oral hypoglycaemic agents should still be used in "comfort care" or "palliative care" patients, because the signs and symptoms of uncontrolled hyperglycaemia decrease quality of life due to a range of symptoms and complications such as polyuria, polydipsia, electrolyte imbalance and dehydration. Maintaining a glucose level below 200 mg/dL may be a realistic goal and can benefit patients by minimising the intensity of hyperglycaemia-related symptoms. Clinicians should consider patients' wishes when making treatment decisions about their diabetes, as patients may wish to exert some degree of control over their diabetes in an otherwise untenable situation. In any case, any decisions should be re-evaluated and revised with each significant clinical change in the patients' status and considered in the overall context of the clinical situation and treatment goals.

Impact of Treatments for Diabetes on Cancer Risk and Management

In recent years, several studies have released information about the potential role of metformin, a biguanide-class oral anti-diabetic, in the prevention and treatment of several types of cancer.

Two different mechanisms have been postulated for this effect. On one hand, a direct effect of metformin on cancer cells through stimulation of AMP kinases would lead to a secondary inhibition of mTOR. On the other hand, metformin stimulates an AMP kinase-mediated inhibition of liver gluconeogenesis, and therefore a reduction in circulating insulin levels. Interaction with the IGF receptor in cancer cells would then be reduced, decreasing the proliferation signals through the PI3K pathway.

Despite increasing evidence of the impact of several anti-diabetic agents on the outcome and prevalence of cancer, current evidence does not justify considering the risk of cancer as a major factor when selecting treatment for diabetes. The 2010 joint consensus suggested only giving "more careful consideration" when choosing among available options for diabetes in patients at "very high risk of cancer occurrence (or for recurrence of specific

cancer types)". Conversely, there is no evidence supporting a change in anti-diabetic treatment due to a cancer diagnosis, despite a number of retrospective studies reporting better outcomes for patients receiving metformin.

Potential Drug–drug Interactions with Oral Anti-diabetic Agents

Due to different comorbidities associated with DM and cancer, these patients are often treated with multiple medications, which may also include cytotoxic anti-cancer agents. Thus, DM patients with cancer may be at significant risk of drug–drug interactions due to polypharmacotherapy.

Metformin is currently the most widely used oral anti-diabetic drug in the treatment of DM type 2. Metformin does not undergo significant metabolism in the liver or other tissues and it has not been demonstrated to inhibit or to induce any CYP enzyme. Metformin is excreted mostly unchanged in the urine; thus, its elimination is dependent on renal function. Drugs impairing renal function could cause accumulation of metformin and increase the risk of lactic acidosis, a rare but life-threatening side effect of this drug. Such possibilities should be considered when using potentially nephrotoxic drugs such as angiotensin-converting enzyme (ACE) inhibitors, NSAIDs, loop diuretics, aminoglycosides or ciclosporin, when renal function is already compromised or when using x-ray contrast media in patients with renal function at risk. Conventional cytotoxic chemotherapy drugs with potential renal toxicity should also be considered carefully in this context.

All other oral hypoglycaemic agents are metabolised by the cytochrome P450 system. The majority of these oral anti-diabetics are substrates for CYP2C9, with CYP3A4 and CYP2C8 metabolising most of the remaining ones. In addition, the roles of several transporters, such as organic anion-transporting polypeptide 1B1 (OATP1B1) and P-glycoprotein (P-gp), have been characterised in the disposition of some of these drugs. These mechanisms are the basis for understanding many clinically significant pharmacological interactions of oral anti-diabetics.

First-generation sulphonylureas are rarely used, but the second generation of this class of hypoglycaemic agents (glyburide, glimepiride, gliclazide and glipizide) are metabolised mainly by CYP2C9, although gliclazide and glyburide are also partly metabolised by CYP2C19 and

CYP3A4, respectively. The inhibition of these enzymes is of major importance, as it results in increased plasma concentrations of sulphonylureas, which enhances the risk of potentially fatal hypoglycaemia.

Meglitinide analogues (nateglinide and repaglinide) have a short half-life and consequently are administered several times a day. When inhibitors or inducers of the crucial enzymes are added to or withdrawn from therapy with nateglinide or repaglinide, close monitoring of blood glucose is recommended with subsequent dose adjustment if necessary. Various CYP2C9 inhibitors may moderately increase the plasma concentrations and effects of nateglinide. Increased exposure to and enhanced effects of repaglinide are possible if used with inhibitors of CYP2C8, CYP3A4 and OATP1B1. Most prominent interactions affecting repaglinide occur when inhibitors act via different mechanisms (e.g. CYP2C8 and CYP3A4).

The thiazolidinedione class of insulin-sensitising drugs includes pioglitazone and rosiglitazone. Exposure to thiazolidinediones is altered by drugs which inhibit or induce CYP2C8. Because of increased cardiovascular risks, rosiglitazone was recently withdrawn from the market by the European Medicines Agency (EMA) and its use has been restricted by the United States Food and Drug Administration (FDA).

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral antidiabetic drug, which act by inhibiting DPP-4 and promoting insulin secretion. To date, four DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin and vildagliptin) have received marketing approval. Their use is not associated with a significant risk of serious hypoglycaemia in monotherapy, but the risk is increased when used with sulphonylureas. All DPP-4 inhibitors are substrates for P-gp. In addition, a small proportion of linagliptin is metabolised by CYP3A4, saxagliptin undergoes extensive hepatic metabolism by CYP3A4/5, and sitagliptin is metabolised by CYP3A4 with a minor contribution from CYP2C8. However, with the exception of saxagliptin, DPP-4 inhibitors seem to be free of strong drug–drug interactions involving CYP enzymes.

Clinically, the most significant interactions affecting oral hypoglycaemic agents are those mediated by the inhibition of CYP2C9. Examples of CYP2C9 inhibitors which may affect sulphonylureas or nateglinide are

represented by antifungals such as fluconazole, voriconazole or miconazole; antibiotics such as sulfamethoxazole, isoniazid or metronidazole; or antidepressants such as fluoxetine. Inhibitors of CYP2C8 such as gemfibrozil should also be avoided with repaglinide and thiazolidinediones. Inhibitors of P-gp or CYP3A4 (e.g. clarithromycin, erythromycin, indinavir, ritonavir, itraconazole or ketoconazole) can markedly elevate the concentrations of linagliptin and saxagliptin, but the clinical relevance of these potential interactions appears to be limited. On the other hand, the induction of the CYP-mediated metabolism of oral anti-diabetics by rifampicin, and probably also by carbamazepine, phenytoin and St John's wort, may result in failure of glucose-lowering therapy.

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Cancer Treatment in Patients with Heart Disease

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The management of cardiac disease in the cancer patient is unique and in many ways unlike managing cardiac disease in patients without cancer. All large seminal prospective randomised trials of cardiac therapy upon which the management of heart failure or coronary disease was developed have excluded patients with cancer. Therefore, we do not have true evidence-based guidelines that apply to the management of patients with cancer. For a successful partnership, cardiologists and oncologists need to develop data that will allow the development of evidence-based guidelines specific to the management of cardiac disease during and after cancer therapy.

Detection of Anti-cancer Drug-induced Cardiotoxicity

Potential cardiac toxicities induced by anti-cancer therapies are summarised in Table 1.

Table I *Potential Cardiac Toxicity Induced by Anti-cancer Chemotherapeutic Agents*

Drug	Toxic dose range	Cardiac toxicity	%
Doxorubicin Epirubicin Idarubicin	>450 mg/m^2 >900 mg/m^2 No dose data available	Left ventricular dysfunction	3–12% 0.9–3.3%
Paclitaxel Docetaxel	Conventional dose	Left ventricular dysfunction	5–15% 2.3–8%
Cyclophosphamide Ifosfamide	>100–120 mg/kg	Left ventricular dysfunction	3–5%
Capecitabine Fluorouracil	Conventional dose	Cardiac ischaemia	3–9% 1–68%
Paclitaxel Docetaxel	Conventional dose	Cardiac ischaemia	<1–5% 1.7%
Trabectedin	Conventional dose	Cardiac ischaemia	1%
Arsenic trioxide	Conventional dose	QTc prolongation	26–93%
Paclitaxel	Conventional dose	QTc prolongation	0.1–31%

The most frequently used method for detecting cardiotoxicity is periodic measurement of the left ventricular ejection fraction (LVEF), using either echocardiography or multigated acquisition (MUGA) scanning. To date, however, there are no evidence-based guidelines for monitoring cardiotoxicity during or after anti-cancer therapies in adults, while guidelines in paediatric oncology are subject to debate. Although several guidelines are available, none specify how often, by what means, or for how long cardiac function should be monitored during and after cancer treatment. Serial evaluation of LVEF is recommended for patients treated with trastuzumab, which is associated with risk of cardiotoxicity (Table 2).

LVEF measurement is a relatively insensitive tool for detecting cardiotoxicity at an early stage, as no considerable changes in LVEF occur until a critical amount of myocardial damage has taken place and only becomes apparent after compensatory mechanisms are exhausted. In addition, the measurement of LVEF presents a number of challenges related to image quality, assumptions of left ventricular geometry, load dependency and expertise. MUGA scanning can reduce interobserver variability, but it has the disadvantages of exposure to radioactivity and it provides limited information on cardiac structure and diastolic function.

Table 2 *Cardiotoxicity in the Major Adjuvant Trastuzumab Trials for HER2+ Patients*

Trial	Design	Asymptomatic drop in LVEF	Symptomatic drop in LVEF	Severe CHF/ cardiac events (CHF or death)	Discontinued H for cardiac reasons
NSABP B31, n = 2043	AC × 4 + T vs AC × 4 + TH + H	34% vs 17%		3.9% vs 1.3%	18% (1)
NCCTG N9831, n = 2766	AC × 4 + T vs AC + T + H vs AC × 4 + TH + H			3.3% vs 2.8% vs 0.3%	(2)
BCIRG 006, n = 3222 – update with SABCS 2009	AC × 4 + T vs AC × 4 + TH + H vs TCaH (3)	18% vs 10% vs 8.6%		1.87% vs 0.38% vs 0.38%	
HERA, n = 5102	Adj chemo (4) → H vs adj chemo alone	3.04% vs 0.53% OR 7.03% vs 2.05%	1.7% vs 0.06%	0.6% vs 0%	4.3%
FinHer, n = 232	V or T ± H (5) → FEC × 3	3.5% vs 6.0%		0%	

Abbreviations: A, anthracycline; C, cyclophosphamide; Ca, carboplatin; CHF, cardiac heart failure; E, epirubicin, F, 5-fluorouracil; H, trastuzumab; T, taxane; V, vinorelbine

1. 3.23% did not receive H after A due to unacceptable drops in LVEF
2. 5.0% did not receive H after A due to unacceptable drops in LVEF
3. Included an anthracycline-free arm
4. 96% of chemotherapy was A-containing
5. No prior anthracycline before H exposure; H exposure limited to 9 weeks

Magnetic resonance imaging (MRI) is considered the gold standard for evaluation of left ventricular volume, mass, and function. However, lack of availability and high cost limit its routine use.

In the past decade, a new approach based on the use of cardiac biomarkers, in particular troponins, has emerged, which has proven to be a more sensitive and more specific tool for early, real-time identification, assessment and monitoring of anti-cancer drug-induced cardiac injury. Strong data indicate that troponin detects anti-cancer drug-induced cardiotoxicity in its earliest phase, long before any reduction in LVEF has occurred. Evaluation of troponin during high-dose chemotherapy allows for the early identification of patients at risk of developing cardiac dysfunction, the stratification of risk in cardiac events after chemotherapy, and the

opportunity for a preventive therapy in selected high-risk patients. In patients treated with trastuzumab, troponin might help to distinguish reversible and irreversible cardiac injury by identifying myocardial cell necrosis. Measurement of troponin immediately before and after each cycle of cancer therapy seems to be effective, and is also transferable from clinical research to real-world routine assessment.

The Cancer Patient with Heart Failure

In cardiac patients, heart failure can be associated with coronary ischaemia and/or infarction, chronic hypertension, viral infection, chronic inflammation, hereditary traits, toxic agents (e.g. cocaine, alcohol), and acute and chronic stress. In cancer patients, the cardiologist should find ways to limit and/or modify the cardiac damage while permitting cancer therapy to continue. A careful assessment of cardiac risk factors is important before beginning chemotherapy. Evaluation of cardiac status with cardiac imaging should be performed before initiating chemotherapy in these patients to establish risk and to guide management. It is important to develop improved methods for follow-up of these patients, including agreement on measures of cardiac function.

Oncologists define cardiac toxicity by serial measurement of LVEF. On the other hand, cardiologists know that the correlation between ejection fraction and symptomatic heart failure is not reliable, and that diastolic heart failure is associated with a similar prognosis, since heart failure is associated with reduced LVEF. As noted above, measurement of LVEF is limited only to the description of cardiac toxicity. The use of MRI can provide data on anatomy, ventricular structure, and haemodynamic parameters. This procedure has not been validated in the setting of patients with cardiac disease, and costs, availability, expertise and duration of procedure can be limiting factors for use in cancer patients.

Advances in biomarker detection and use to define myocardial damage have been revolutionary in the management of cardiac patients. Troponin and B-type natriuretic peptide have simplified the diagnosis and management of myocardial infarction and heart failure, and can predict outcome

in cardiac patients. These advances have also been applied in cancer populations, and early results hypothesise a role in surveillance.

Although current heart failure guidelines suggest treating asymptomatic New York Heart Association Class I heart failure patients with beta-blockers and ACE inhibitors, there is no definitive information as to whether these strategies are appropriate or effective in patients being treated with current chemotherapeutic agents. In patients with left cardiac dysfunction, hypotension is frequent and may lead to excessive fatigue and/or worsening of renal function, such that different strategies may need to be devised for their treatment. The role of device therapy such as biventricular pacing has not been evaluated in cancer patients or cancer survivors with impaired systolic dysfunction. The role of implantable cardiac defibrillators is even less clear, because of the uncertain life expectancy of cancer patients.

The Cancer Patient with Coronary Heart Disease

The management of coronary heart disease is based on platelet inhibition with a variety of agents and revascularisation strategies. Placing coronary stents requires antiplatelet therapy for prolonged periods of time, which may make the use of drug-eluting stents (DESs) or bare metal stents (BMSs) problematic in cancer patients. In addition, cancer patients with high to moderate thrombotic risk have not been included in the safety analysis of this approach to revascularisation. Several issues may arise in cancer patients. Chemotherapy may lead to thrombocytopenia, which makes maintenance of antiplatelet therapy problematic. The drugs used to inhibit in-stent restenosis have the unwanted adverse effect of delaying re-endothelialisation. Antineoplastic and anti-inflammatory therapies may also have a direct effect on stent re-endothelialisation. Stent thrombosis occurring at withdrawal of antiplatelet therapy, even with continuation of aspirin, has been reported in cancer patients. The management of coronary stents in patients with active cancer or undergoing chemotherapy has never been evaluated, and this must be considered by the cardio-oncologist in planning therapy.

The patient with coronary disease, even if stable, may have to undergo cancer surgery. If the underlying coronary disease is severe, cancer surgery may be deferred until the obstructed lesions are revascularised, provided that there is no need for urgent cancer resection to prevent metastasis. In the cancer patient with coronary disease who has no indication for cardiac surgery, the need for revascularisation must be very carefully considered, as there is a low to moderate risk of coronary complications related to cancer surgery.

Emergency Situations in Patients with Coronary Stents: Recommendations for Anticoagulant Therapy

Clopidogrel is currently essential in the management of newly placed coronary artery stents, especially DESs. Clopidogrel is a prodrug that requires hepatic metabolism to become active. In cancer patients, where liver impairment is common, the efficacy of clopidogrel should be established. Prasugrel, a newer thienopyridine that interacts with platelets, may bypass this problem, but has been shown to be associated with more bleeding than clopidogrel and may promote the metastatic nature of colon cancer. Its safety in cancer patients, many with thrombocytopenia, has not been established.

Dual antiaggregation (antiplatelet) therapy is mandatory in patients stented during percutaneous coronary intervention and usually consists of acetylsalicylic acid (100 mg per day) and clopidogrel (75 mg per day) for at least 6–12 months, depending on the type of stent. Such therapy has been shown to reduce unwanted clinical events significantly, although it increases slightly the risk of bleeding. Rare cases exist in the literature in which coronary stents were implanted in patients who had or later developed thrombocytopenia. In these patients the risk of bleeding was increased. In some case reports of patients with thrombocytopenia (<50 000/μl), after evaluation of platelet function with the adenosine diphosphate (ADP) aggregation test (which indicates the degree to which platelet function is blocked by clopidogrel) and the aspirin resistance test (which indicates the degree to which platelet function is blocked by acetylsalicylic acid), it was possible to adapt and personalise therapy with clopidogrel to reduce the risk of bleeding. In other case studies of patients with acute coronary syndrome, thrombocytopenia (from 17 000

to 72 000/μl) and cancer who underwent percutaneous coronary intervention with stenting, all were given aspirin either alone or with clopidogrel. Aside from the occasional use of antiplatelet and thrombolytic agents in patients with thrombocytopenia, no therapeutic recommendation can be made until data are available on a larger patient population.

No data are available regarding the management of cancer patients requiring interruption of long-term vitamin-K antagonist (VKA) therapy. Cancer patients receiving VKA therapy pose a clinical challenge when anticoagulant therapy must be interrupted for surgical/invasive procedures or due to chemotherapy-induced thrombocytopenia. Interruption of anticoagulant therapy exposes patients to an increased risk of thromboembolic events (TEE) (e.g. stroke or mechanical valve thrombosis), although such risk varies depending on the indication for the antithrombotic therapy and the presence of comorbid conditions. Conversely, the administration of anticoagulants during surgical procedures increases the risk of major bleeding.

To manage such situations, two options are available. The first strategy is to continue oral anticoagulant therapy with a temporary adjustment of warfarin intensity to a preoperative international normalised ratio (INR) of 1.5–2.0. However, such an approach is associated with a high rate of bleeding in non-cancer patients. Another strategy involves switching VKA therapy to low-molecular weight heparin (LMWH; so-called "bridging therapy") several days before the procedure, at doses and timings related to the individual thrombotic burden as well as the risk of bleeding due to the procedure. The latter approach has been proven to reduce the thrombotic risk without increasing the occurrence of major periprocedural bleeding. There are data from non-randomised prospective trials in which the use of fixed doses of LMWH at a subtherapeutic dose (3800 or 4000 anti-factor Xa IU, according to the use of nadroparin or enoxaparin) as a bridging regimen in cancer patients on long-term VKA therapy is feasible and appears to be safe, because it is associated with a relatively low risk of recurrent thrombosis and major bleeding.

American Society of Clinical Oncology guidelines suggest that, with the exception of patients with active bleeding or with contraindications to anticoagulation, antithrombotic prophylaxis should be considered in hospitalised cancer patients when platelet counts are >50 000/μl. The risk of

spontaneous bleeding increases dramatically for platelet counts <10 000 to 20 000/μl and differs among patients according to the cause of thrombocytopenia. Regardless of thrombocytopenia, thromboprophylaxis is mandatory in patients with acute promyelocytic leukaemia and in patients with disseminated intravascular coagulation (DIC) in intensive care units.

In conditions of high thrombotic risk, an individualised antithrombotic strategy is safe and efficient. In patients at intermediate to high risk of cardiovascular events (previous cardiovascular event or recent stent implantation) who are hospitalised for a medical condition (e.g. ischaemic stroke, acute medical illness, congestive heart failure, acute respiratory disease, sepsis), maintaining antiplatelet therapy and adding LMWH or fondaparinux for venous thromboembolic event (VTE) prophylaxis is recommended as long as the additional risk factor for thrombosis is present. In patients at low cardiovascular risk or with a high tendency to bleed, the risk–benefit ratio between cardiovascular recurrence and VTE prevention should be carefully evaluated. In these patients, withdrawing aspirin during VTE prophylaxis with LMWH or fondaparinux (i.e. during hospitalisation or at the time of exposure to new VTE risk conditions) may be considered.

The Cancer Patient with Venous Thromboembolism

Venous thromboembolism represents one of the most important causes of morbidity and mortality in cancer patients. According to population-based case-control studies, the two-year cumulative incidence of VTE is 0.8–8%. The increased risk of recurrent VTE in cancer patients is greatest in the first few months after malignancy is diagnosed and can persist for many years after an initial episode of symptomatic VTE.

Primary Thromboprophylaxis

Prophylaxis with LMWH or fondaparinux is recommended in hospitalised cancer patients confined to bed with an acute medical complication. According to the results of recent prospective randomised studies, a LMWH or semuloparin reduces the relative risk of VTE by 50–60% in ambulatory cancer patients receiving chemotherapy, although the absolute benefit was only 2%. Furthermore, semuloparin is not available for clinical practice. Based on the results of several studies, extensive,

routine prophylaxis for advanced cancer patients receiving chemotherapy is not recommended, but may be considered and discussed with high-risk ambulatory cancer patients.

The risk for VTE varies widely between various subgroups of cancer patients and even in the same cancer patient over time. Because the natural history of cancer is dynamic, the risk for VTE may increase or subside over time as a result of hospitalisation, chemotherapy, metastasis, remission, and many other factors. As a result, risk factor assessment is an ongoing process throughout the course of care for the cancer patient. It is essential to identify risk factors predictive of VTE in order to better assess the potential for thromboprophylaxis therapy.

Single risk factors or biomarkers have not, in general, been able to identify sufficiently high-risk populations. Khorana et al. investigated biomarkers and risk assessment tools in an attempt to clarify approaches to risk stratification. Clinical risk factors identified included primary site of cancer, chemotherapy, anti-angiogenic therapy, surgery and hospitalisation. Predictive and candidate biomarkers included platelet and leukocyte counts, haemoglobin, D-dimer and tissue factor. The Khorana score, a clinical risk score incorporating five simple clinical and laboratory variables (Table 3), has now been studied in more than 10 000 patients and can successfully categorise patients at low and high risk for VTE.

Table 3 *Predictive Model for Chemotherapy-associated VTE*

Patient characteristics	Risk score
Site of cancer	
Very high risk: stomach, pancreas	2
High risk: lung, lymphoma, gynaecological, bladder, testicular	1
Prechemotherapy platelet level count ≥350 000/mm^3 (≥350 000/μl)	1
Prechemotherapy haemoglobin level <10 g/dL and/or planned use of erythropoiesis-stimulating agents	1
Prechemotherapy leukocyte count >11 000/mm^3 (>11 000/μl)	1
Body mass index ≥35 kg/m^3	1
High-risk score: ≥3 Intermediate-risk score: 1–2 Low-risk score: 0	

Treatment of VTE

The standard initial treatment of an acute episode of VTE in both cancer and non-cancer patients consists of administration of subcutaneous LMWH at a dose adjusted to body weight: 200 U/kg (200 units of anti-Xa activity per kg of body weight) administered once daily (e.g. dalteparin) or 100 U/kg (100 units of anti-Xa activity per kg of body weight) administered twice daily (e.g. enoxaparin), or unfractionated heparin (UFH) administered intravenously (IV) in continuous infusion. UFH is first administered as a bolus of 5000 IU, followed by continuous infusion of nearly 30 000 IU over 24 hours, adjusted to achieve and maintain an activated partial thromboplastin time (aPTT) prolongation of 1.5–2.5 times the basal value. In patients with severe renal failure (creatinine clearance <25–30 ml/min), IV UFH or a LMWH with anti-Xa activity is recommended. The results from recent randomised clinical trials demonstrate that, in these patients, long-term treatment for six months with 75–80% (i.e. 150 U/kg once daily) of the initial dose of LMWH is safe and more effective than treatment with VKA. This schedule is recommended for long-term anticoagulant therapy in cancer patients.

The Cancer Patient with Pericardial Effusion

Pericardial problems are another common reason for cardiac consultation in patients with cancer. Pericardial effusion is common in a variety of cancers and many of these patients may present with pericardial tamponade, whereas pericardial tamponade is otherwise rare except in patients who have had cardiac surgery.

The diagnosis of pericardial tamponade has been greatly simplified using echocardiography. Cardiologists seeing these patients should be familiar with the echocardiographic signs not only of effusion but also of tamponade. The management of tamponade is related to the underlying disease process as well as the potential for recurrence. Pericardiocentesis has been made simpler and much safer using imaging with echocardiography to identify the simplest and safest port of entry. Although pericardiocentesis alone may be definitive, especially if chemotherapy is effective in controlling the malignancy, other techniques such as intrapericardial chemotherapeutic diffusion may need to be used. The role of pericardial sclerosis,

pericardectomy, partial pericardectomy and pericardial biopsy should be re-evaluated, as newer and simpler percutaneous or minimally invasive surgical techniques have made these more aggressive techniques safer and better-tolerated by patients.

The Cancer Patient with Atrial Fibrillation

Acute atrial fibrillation, usually with rapid ventricular rate in acutely ill patients, is also a common precipitant of a cardiac consultation by cancer patients. Atrial fibrillation is a common complication of the early postoperative period in lung cancer thoracotomy and can adversely influence the clinical course of the sickest patients. Its clinical incidence and short- and long-term impact on overall mortality have never been definitively assessed; moreover, it is unclear whether the arrhythmia represents an independent cardiac risk factor. In any case, the frequent association of atrial fibrillation with thrombocytopenia makes the standard guidelines for anticoagulation no longer applicable; rather, there is a need for personalised management.

The Cancer Patient with QTc Prolongation

Prolongation of the QT interval can lead to life-threatening cardiac arrhythmias, including "torsade de pointes". Although prolongation of the QT interval is not the best predictor of proarrhythmic risk, it represents the principal clinical surrogate marker by which to evaluate the arrhythmic risk of a drug and has led to withdrawal of several anti-cancer drugs from the market. Although drugs leading to prolonged QT may possess significant risks of serious adverse events, the clinical benefit of therapy in the oncological setting, including the possibility of cure for a cancer patient, may outweigh the potential risks of QTc prolongation, even when the prolongation is significant.

Patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant cardiovascular disease, bradycardia, thyroid dysfunction or electrolyte disturbances should be screened and monitored. Periodic monitoring with on-treatment ECGs and electrolytes should be considered.

The Cancer Patient with Hypertension

Cardiologists can contribute to the monitoring and management of hypertension, which is an unwanted adverse effect of many anti-angiogenic agents including vascular endothelial growth factor receptor (VEGFR) inhibitors (Table 4). Aggressive management of hypertension beginning at the initiation of therapy is important to avoid stress on the myocardium. An understanding of the potential cardiac toxicities of the chemotherapeutic regimen used is essential, giving further support to the concept of a multidisciplinary strategy for management.

Table 4 *Rates of Hypertension with Selected Angiogenesis Inhibitors*

Cancer	Drug	Grade 3/4 hypertension rates	
		Anti-angiogenic agent	Control
Colon	Bevacizumab	11%	2.3%
Renal	Bevacizumab	36%	n/a
Lung	Bevacizumab	7%	0.7%
Breast*	Bevacizumab	14.8%	0
Breast†	Bevacizumab	17.9%	0.5%
Renal cell	Sunitinib	8%	1%
Gastrointestinal stromal tumour	Sunitinib	3%	0
Breast	Sunitinib	6%	n/a
Breast	Sorafenib	17%	12%
Lung	Cediranib	35%	n/a
Breast	Cediranib	42%	n/a
Phase I	Sorafenib and bevacizumab	33%	n/a

* N Engl J Med 2007; 357(26):2666–2676. † J Clin Oncol 2005; 23(4):792–799.

Patients who are candidates for VEGFR inhibitors should be considered at risk in cases of: systolic blood pressure (BP) ≥160 mmHg or diastolic BP ≥100 mmHg; diabetes mellitus; established cardiovascular disease including any history of ischaemic stroke, cerebral haemorrhage or transient ischaemic attack; myocardial infarction, angina, coronary revascularisation or heart failure; peripheral arterial disease; subclinical organ damage previously documented by ECG or echocardiogram revealing left ventricular hypertrophy; cigarette smoking; and dyslipidaemia. Repeated BP measurements are recommended and aggressive management of BP elevations is recommended to prevent clinically limiting complications.

Conclusion

Current cancer therapies frequently have short- and long-term side effects involving the heart and circulation, as well as exacerbating and/or unmasking existing heart disease. Many cancer patients have multiple risk factors for both cardiac and coronary disease, such as cigarette smoking, diabetes, alcohol consumption, obesity and advanced age. The development of cardiovascular disease during the course of cancer treatment can adversely impact the management of the underlying malignancy. The risk–benefit ratio for an anti-cancer treatment must be interpreted in the context of the specific nature and severity of the disease, as restrictive approaches have the potential to delay or prevent access to therapy.

More research is needed to assess and manage patients with heart disease and cancer, beginning with a dynamic partnership between oncologists and cardiologists, and with the development of a new generation of "cardio-oncology" investigators. A thoughtful risk management plan generated by an organised collaboration between oncologists and cardiologists can support management guidelines for the anti-cancer treatment of patients with cardiac disease.

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Dr Curigliano has reported no conflicts of interest.

Professor Mandala has reported no conflicts of interest.

Dr Cipolla has reported no conflicts of interest.

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Cancer Treatment in Patients with Religious Constraints

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Although many Western patients and some patients in other countries do not adhere to any religious faith, religious beliefs often counter existing healthcare protocols aimed at improving the health of cancer patients. When such beliefs impact or negatively affect a patient's cancer treatment, they are considered to be religious constraints. Although not all issues can be addressed within the context of this chapter, we offer some general considerations that may help healthcare professionals to better understand the complexity of the issue.

Initial Stage of Diagnosis and Acceptance of Disease

Firstly, it is important to recognise an initial phase, in which a patient learns of and begins to accept a cancer diagnosis. On a medical level, this will be experienced differently according to the type and stage of the cancer and the possible effectiveness of the proposed treatment(s). In learning of a cancer diagnosis, the patient enters into a process of self-confrontation regarding how the new situation will affect all aspects of his or her life. In this initial phase, the patient's capacity to understand this new reality is often conditioned by emotional factors and a number of defence mechanisms, such as anger or denial as the patient refuses to accept the diagnosis. There are many variables that will influence how a patient faces the disease, including cultural differences regarding health and illness as well as attitudes to pain, death and facing death, which include significant religious and cultural differences.

Undoubtedly the behaviours, beliefs and values shared by a particular social group are of major importance when it comes to understanding cancer patients, a reality made more complex when the patient is culturally different from his or her physicians and caregivers. In a pluralistic society, it is important to underline each person's individuality when coming to terms with the disease and making decisions about therapeutic options. The definition of quality of life is largely subjective and may vary from one person to the next. In this sense, even if a physician believes that his or her therapeutic proposal is the most appropriate in terms of improving the quality of life of cancer patients, he or she may be confronted with conflicting views due to a patient's cultural background including religious beliefs.

Intermediate Stage of Therapeutic Intervention

Once a patient reaches the curative treatment phase, religious and cultural issues may influence the patient's decision on whether to follow or reject a specific proposed treatment. Patient autonomy is defined as the right of patients to make their own medical decisions, rather than the decisions being made by physicians on their behalf. For physicians, an ethical conflict may arise between showing respect for the patient's autonomy and maintaining the standards of a curative, widely recommended treatment (e.g. Jehovah's Witnesses' rejection of blood transfusions). Healthcare professionals, aiming to respect the ethical principles of beneficence and non-maleficence, find themselves facing a limitation: consent from the patients themselves. They must ensure, however, that autonomous decision-making by the patient is manifested. Respect for a patient's wishes must be honoured even if those wishes do not concur with professional criteria.

Culture also has a significant influence on the medical information process, involving both adult and paediatric cancer patients alike. Typically in Western cultures, where autonomy and individual independence are valued, the main protagonist is the patient. Even children as cancer patients will be made active participants in the therapeutic process. In some cultures, one or more family members may make decisions on behalf of the patient, thus adopting a paternalistic or even authoritarian

attitude. Healthcare professionals should be well informed regarding how culture and beliefs may influence patient and family attitudes and behaviour, in order to help avoid potential sources of conflict when recommending cancer treatment.

Advanced and End-Stage Disease

As the disease progresses to an advanced phase, particularly when there is a poor response to a specific treatment, psychosocial suffering and other emotional disturbances can affect the patient as well as the family and healthcare team. It is important to differentiate this phase from the biologically-terminal phase, which refers to the moment when the patient's vital signs (e.g. pulse, arterial pressure, temperature, breathing and state of consciousness) are deteriorating, specific therapies are no longer an effective option, and palliative care is appropriate. In this end-stage phase, a patient's beliefs and values may take on a greater importance than ever before. Most patients in this phase, including those who do not practice any religion, face spiritual questions as they wonder about the meaning of life. Knowing their beliefs and attitudes towards death will aid healthcare professionals in helping patients to live with respect and dignity through this last, definitive phase of their lives.

It is important to mention that there is a common aspect among most religions, in that they consider death not as the end of existence but as a stepping stone to a new life. This is why ill people with religious beliefs may experience their faith as a source of hope, including the acceptance of death. Occasionally the opposite may occur: they may experience fear towards that other, unknown life and cling intensely to biological survival. While a patient's faith can serve as a source of hope and consolation, his or her beliefs may also waver, leading to sudden changes in attitude towards cancer treatment.

Specific Religious Constraints

Having outlined these general considerations that are applicable to various beliefs or cultural environments, we present more specifically some religious constraints that healthcare professionals may face within the

context of a multicultural and multi-religious society (Table 1). Given the complexity of the issue, we have made a selection based on the available literature and on patient experience. It is important to bear in mind that there are major differences at an individual level within religious beliefs and practices; therefore, open communication with patients and their loved ones will allow individualised adaptation of treatment(s) based on their spiritual and cultural needs. Maintaining an open approach with cancer patients may help them to overcome certain attitudes or fears, allowing caregivers to take a recommended course of action that may ultimately be of greater benefit to the patient.

Table 1 *Specific Religious Constraints that Healthcare Professionals May Encounter*

Christianity
Christianity as a faith encompasses many different denominations, such as Protestant and Catholic. As with other religions, the ways that people experience their Christian beliefs and practices vary widely among individuals. For this reason, it is advisable to ask patients themselves or their families regarding any spiritual needs and religious constraints. Overall, we highlight the following major elements to be taken into account:
■ **Diet:** many practising Catholics and orthodox Christians avoid eating meat but will eat fish on the Fridays of Lent and Good Friday, although in cases of illness they are excused from obeying this rule.
■ **Therapeutic limitations:** certain therapeutic measures, especially those that offer life support such as assisted breathing, artificial nutrition and hydration, cannot be rejected, nor is limitation of them acceptable. Such therapies are interpreted as basic measures that cannot be renounced.
■ **Sedation:** some practising Christians consider it is essential not to lose their state of consciousness at any time, especially in the end-stage of the disease. Thus, they will not accept proposed palliative or terminal sedation.
■ **Organ donation:** this custom is considered an act of solidarity. Many Christians carry organ donor cards that facilitate the process of informed consent with their families.
Jehovah's Witnesses
As a religious denomination of Christian origin but with many differences, the Jehovah's Witnesses collective declares itself to be essentially vitalist, and clings strongly to life. When faced with disease and suffering, its members show collaboration. Due to their religious beliefs, they practice certain customs (e.g. door-to-door preaching, distribution of literature) and argue against others (e.g. refusal of military service and blood transfusions) that are considered outside mainstream practice.
■ **Diet:** any meat ingested must strictly contain no blood. If members ignore this doctrine they have to leave the community.

- **Personal hygiene:** Jehovah's Witnesses place high value on the hygiene of their surrounding environment, of their own body and of their clothes.
- **Communication:** in general, patients who are members prefer to be alone or alternatively surrounded by other members of their own religious community.
- **Rejection of blood:** strict rejection of blood donation and transfusions, as well as products originating from blood (e.g. human insulin), even when there is a risk to life. This rejection extends to procedures of dilution of blood during an operation, if it involves blood preservation. Overlooking this rejection, a matter left to each member's own conscience, means expulsion from the community and suffering divine condemnation.
- **Organ transplants:** according to the official declarations by Jehovah's Witnesses, decisions on organ transplants are subject to personal judgement and always take into account the indication against blood transfusions. Advances in the application of bloodless therapeutic strategies minimise the number of cases where patients refuse transplants.
- **Post-mortem examination (autopsy):** this type of examination is allowed providing that there are important reasons (e.g. ascertaining the cause of death). Afterwards, any organs that have been removed must be returned to the body prior to burial.

Islam

Not all Muslims observe all of the rules of Islam, and many live their religion in an individual way and with differing nuances. Suffering and illness are considered to be the result of not following preventative health measures, and they represent a difficult test that allows individuals to redeem their sins relating to any misdemeanours committed up to that point. The healing process is expected to come from God and not from medicine itself. We highlight the following elements:

- **Diet:** dietary rules are prescribed by the Quran and the Sunnah, classifying food into allowed (vegetable products) and forbidden (pork, etc). Especially important is the time of fasting at Ramadan, although many Muslims wish to follow the rules in any event. According to regulations, Muslims must make up for uncompleted days of fasting at a later time.
- **Personal hygiene:** in Islam, purity of the body and purity of the soul are inseparable, and practising proper daily hygiene, including access to running water, is very important.
- **Prevention:** in many Islamic countries, cancer patients often reach a cancer diagnosis at a more advanced stage, since fewer resources are available and are dedicated to prevention and early detection. Screening measures, such as programmes for detecting breast cancer in women, come up against complex cultural barriers and therefore are not undertaken regularly as in some other countries.
- **Patient care:** in Islamic culture, visiting the sick is a "sacred duty". As large groups of people visit patients, this may cause difficulties in the hospital environment.

- **Communication:** due to their culture, Muslim patients and their families do not usually ask questions, as they do not want to trouble or take the time of doctors or healthcare professionals. Moreover, they expect to be given clear instructions, and not receiving them is viewed as a lack of competence on the part of the physician. Healthcare professionals are expected to share information and to define clearly what is expected of the patient, even when the head of the family makes decisions on behalf of a patient. In general, the participation of women in decision-making is limited, even when they are the patients.
- **Medication:** medicines or other substances that may contain alcohol are often rejected by the majority of Muslims. During Ramadan, medicines, injections and measurement of rectal temperature are often rejected, as they are considered to interrupt the month's fast. Patients may temporarily abandon treatment or otherwise not follow therapeutic recommendations, especially those who are not hospitalised.
- **Organ donation:** the human body is considered to be untouchable even after death. Nevertheless, organs originating from brain-dead patients may be transplanted. In the Muslim tradition, saving a human life has preferential ranking with respect to other principles. For this reason, it is necessary for the patient to have made his or her wishes explicit in a living will.
- **Post-mortem examination:** allowed only in exceptional cases, such as to clarify the circumstances of a violent death.

Buddhism

A fundamental characteristic of Buddhism is that it focuses its doctrine not towards a God, but towards the personal responsibility of its members. Therefore, Buddhist patients want to be protagonists in approaching their health problems and the dying process. The following issues are of particular importance in the Buddhist faith:

- **Diet:** the majority of Buddhists are vegetarian and in general do not eat excessively, as they believe that this promotes health and keeps them more alert.
- **Personal hygiene:** Buddhists, especially from Asian countries, wish to be cared for by healthcare personnel of the same sex.
- **Alleviating suffering and pain:** Buddhists consider the idea of alleviating suffering and pain as very positive, although their preference is to use resources such as meditation, yoga or prayer. Thus, analgesics, sedatives and other medicines that can affect the patient's state of awareness may be rejected, since maintaining a state of vigilance and perception without limitations is a very important spiritual value for them. The mental state of a person at the time of their death determines the direction their reincarnation will take. Individuals close to the terminal patient must provide serenity and harmony, as Buddhists consider a calm state a necessary condition to the start of their new existence.

- **Information regarding death:** it is very important for Buddhists to be informed in a timely manner about their prognosis when death is near, so that they can thoroughly prepare themselves. They view death in a serene way and as the start of a new existence, as they believe in reincarnation. For this reason, especially in situations of clear diagnosis and poor prognosis, it is crucial to give the information with veracity and with enough time for the patient to prepare for death. For preparation in the dying process, it is desirable that a Buddhist teacher or practising Buddhist is involved.
- **Treatment following death:** when breathing has stopped, death, according to Buddhist beliefs, has not yet taken place. This process of separation of body and spirit will last for three days, until the consciousness is totally separated from the body. It is important not to touch the body for several hours until the Buddhist practitioner has proceeded with the appropriate ritual. The only exception is in the event of death by accident, when it is believed that the consciousness separates from the body immediately.
- **Organ donation:** organ donation is encouraged as an act of magnanimity; however, this possibility arises only in the case of death by accident, where the body can be touched without waiting for several hours. Furthermore, many Buddhists in Asian countries are very concerned about illegal practices of organ donation.
- **Post-mortem examination:** in general, post-mortem examination is rejected, as according to Buddhist belief the consciousness is maintained within the body for three days (except in the event of accidental death).

Judaism

In Judaism, priority is placed on life and the living above death or dying. Care and attention to a patient's family members is often exercised at the expense of terminally ill patients themselves. In this sense, it is important to highlight some important aspects:

- **Diet and care:** Jewish families normally want to take charge of the care and feeding of the patient themselves. Specifically, dietary rules become stricter in the case of illness. Observing these rules is in general highly valued by patients themselves and their families, even though they may not coincide with established therapeutic guidelines.
- **Personal hygiene:** this must be carried out by healthcare personnel of the same sex. Personal hygiene is excluded on the Sabbath.
- **Communication:** it is important to give terminally-ill patients information about their condition in a timely manner so that they can be better prepared for death.
- **Organ transplants:** In Judaism, organ donation is considered as an act of love. However, Orthodox Jews accept organ transplants only when a living donor is involved. Donations originating from deceased donors are viewed as problematic for two specific reasons: (1) Jewish people have specific rituals during the time between death and the funeral which can be incompatible with procedures for obtaining organs that require immediate intervention; and (2) in Judaism, brain death is a controversial issue. The majority of rabbis consider this as an intermediate stage between life and death.
- **Post-mortem examination:** according to Jewish law, all mutilation of the body is prohibited.

Conclusions

From the information covered in this chapter, it can be concluded that we live in a pluralistic society composed of individuals who are believers in various faiths. Religious beliefs may present difficulties relating to cancer care and treatment, both in the initial stage of diagnosis and acceptance of the disease, in the intermediate stage of therapeutic intervention, and particularly when facing death in the advanced or end-stage of the disease. Healthcare professionals need to take religious beliefs into account, making an effort to adapt respectfully to the context of the patient as needed in each individual case.

Declaration of Interest:

Dr Plana has reported no conflicts of interest.

Dr Terribas has reported no conflicts of interest.

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Cancer Treatment in Patients Unable to Consent

10

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The Process of Consent in Cancer Care

Informed consent is the acceptance of a proposed plan of action after a patient has been appropriately informed about the potential consequences of the plan. In cancer treatment, consent is more than a mere agreement to accept and follow a specific therapeutic course of action; it includes other aspects related to the complexity of the treatment in a severe and uncertain clinical condition. Thus, the act of consent for a diagnostic or therapeutic procedure requires a multidimensional approach, for which both the patient and health professionals should follow a sequential decision-making process. We propose a six-step process of consent for doctors to assess a patient's capacity to make those decisions serving in his/her best interest (Table 1).

Table 1 *A Six-step Process to Assess a Patient's Consent*

The patient:
(1) has a choice between at least two alternative courses of action, including among them the "do nothing" option;
(2) receives proper and well-balanced information on each of the alternatives in a clear and non-coercive way;
(3) understands the nature of the clinical condition he/she suffers and its potential disease evolution;
(4) is able to evaluate the benefits and risks of each potential course of action proposed including any major consequences;
(5) is capable of making proper judgements resulting in appropriate decisions for obtaining the best care;
(6) can follow the proposed therapeutic plan and consistently maintains his/her decision over time.

During this process, patients should be able to communicate their preferences clearly. They should not be in an altered state of mind due to the disease, comorbidities, frailty, or other treatments. A more comprehensive evaluation should assess if the decisions made by the patient were achieved with sound judgement, and if they correspond with the patient's goals and values. However, a complete assessment of the goals and values of a patient and how they evolve over time during the course of therapy is a difficult task that is beyond the scope of this chapter.

The act of consent has both ethical and legal implications. The latter is defined generally as a legal mandate to institutions to be authorised to perform diagnostic and treatment procedures involving potential risks and benefits. The aim is to protect the individual patient together with institutions and professionals from any potential liability or claim made by patients. From a legal aspect, informed consent is perceived primarily as a signed consent rather than a general, more comprehensive assessment of the patient's wishes. Therefore, the ethical implications of the informed consent will be the basis for the content of this chapter, with a focus on how to proceed in the treatment of cancer patients who are unable to consent. In this sense, this chapter is not about research on the topic or about informed consent in cancer research.

It is advisable that treatment decisions be made within the physician–patient relationship and well in advance of decision-making. In order to determine a patient's preferences in advance, physicians should discuss consent with a patient early in the relationship, including how to proceed in the case of lack of capacity to consent. In the event of a situation in which the patient is unable to give consent directly, the patient's wishes can be honoured because he/she has previously expressed his/her preferences to a physician.

Statements given in advance are decisions made by competent patients about the medical care that they are willing to receive in the future, in the event that they lose their capacity to consent. These statements might be orally expressed to their doctors, family members or friends, or they might be written in the form of a living will or durable power of attorney.

Despite the best intention of patients who express their wishes in advance, these statements present serious challenges to physicians. Physicians have to cope with several aspects of any statements made in advance, including their interpretation, the potential course of events, and consideration of all potential consequences of a patient's decision. In addition, physicians have to judge whether the statements made previously are in accordance with a patient's best interest, as well as to assess the level of stability of the decisions made over a period of time.

Most European countries have developed a legal framework for living wills. However, all the possible human and clinical situations occurring in oncological daily practice cannot be incorporated into strict regulations, and some of them require expertise and interpretation.

Complexities of Obtaining Consent

Obtaining consent for cancer treatment increases the level of complexity of cancer diagnosis and treatment (Table 2). This has been clearly described by Rebecca Dresser, a bioethicist at the Washington University in Saint Louis, USA, when she rejected feeding by a gastric tube after her head and neck cancer surgery. Despite the fact that the procedure was recommended by her doctors, they accepted her wishes of not being fed by a gastric tube. They considered her to be a well-informed patient, a bioethicist expert and a person competent to make decisions that served her best interest. In the end, she accepted feeding following her doctors' advice and her husband's pressures. In her book, she expressed her acknowledgement to her husband and to her doctors for not giving up on their recommendation and for encouraging her to accept the procedure. She also wrote about making bad decisions in a state of irrational fear.

This example shows that even well-informed patients with high levels of health literacy could have serious difficulties in making cancer treatment decisions serving their best interest due to vulnerability, psychological distress, and impaired judgement. It illustrates that, in cancer treatment, there is not a clear-cut point to identify whether or not a patient can follow and be evaluated by the six-step sequential process of consent.

Table 2 *The Complexities of Obtaining Consent in Cancer Treatment*

■ Cancer is perceived as a dramatic and potentially life-threatening event
■ Availability of multiple diagnostic and therapeutic options
■ Information overload
■ Asymmetry of knowledge between patients and professionals
■ Patient frailty and vulnerability
■ Irrational fear
■ Psychological distress
■ Uncertain evolution of the disease and effects of the therapy in an individual patient
■ Cognitive and emotional biases might cloud the ability to make proper judgements
■ Need to make quick decisions
■ Patient fear of uncertainty and unexpected consequences

We should point out the differences between oral and written consent. Oral consent requires an effort on the patient's side to retain complex information provided in a short period of time. Therefore, it is difficult for the physician to discern how much information the patient is capable of understanding and using to make a proper judgement serving his/her best interest. In addition, a patient's legal protection could be jeopardised if there is no formal signed agreement about the adequacy of the information given to patients. This form of consent provides patients with the opportunity to read the proposed therapeutic course of action several times and to request advice from family members as well as other medical experts. However, a lengthy written informed consent including technical terminology might be difficult for patients to understand.

The act of consent can be classified in three major scenarios: (1) agreement with proposed procedures and consent, (2) expressing doubts, including having a shifting decision, and (3) refusal of the proposed procedures. The latter deals with the ethical and legal requirement to respect the patient's decision and to offer him/her the best alternative care he/she agrees to receive. The scenario of doubts and shifting decisions requires further exploration in the specific case concerned and goes beyond the scope of this chapter.

The Concept of a Patient Unable to Consent

In daily practice, the process of obtaining the consent of cancer patients using the six-step process can be classified in three major categories: (1) the patient understands and can follow the entire process of consent, (2) the patient understands and can follow the process partially, and (3) the patient cannot understand or follow the process and, therefore, is unable to consent. This section deals primarily with the third category. Table 3 displays the most common situations in which patients are unable to consent.

Table 3 *Patients Unable to Consent in Cancer Treatment*

■ Minors
■ Patients who are unconscious
■ Emergency care
■ Impairing neurodegenerative diseases that alter cognitive function: senile dementia, advanced Alzheimer's disease*
■ Impairing psychiatric diseases*

* Impairing in this context means that the patient lacks the ability of understanding, evaluating or reasoning

In addition to the six-step process of consent, Raymond Devettere defines three major abilities related to a patient's decision-making capacity: understanding, evaluation and reasoning. For patients with psychiatric and neurodegenerative diseases, the capacity to consent must be assessed by an expert. There are also situations in which patient evaluation is very complex, for example with patients who are depressed, elderly or disabled, and those who are under the influence of family members or other third persons' interests. An exception to the general rule of informed consent exists when a doctor applies the so-called therapeutic privilege, which gives the doctor the right not to disclose to a patient any information regarding his/her care that could do more harm than benefit.

The concept of consent is based on two major principles: the principle of autonomy and the principle of body integrity. To obtain consent, the professional seeking the consent must adequately inform the patient and make sure that he/she fully understands the information. In addition, the consent should be obtained in a non-directive and non-coercive manner.

We focus on the decision-making capacity of a patient to make autonomous decisions in accordance with his/her values and goals. Patients who lack this capacity are unable to give their consent and should be judged as not competent to make decisions serving their best interest. The question of competency poses a potential conflict of interest between the physician who has the knowledge to recommend the most beneficial diagnostic or treatment procedure and the patient whose autonomy enables him/her to take a course of action under the influence of his/her values and preferences. In the case of conflict of interest, physicians are forced to respect the patient's autonomy over their own preferred course of action and to provide the patient with the best alternative care in accordance with his/her wishes. In those cases, physicians should avoid false paternalisms and disclose any situation linked to conflicts of interest that may affect their ability to serve the patient's best interest.

Surrogate Procedures When Patients are Unable to Consent (Table 4)

As Bernard Lo has pointed out, by law all patients are competent to make decisions unless a court indicates the contrary. When faced with a legal situation, physicians, patients, families and institutions may take action to declare that a patient is unable to make decisions so that surrogate procedures can be used to obtain consent.

Table 4 *Assessment of Surrogate Procedures*

■ Selection of surrogate procedures
■ Surrogate procedures intended to determine action in future situations
■ Clear identification of the person to serve as a surrogate
■ Patient's choices have been indicated
■ Surrogate procedures discuss how to act in specific clinical situations
■ Surrogate procedures fit with the patient's preferences and values
■ Course of action has been communicated to several individuals

European directives guide the regulations related to informed consent in patients unable to consent. The role of physicians in out-of-court decisions is to assess a patient's decision-making competency, a difficult and

subjective task as there is not a clear-cut point to determine the competency of a patient. In the case of a non-competent patient, the physician should define surrogate procedures with respect to the patient's best interest.

Despite the theoretical framework and regulations regarding the action to be taken when a patient is unable to consent, the application of surrogate procedures is often difficult. When a patient is cognitively impaired, lacks capacity or suffers a serious or life-threatening disease, physicians must obtain valid, informed consent from a surrogate decision maker who makes decisions on his/her behalf. The surrogate may have been chosen by the patient previously, such as a family member or someone who has a durable power of attorney agreement to represent the patient. Otherwise, a surrogate may be appointed to act on behalf of the patient, such as a court-appointed guardian.

When the patient is unable to consent, the patient's statement has not been given in advance, and trustworthy family members or other proxies are not available, the doctor should ask for the intervention of an ethical committee at his/her institution to assess the situation and to solve potential disagreements on the course of action. Legal intervention should be reserved for conflicting cases requiring court action. The situation can be quite complex if several people claim to represent the patient's best interest and have differing opinions on how to take action. Regarding formal evaluation of a patient's decision-making capacity, once again, patients responding partially to the six-step process are the most difficult to assess.

Conclusions

There is no doubt that one of the most difficult tasks facing oncologists is managing clinical situations in which the patient is unable to consent. Where possible, the oncologist should implement advance directives. To achieve this goal, the oncological team should initiate a dialogue with the patient as soon as the process of patient care begins, to discuss in advance how to proceed with respect to the decisions that can be made during therapy, including provisions for advance directives in the event that the patient is unable to consent. In addition, patients should report to their doctors the name of the person who represents their best interests, should this be needed in the event that competence to make a decision is lacking.

Declaration of Interest:

Dr Jovell has an academic position and is not involved in the prescription of any medical tests or therapies, nor sits on any committees involved in the regulation of drugs or procedures.

Dr Navarro has an academic position and is not involved in the prescription of any medical tests or therapies, nor sits on any committees involved in the regulation of drugs or procedures.

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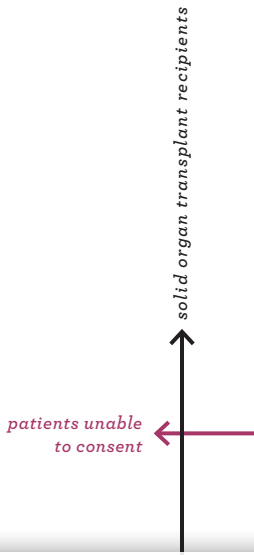
CANCER TREATMENTS
IN SPECIAL CLINICAL SITUATIONS

Veronika Ballová and Mariano Provencio Pulla

This handbook is designed to assist medical oncologists with challenging or complex situations, when modification of standard treatment in clinical practice is necessary. The aim of this book is to help physicians treat cancer patients in special medical as well as personal situations, where it is difficult to obtain the necessary information through a quick bibliographic search.

This volume deals with clinical topics as well as social topics that relate to interpersonal relationships, beliefs and the patient's capacity to make decisions. By exploring some of these special situations that affect cancer patients during their cancer diagnosis and treatment, medical oncologists will learn how to better anticipate and to manage these situations, particularly when multiple illnesses are present or a patient's personal preferences contradict standard clinical practice.



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