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How I treat acute myeloid leukemia

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More than one quarter of a million adults throughout the world are diagnosed annually with acute myeloid leukemia (AML). Despite considerable progress during the past 3 decades in the therapy of AML, two-thirds of young adults and 90% of older adults still die of their disease. The reported median age has increased over the past few decades, mostly because of a greater willingness of physicians to diagnose and treat older patients, and now is 72 years. The greatest challenge is in this age group. However, much improvement in therapy is needed for all adults with AML. Recent advances in allogeneic transplantation, a better understanding of prognostic factors, and development of targeted agents have only modestly improved overall outcome when large populations of patients are considered. Although an explosion in knowledge about the molecular pathogenesis of AML has outpaced treatment advances, such insights hold promise for the development of new therapies directed at specific molecular abnormalities that perturb malignant cell survival pathways. The current approach in 2010 to the management of this disease is presented through a discussion of illustrative cases. (*Blood*. 2010;116(17):3147-3156)

Introduction

Few diseases other than acute myeloid leukemia (AML) engender so much personal and institutional passion regarding treatment strategies. This is attributable to dramatic progress in deciphering the pathogenesis of the disease, the identification of prognostic factors, and burgeoning treatment options. However, there is a "great divide" between our understanding of the molecular basis and the development of effective treatment. The median age of AML is 72 years, as reported by the Swedish Acute Leukemia Registry, a model for collection of real world data.[1] Although some improvement during the last 4 decades is apparent among younger patients, still only approximately 35% of such patients entered on clinical trials are cured of their disease (Figure 1).[2-5] Little, if any, progress among older adults has occurred. Indeed, only patients with acute promyelocytic leukemia (APL), a rare subtype, enjoy the excellent outcome and likelihood of cure we all desire. Nevertheless, recent advances in molecular prognostic factors, allogeneic hematopoietic cell transplantation, and drug development provide excitement for the future.

To some extent, the management of adults with AML appears to be standardized. However, much of the so-called conventional therapy has been established with a lack of data or without rigorous review of the existing evidence; and so, considerable uncertainty remains. Such uncertainty is reflected in the significant diversity in the management of patients with AML, both in induction of older patients and postremission therapy of all patients. The suggested management described herein reflects an approach for the treatment of AML. The recommendations made here, through clinical vignettes describing patients commonly encountered in daily practice, are not a substitute for enrolling patients on carefully designed prospective clinical studies, which remain vital for improving the current and future management of AML. Rather, they represent how we treat adults with AML bolstered by data where they exist and by a dose of healthy skepticism where conventional wisdom prevails, but without definitive supporting evidence.

Patient 1

A 43-year-old woman is diagnosed with AML. Her complete blood count at presentation reveals a white blood cell count (WBC) of 23 000/μL with 23% blasts; her hemoglobin is 8.7 g/dL, and the platelet count is 32 000/μL. Her bone marrow is diffusely infiltrated with myeloblasts that express CD34, CD13, and CD33. The karyotype is normal, and evaluation for mutations of the genes encoding for *FLT3*-ITD, *NPM1*, and *CEBPA* is negative. The patient has a human leukocyte antigen (HLA)-identical sibling.

Question: What is the optimal induction and postremission therapy? Is it reasonable to offer standard chemotherapy consolidation and "reserve" an allogeneic transplantation to be used if the patient relapses?

Although in the early 1990s several randomized studies of induction therapy suggested that using idarubicin, mitoxantrone, aclarubicin, or amsacrine demonstrated superior results compared with daunorubicin, there is no evidence that these studies reflected a true biologic advantage rather than a lack of dose equivalence.[6] It has now been established that the traditional approved dose of daunorubicin (45 mg/m^2 for 3 days) is no longer appropriate as induction therapy for AML. A recent randomized trial for younger patients under age 60 years reported a significantly higher complete remission (CR) rate for patients receiving 90 mg/m^2 of daunorubicin compared with 45 mg/m^2. The overall survival was also improved with the higher dose of daunorubicin (Figure 2A-B).

Approximately 70% of young adults undergoing induction therapy are expected to achieve a CR. The published data on responses to induction vary considerably between the cooperative trial groups, reflecting different criteria for assessment of remission as well as different inclusion criteria for clinical studies. For

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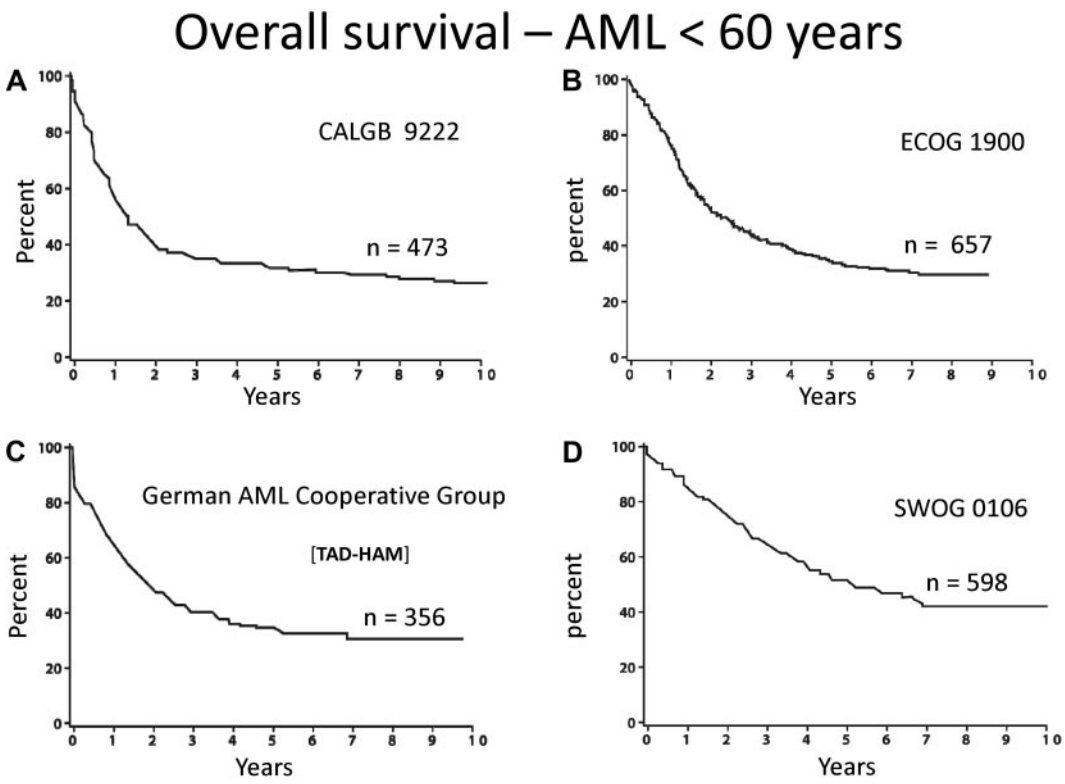

Figure 1. Overall survival from diagnosis for younger adults with AML. Recent publications/presentations from 4 cooperative oncology groups. (A) CALGB 9222. Reprinted from Moore et al[2] with permission. (B) ECOG 1900. Reprinted from Fernandez et al[4] with permission. (C) German AML Cooperative Group. Reprinted from Buchner et al[3] with permission. (D) SWOG 0106.[5]

example, studies in which patients with antecedent hematologic disorders or therapy-related AML are included would have inferior results compared with those that exclude such patients. A dose of 90 mg/m^2 of daunorubicin is clearly safe and should become the standard of care, although doses between 60 mg/m^2 and 90 mg/m^2 may be as effective.

This patient is in the intermediate-risk category given that her karyotype is normal.[7] Advances in the molecular classification of AML, particularly among patients with a normal karyotype, have recently refined this risk group from the traditional 50% to 70% among AML patients[7-9] to no more than 25% to 30%.[10] In this patient, the absence of unfavorable mutations, such as *FLT3*-ITD, or the more favorable mutations, such as *NPM1* and *CEBPA*, suggests that this patient remains best classified in the intermediate-risk category,[11] recognizing that even in this group further discrimination is likely in the coming years with the use of genetic profiling and further molecular characterization.

Allogeneic hematopoietic cell transplantation (allo-HCT) provides the most potent antileukemic effect of any postremission strategy in AML, as demonstrated by the lowest rates of relapse in all clinical studies. For patients, such as this who have an HLA-identical sibling donor, an allo-HCT should be offered, preferably if the patient remains negative for minimal residual disease (MRD) before transplantation.[12] Despite substantial transplantation-related mortality of 15% to 20%, the reduction in the relapse rate significantly outweighs the transplantation-associated risk and is considered standard of care for such a patient (Table 1).[10] An exception to this approach may be made for patients whose leukemia cells express more favorable mutations at diagnosis. Several recent reports have indicated a more favorable outcome among patients with a normal karyotype for those who present with mutations of *NPM1* or *CEBPA*. One recent analysis suggested that patients whose cells are *NPM1*$^+$/*FLT3*-ITD$^-$ belong more appropriately in the favorable-risk group and may not benefit from an allo-HCT.[11] Although fairly widely accepted and having moved into routine practice in many centers,[13] the data supporting such a practice are based on only 38 patients with a donor.[11] The *CEBPA* mutation also confers a more favorable prognosis for patients with a normal karyotype[11,14]; therefore, the same consideration as applicable to *NPM1*$^+$ should be given, although there have been no specific reports that have demonstrated this. Of note, recent data suggest that the more favorable prognosis in this group is limited to patients with the biallelic *CEBP* mutations.[15]

Although there are multiple reports of the use of reduced-intensity conditioning (RIC) regimens in AML, there have been no prospective comparisons with standard regimens, particularly in younger adults. Therefore, at present, RIC should be reserved for older adults with AML or those with significant comorbidities, which preclude conventional myeloablative conditioning for transplantation. The standard of care for younger adults remains a fully myeloablative conditioning regimen, for which abundant data exist.

Table 1. Suggested indications for allo-HSCT among young adults with AML in first complete remission

Cytogenetic risk factor	HLA-matched sibling	MUD/haplo/cord
Favorable, all except	No	No
c-KIT	Yes	Possible
Intermediate, all except	Yes	Possible
NPM$^+$/*FLT3*-ITD$^-$	Possible	No
Biallelic *CEBPA*$^+$/*FLT3*-ITD$^-$	Possible	No
FLT3-ITD$^+$	Yes	Yes
Unfavorable	Yes	Yes

Adapted from Rowe.[36]

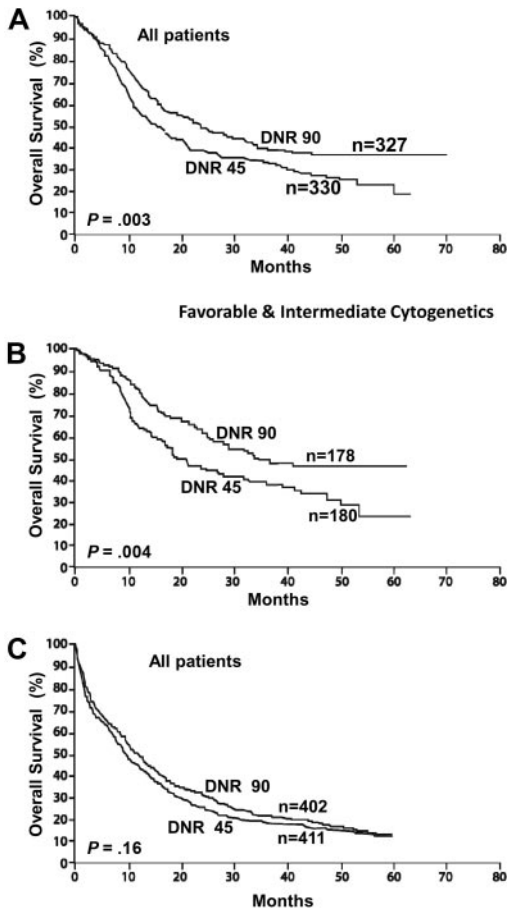

Figure 2. AML: intensifying induction therapy (overall survival from diagnosis). Randomized study conducted by ECOG in adults younger than 60 years comparing daunorubicin (DnR) 45 versus 90 mg/m^2 for 3 days, both with cytarabine 100 mg/m^2 for 7 days. (A) All study patients. (B) Patients with favorable and intermediate cytogenetics. Reprinted from Fernandez et al[4] with permission. (C) Similar randomized study conducted by HOVON/SAKK in older adults (older than 60 years). Reprinted from Lowenberg et al[55] with permission.

Although there are no prospective trials that have addressed the need for any postremission consolidation chemotherapy before an allo-HCT, 2 retrospective analyses from large international registries suggest that there is no benefit to adding any consolidation therapy before an allo-HCT.[16,17]

Finally, although the concern for the high transplantation-related morbidity and mortality is appropriate, this should not lead to delaying an allo-HCT in first complete remission (CR1) and reserving such treatment for patients in the event of a relapse. Reports indicating a successful outcome after relapse with a curative potential of approximately 30%[18,19] are highly selective and relate only to patients who have survived their relapse and are fit enough to receive a transplantation in second remission. The predictive overall survival of relapsed AML patients is exceedingly poor, no more than approximately 10%[20-22] (Figure 3). In our view, delaying transplantation until after relapse is a misleading strategy, although we recognize that no trial has ever randomized patients with donors between immediate and delayed transplantation.

Proposed treatment: This patient should receive induction therapy with daunorubicin 90 mg/m^2 for 3 days together with cytarabine 100 mg/m^2 for 7 days. A dose of daunorubicin between 60 mg/m^2 and 90 mg/m^2 is also reasonable. As postremission therapy, the patient should be referred for an allogeneic transplantation from her HLA-identical sibling and a conventional myeloablative conditioning should be used. "Reserving" an allogeneic transplantation for relapse is definitely not recommended. If possible, any consolidation chemotherapy before the allogeneic transplantation should be avoided.

Patient 2

A 54-year-old man presents with gingival hypertrophy and bleeding. At presentation his WBC is 39 000/μL with 60% monoblasts; the hemoglobin is 7.9 g/dL, and the platelet count is 6000/μL. His bone marrow is diffusely infiltrated with monoblasts. Cytogenetic analysis shows a normal karyotype, and the leukemic cells express the mutated *FLT3*-ITD. He does not have any siblings. He received standard induction therapy. His day 14 bone marrow demonstrated some cytoreduction but unequivocal residual leukemia, after which he received a second cycle of identical induction therapy and achieved CR.

Question: Should this patient be referred for an alternative donor transplantation? What would be the postremission strategy in the absence of the mutated *FLT3*-ITD?

This patient's course raises several important issues. First, historically, patients with monocytic leukemia were considered to have a poor prognosis, and those who did not clear their blasts by day 14 were also considered to be in a poorer risk category, irrespective of subsequent response to therapy. However, although monocytic leukemia presents with unique clinical features, such as extramedullary tissue infiltration and central nervous system involvement, once a CR is achieved, there is no evidence that with contemporary therapy the ultimate prognosis is determined by this unique morphology alone.[23]

Although a day 14 bone marrow generally predicts for a lesser likelihood of achieving a CR with induction, recent data from the Eastern Cooperative Oncology Group (ECOG) suggest that patients who receive a second cycle of induction therapy on day 14, based on the presence of unequivocal residual leukemia, and subsequently achieve a CR, have a prognosis that is similar to those achieving CR with one cycle of induction.[24] Thus, the presence of residual leukemia on day 14 in and of itself should not alter the postremission strategy if the patient responds successfully to the induction therapy. The choice of postremission therapy should be based solely on the cytogenetic and molecular determinants at diagnosis and possibly on MRD after induction therapy, as determined by refined molecular or immunophenotypic analyses.[25,26] Although the presence of MRD is of concern to any treating physician, at present we do not alter the postremission strategy based on such findings.

The presence of the mutated FLT3-ITD confers a poor prognosis for this patient.[27,28] The practical issue is whether to offer a

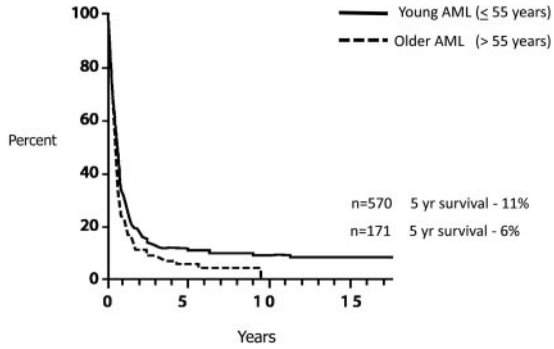

Figure 3. AML: survival from relapse by age. Data based on 2441 patients entered on 8 consecutive ECOG studies.[22] Reprinted from Rowe et al[22] with permission.

transplantation from an alternative donor, either a matched unrelated donor (MUD), a genetically haploidentical donor, or an umbilical cord donor.

Although the indications for an alternative donor transplantation have not been properly defined, its performance is nevertheless becoming more widespread as the clinical experience is increasing. The only prospective data demonstrating the beneficial effect of a MUD transplantation have been in patients with unfavorable-risk AML.[29] Historically, the hesitation to offer an alternative donor transplantation was based on the higher morbidity and mortality compared with sibling transplantations, possibly altering unfavorably the risk-benefit balance for AML patients in CR1. Recent publications of an almost identical outcome after an 8 of 8 MUD transplantation,[13,30,31] that is confirmed also by molecular high-resolution typing, are encouraging. However, such data need to be cautiously interpreted because they probably reflect a selection bias in that the eligibility criteria for a MUD transplantation are significantly more stringent than for a sibling donor transplantation. Furthermore, although there is a perception, based on a sound rationale, that immunologic graft-versus-leukemia effect may be particularly potent using MUD because of a higher likelihood of allelic disparity at minor histocompatibility antigens,[32] a recent study from the Center for the International Blood and Marrow Transplant Research described somewhat surprising results regarding the outcome of myeloablative MUD transplantations as well as a well-matched cohort of HLA-identical sibling transplantations.[33] There was an increased relapse rate in MUD transplantations for AML patients in CR1 and the leukemia-free survival was also significantly improved for patients receiving a sibling transplantation. Unexpectedly, although the presence of graft-versus-host disease is associated with reduced relapse of AML, it does not appear that such an effect is dependent on the degree of genetic disparity and the best donor remains the most closely matched donor. It is of interest that similar observations were recently reported in chronic myeloid leukemia[34] and in a Center for the International Blood and Marrow Transplant Research study of reduced intensity HCT in older patients with AML.[35]

In the absence of a sibling donor, this high-risk patient would be offered the option of a transplantation from a fully MUD, although there are no prospective data that establish this as standard of care. In the absence of the *FLT3*-ITD mutation the patient who does not have a sibling donor would receive postremission therapy without allogeneic transplantation.

There is much controversy regarding the optimal postremission therapy, including the number of cycles of intensive chemotherapy, the best agent and even regarding the preferred doses.[36] In our opinion, a patient not on a clinical study would receive 2 cycles of consolidation therapy with high-dose cytarabine followed by an autologous transplantation. The rationale for using an autologous transplantation is based on the fundamental concept that the optimal approach to postremission therapy is based on the regimens with the most potent antileukemic activity, provided this effect is not abrogated by unacceptably high mortality. In the majority of major prospective studies published over the past decade, a lower relapse rate was reported for patients undergoing an autologous transplantation compared with chemotherapy. In a meta-analysis of 6 trials, including 4410 patients, auto-HCT was associated with modest improvement of 10% to 18% in disease-free survival.[37] The hesitation to use an autologous transplantation was the relatively high treatment-related mortality reported in older studies that in most instances used bone marrow as the source for hematopoietic cells.[38,39] Currently, the mortality rate associated with an autologous transplantation, in experienced centers using hematopoietic cells collected from the peripheral blood, is less than 2%,[40,41] which offers a compelling argument for adding autologous transplantation to chemotherapy-based consolidation.

Although for the majority of patients MUD transplantation is the preference when a sibling donor is not available, there are other alternatives for which data are available. In experienced centers, a transplantation from a genetically haploidentical donor can be performed with overall results that are similar to those reported for MUD transplantation.[42] An important advantage with this form of transplantation is the almost universal availability of a donor, with minimal delay to transplantation. Similarly, double unrelated umbilical cord transplantation is increasingly used, and rapidly accumulating data suggest that this is also an option when a sibling donor or MUD is not available.[43]

Proposed treatment: The decision for induction or postremission therapy should be based on cytogenetic and molecular determinants and is not altered by the presentation with the monocytic variant morphology or by the fact that remission was only achieved after 2 cycles of induction. As postremission therapy, this patient should be referred for MUD transplantation. In the absence of *FLT3*-ITD mutation, or other high-risk feature, this patient with a normal karyotype would receive 2 cycles of consolidation therapy with high-dose cytarabine followed by an autologous transplantation.

Patient 3

A 43-year-old man presents with a one-week history of weakness and progressive dyspnea. His WBC at presentation is 260 000/μL; the hemoglobin is 8 g/dL, and the platelet count is 32 000/μL. Cytogenetic analysis reveals t(8;21)(q22;q22), and molecular analysis reveals only the presence of the *c-KIT* mutation.

Question: What is the best emergent management? Is standard induction appropriate? Is central nervous system prophylaxis recommended? What is the appropriate postremission therapy?

This patient presents with a very high WBC count, where apart from any long-term prognostic considerations, there are emergent issues. Hyperleukocytosis in AML is associated with leukostasis with potentially lethal central nervous system and pulmonary complications. The optimal emergent management is uncertain, and one approach is to initiate immediate induction therapy. An alternative strategy consists of daily leukapheresis with the concurrent administration of hydroxyurea at doses of 2 to 6 g/day. Although not substantiated by any data, it is customary in our institutions to continue this approach and wait for the initiation of induction therapy until the WBC has fallen below 40 000 to 50 000/μL. It is presumed, but not proven, that this increases the likelihood of achieving CR with a single cycle of chemotherapy. Once induction therapy is initiated, standard doses should be given with no modification.

The issue of prophylaxis for the central nervous system is controversial in any patient with AML and is often considered in a patient who presents initially with a high WBC.[44] Although there are theoretical considerations for administering prophylaxis, in our institutions this is not customarily performed for any patient with AML, in the absence of any symptoms related to the central nervous system.

This patient presents with t(8;21)(q22;q22) karyotype. Although frequently described as associated with a favorable prognosis, this is a misnomer, considering that the long-term survival rate of patients is less than 50% in series reporting large numbers of patients[45] (Figure 4). Despite this prognosis, multiple prospective

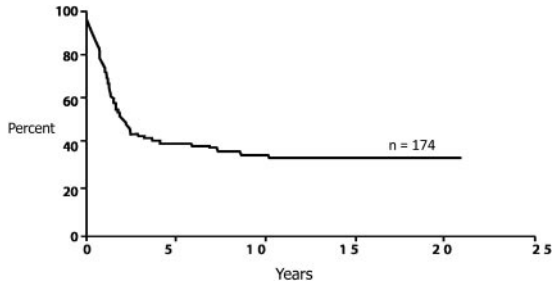

Figure 4. Long-term survival from diagnosis for AML patients with t(8;21). Adapted from Appelbaum et al[45] with permission.

studies as well as meta-analyses have not established any benefit to an allogeneic transplantation in patients with t(8;21)(q22; q22).[13,46,47] The reduction in relapse is abrogated by the transplantation-related mortality. This recommendation probably is not altered by the presence of other cytogenetic abnormalities.[10,48] However, there are increasing number of reports that have suggested that patients with core-binding factor translocations with mutations in *c-KIT* have a very high relapse rate, almost comparable with patients with unfavorable risk cytogenetics.[49-51] For this reason, it is important to routinely obtain all the common molecular markers, which would also include *FLT3*-ITD, *NPM1*, and *CEBPA*.

The high WBC count has also been reported to be associated with *c-KIT* mutations, especially in patients with t(8;21).[52] These reports in adult patients need to be cautiously interpreted because of the small numbers, and it should be noted that a recent publication in pediatric patients could not confirm the poorer prognosis for patients with *c-KIT* mutations.[53] Nevertheless, given the preponderance of data in adults, this patient would be referred for a matched sibling transplantation or an alternative donor transplantation in the absence of an available HLA-matched sibling.

Proposed treatment: The patient should receive urgent leukapheresis together with hydroxyurea until the WBC is less than 50 000/μL. At that point, standard induction therapy should be given. Central nervous system prophylaxis is not routinely administered. For postremission therapy, the patient should be referred for an allogeneic transplantation from an HLA-identical sibling or from an alternative donor.

Patient 4

A 70-year-old woman presents with AML. At diagnosis, her WBC is 2400/μL; her hemoglobin is 10.2 g/dL, and the platelet count is 17 000/μL. Cytogenetic analysis was not available.

Question: What is the optimal induction and postremission therapy for this patient? How would cytogenetics affect the management of such a patient?

This patient presents with what is probably the most important challenge in managing patients with AML. Given that the median age is 72 years, this is a group with a much higher incidence of AML and among whom the overall survival remains approximately 10%, at best. There has been much discussion, controversy, and a lack of accurate data, given the widely disparate treatment approaches for such patients. Less than 10% of younger AML patients are referred for cooperative group trials, and among older patients the number is far below 5%. In addition, patients referred to a tertiary cancer center and then entered on clinical trials are a highly select subgroup.[54] In a recent elegant population-based study from the Swedish Acute Leukemia Registry, a compelling case is made for the administration of standard intensive therapy for all fit older patients rather than adopting a purely palliative approach.[1] The approach in our center is unequivocal in offering all AML patients induction therapy, unless presenting with prohibitive comorbidities. There are several important principles in the management of such an older patient. Once the decision is made to treat, then standard doses of induction should be given. Attenuation of induction is contraindicated. A low dose will not reduce the toxicity and is more likely to lead to ineffective therapy with a similar degree of myelosuppression. Fit older adults tolerate chemotherapy at least as well as younger patients, but they do not tolerate prolonged aplasia. A recent randomized trial from the HOVON/SAKK Collaborative Group confirmed the safety of higher doses of daunorubicin, up to 90 mg/m^2 for 3 days in older adults.[55] In one report, 2 sequential studies of older patients were compared. No significant survival benefit was reported in the study that included postremission therapy compared with the study that offered no such therapy.[56] The reticence by many to treat older adults with standard doses of induction chemotherapy has often been based on a mistaken perception that such doses could not be tolerated. In the HOVON/SAKK study, the higher dose of daunorubicin led to a more rapid initial response as well as a higher response rate than a more conventional dose of 45 mg/m^2, although there was no significant improvement in the overall survival (Figure 2C). For this reason, this patient would receive a dose of 60 mg/m^2 for 3 days as induction recognizing that higher doses may be preferable and may in time become the standard of care. The achievement of CR remains of paramount clinical significance, and this is an important endpoint also in older patients,[57] particularly when considering quality of life.[1]

Several suggestions have been made on how to treat patients who are older than 75 years with a suboptimal performance status. Our own approach would be to avoid using an arbitrary age cut-off and offer standard induction therapy to any patient who we think will tolerate intensive induction chemotherapy. In line with Juliusson et al,[1] we would not withhold induction therapy for any patient based on age alone. The presence of comorbidities encompasses a broad spectrum, ranging from those that should be treated with supportive care only, which composes the administration of blood products and antibiotics, to therapy with hydroxyurea and escalating to low-dose cytarabine or some of the new hypomethylating agents, the farnesyltransferase inhibitors or, preferably always, a clinical trial exploring an investigational agent.

There is enormous uncertainty and controversy regarding the optimal postremission therapy in older patients. In contrast to younger adults, the value of postremission therapy has never been unequivocally established for older patients.[58] Despite this, it is common practice and virtually every published clinical trial for older patients with AML includes one or more courses of consolidation therapy. The Medical Research Council (MRC) in Great Britain conducted a large study of 1314 older patients that attempted to determine whether the addition of multiple cycles of consolidation is superior to a single cycle. In this study, patients received standard induction therapy and, if in remission, received the identical course of induction as their first course of consolidation therapy. Patients were then randomized to receive 3 further cycles of consolidation or only observation. The outcomes in both groups were identical, demonstrating that there is no particular value in intensifying postremission therapy beyond a single course of consolidation[59] (Figure 5). However, the MRC study did not address whether or not any consolidation is required in older adults. This important issue remains open.

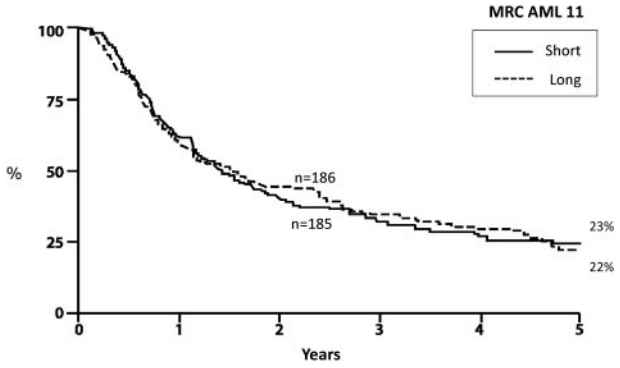

Figure 5. Overall survival from postremission randomization: AML in patients more than 55 years of age. Randomization after induction and 1 cycle of intensification to 3 cycles of consolidation (long) versus observation (short). Adapted from Goldstone et al[59] with permission.

There is information from prospective trials regarding cytogenetics that may also affect the decision regarding the optimal postremission therapy. Between 25% and 30% of patients who present with unfavorable cytogenetics can achieve a CR.[60,61] However, despite the administration of intensive consolidation therapy, the 5-year survival is less than 5%[60-62] (Figure 6). Therefore, for such patients, it is hard to justify the administration of consolidation, and a strong case can be made for putting such patients on a clinical trial of novel investigational therapies. Despite this, most current investigations, which include older patients, prescribe postremission therapy, irrespective of the cytogenetics at presentation.

It is clear that older patients cannot tolerate the same doses of consolidation therapy that are administered to younger patients, often resulting from gastrointestinal toxicity and, if high-dose cytarabine is used, central nervous system toxicity. Typically, doses are decreased for patients between 55 and 70 years of age and are further reduced for those older than 70 years, although there is considerable arbitrariness in such a recommendation.

The advent of RIC regimens as preparative regimens before allogeneic HCT may, for the first time in decades, make a significant impact on the long-term survival of such patients with AML.[63] Although there is a paucity of prospective data regarding RIC transplantations, recent studies emphasize the feasibility of this procedure, the curative potential and tolerability in older patients.[35,63-67] Despite reports that more than one-third of patients can achieve a long-term survival with this regimen,[35] prospective

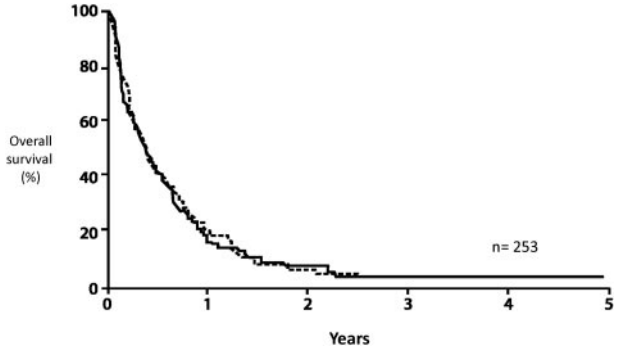

Figure 6. AML in older adults (older than 60 years): long-term survival for patients with unfavorable cytogenetics. Patients received induction and consolidation therapy on trial and were randomized to receive either TAD-HAM or HAM-HAM with results that were superimposable. Reprinted from Büchner et al[62] with permission.

data are needed to establish the true long-term survival rates in a nonselect population. Indeed, very few older patients ultimately undergo such a procedure even in sophisticated centers.[68] RIC transplantation has become common practice in many centers, but attempts at accruing a significant number of patients into prospective clinical studies of RIC have fallen short. Whenever possible, patients should be entered on a clinical trial that prospectively evaluates the role of RIC transplantation. Nevertheless, given the emerging data in our centers and others, patients not entered on a clinical study would be offered RIC transplantation from either a matched sibling donor or MUD.

Several issues are completely unresolved when considering such an approach. First, should any consolidation be administered before RIC transplantation? Although for patients receiving standard ablative conditioning allogeneic transplantation there are data suggesting that there is no benefit for the administration of any prior consolidation in CR1,[14,15] no such data exist for patients undergoing RIC transplantation. Although a strong rationale exists for administering some form of intensification before RIC, in an attempt to minimize the leukemia burden and allow time for generation of the graft-versus-leukemia effect, in practice the design of cooperative group studies is not uniform. In a recently published HOVON study for older patients, RIC was offered after one cycle of consolidation,[55] whereas in a newly designed study by the ECOG, E2906, RIC allogeneic transplantation is offered after successful achievement of CR before any consolidation. This is the approach taken by us, which, although unproven, is driven by an attempt to reduce the transplantation-related toxicity.

A second unresolved issue is whether RIC should be offered also to patients with unfavorable cytogenetics. This is the group that, even among younger AML patients, has a poor prognosis.[7,8,47] There are almost no data on RIC transplantations performed in patients with unfavorable cytogenetics because younger patients with unfavorable cytogenetics almost always undergo myeloablative conditioning. In practice, in very experienced centers, an older patient with a good performance status who achieved a CR would be referred for an RIC transplantation, but for these patients we administer one course of consolidation therapy, acknowledging that there are no published data to support such an approach.

Proposed treatment: This woman should receive induction therapy with a dose of daunorubicin that is not less 60 mg/m^2 for 3 days. Cytogenetics would not alter the initial attempt to achieve CR. As postremission therapy, she should then receive 1 cycle of consolidation therapy, using an attenuated high-dose cytarabine regimen. If an HLA-matched donor is available, the patient should be offered an RIC HCT in CR1, without any prior consolidation; an exception is for patients with unfavorable cytogenetics.

Patient 5

A 52-year-old woman presented with AML with the following chromosomal abnormalities: del(5q), del(7q), del(12p), and abn(11q; p3). The patient has a long history of prior chemotherapy given for diffuse large cell lymphoma. She was last treated with autologous transplantation 4 years previously and is now free of lymphoma.

Question: What is the appropriate induction and postremission therapy? How is this affected by cytogenetics?

The patient presents with therapy-related AML. In general, the management of this type of AML is fraught with uncertainty because, among other reasons, most early studies included small numbers of patients and were retrospective. There have been no prospective randomized studies specifically directed at the treatment of therapy-related leukemias. Furthermore, the published data

Table 2. Results of induction therapy in adults younger than 60 years with AML, by cytogenetics

Reference	Favorable CR	Intermediate CR	Unfavorable N	Unfavorable CR
MRC (1998)[8]	90	84	130	57%
ECOG/SWOG (1998)[38]	84	76	184	55%
GOELAMS (1997)[90]	87	76	36	58%

Adapted from Appelbaum et al.[91]

often included patients with myelodysplastic syndromes. Finally, the data are confounded because of variable definitions. Until recently, the term "secondary leukemia" broadly included any AML with a history of prior malignancy as well as patients with any antecedent hematologic disorder and, in some series, any patient who presented with unfavorable cytogenetics. Among therapy-related AML patients, 70% present with abnormalities of chromosome 5 or 7, which is the most typical presentation after the exposure to alkylating agents and/or ionizing radiation.[69] Another important group, recognized only in the 1990s and accounting for approximately 30% of therapy-related AMLs, are those that arise after treatment with topoisomerase-2 inhibitors.[70]

Historically, it was presumed that every patient with therapy-related leukemia had an adverse prognosis and that standard induction therapy was inappropriate; high-dose cytarabine was suggested in one report.[71] However, there is no evidence that any induction therapy is superior to the standard 3 + 7 regimen. Among young adults, quite remarkably, prospective studies report an almost identical CR rate of 55% to 60% for patients treated with recognized unfavorable cytogenetics, and there are no reports that anything is better than this (Table 2). Therefore, this patient should be treated with standard induction therapy assuming, of course, that there are no comorbidities related to her prior therapies that preclude the administration of anthracyclines.

This presence of a complex karyotype classifies this patient in the unfavorable-risk category, irrespective of whether or not she has received prior therapy. It is still somewhat controversial whether therapy-related AML has a prognosis that is intrinsically worse than de novo AML, independent of cytogenetics. In a very large database, the National Cancer Research Institute (formerly MRC) in Great Britain reported a significantly worse outcome for therapy-related AML than de novo AML, within each cytogenetic risk group. This was based on an analysis from the MRC's AML 10, 12, and 15 trials[10,72] (Figure 7). The caveat here is that the impact of prior therapy or organ damage is impossible to reliably ascertain. Furthermore, it is not known whether molecular determinants now recognized to be so crucially important in the prognosis of AML, such as *FLT3*-ITD, *NPM1*, and *CEBPA*, are more or less frequent in therapy-related AML and how this may account for differences between de novo and therapy-related AML.

The management of patients with therapy-related AML should be guided by the cytogenetic and molecular features. Although there is a perception that any patient with therapy-related AML should be considered at high risk and referred to an allogeneic transplantation, there is no evidence that the long-term outcome for patients who present with a favorable karyotype, with no adverse molecular features, is different from patients with de novo AML. Thus, such patients should not be referred to an allogeneic transplantation in CR1.

Proposed treatment: This patient should be treated with standard induction therapy. Postremission therapy should be guided by cytogenetic and molecular determinants. Patients with favorable cytogenetics and no adverse molecular features should not undergo an allogeneic transplantation in CR1.

Patient 6

A 48-year-old man presents with relapsed AML. He receives induction therapy and chemotherapy consolidation with high-dose cytarabine. Fifteen months after achieving CR1, his complete blood count was normal apart from a platelet count of 92 000/μL, but his bone marrow has 18% blasts. The patient has an HLA-matched sibling.

Question: Should this patient undergo an immediate allogeneic transplantation without an attempt at reinduction? If induction is used, what are the best drugs?

Several authors have attempted to define the prognosis of relapsed AML patients.[20,73-75] Nevertheless, the only cure for an adult with relapsed AML is a transplantation, and it is clear that this patient will be referred for an allogeneic transplantation from his HLA-compatible sibling.

However, this patient raises 3 important questions. The first is whether this patient should receive a transplantation in untreated relapse rather than undergo reinduction therapy. Although a transplantation can be performed safely in early relapse with an outcome that is probably not significantly inferior to performing this in CR2,[76,77] in this particular patient, given the long duration of CR1, there is a greater than 50% chance of achieving CR2.[78-81] Because it is always preferable to undergo a transplantation while in CR2, our own choice in this patient would be to attempt reinduction before transplantation. If, on the other hand, the duration of CR1 would be less than 6 months, where the likelihood of achieving CR2 is no greater than 20%,[74,78,79,82] the equation will change such that, given the immediate availability of an HLA-compatible sibling, we would elect to proceed to an allogeneic transplantation in an untreated first relapse. The issue becomes more complex for older individuals, more than or equal to 60 to 65 years, in whom RIC is the preferred option for an allogeneic transplantation. There are absolutely no prospective data or established guidelines in such a scenario, and clinical practice varies enormously. Despite some hesitation, given the low likelihood of a cure when transplanting a patient with 18% blasts with RIC, our own preference in this case would be to administer one cycle of induction therapy in an attempt to obtain a better control of the disease before transplantation.

The second issue relates to the choice of regimen to use for reinduction. There is no evidence that any given regimen is superior and much of standard practice is guided by unsubstantiated opinion. Although in theory the use of a non–cross-resistant

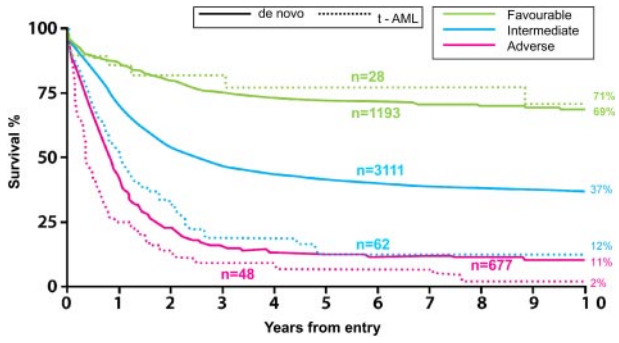

Figure 7. AML in patients less than 60 years of age. Survival, by karyotype, of de novo and therapy-related (t-AML) AML. MRC/NCRI AML Trials: overall survival. Adapted from Grimwade and Hills[10] with permission.

agent has intuitive appeal, there is no evidence that the efficacy of high-dose cytarabine as a salvage regimen is lessened by the prior use of this agent in consolidation, particularly after a long CR1.[83] Furthermore, although commonly used with or without anthracyclines, etoposide, mitoxantrone, fludarabine, amsacrine, or asparaginase, there is no information collected prospectively to indicate that this is more efficacious than high-dose cytarabine alone.[83-87] Somewhat lower doses of cytarabine may be equally effective.[88] Regimens that do not include cytarabine are equally effective for relapsed patients, and the use of mitoxantrone with etoposide is a well-tolerated regimen with published data that are at least as good as cytarabine used alone or in combination.[79,89]

Our preference is to use mitoxantrone with etoposide. With this regimen, close to 60% of patients with a long CR1 can expect to achieve CR2,[79] although similar results can be achieved with cytarabine-containing regimens.[21]

The third issue is as follows: once the patient has achieved CR2, should consolidation be administered before transplantation. For a patient in CR2, some investigators would add consolidation before an allogeneic transplantation if the patient is medically fit, even if this is not the practice in CR1. Our own practice would be, also in CR2, to proceed directly to transplantation, with the primary consideration being to reduce transplantation-related toxicity.

Proposed treatment: This patient should be reinduced with mitoxantrone and etoposide. After achievement of CR2, this patient should be referred for an allogeneic transplantation without any additional consolidation. If a sibling were not available, an alternative donor transplantation in CR2 is recommended.

Conclusion

New insights into the pathogenesis of AML have demonstrated that we are treating patients with ever-increasing disease heterogeneity with different clinical manifestations, genetic abnormalities, and outcome with current therapies. New treatment strategies generate genuine excitement about the future. The care of patients with AML has become increasingly complicated but remains remarkably gratifying.

Authorship

Contribution: J.M.R. and M.S.T. wrote the paper.

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References

1. Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood.* 2009;113(18):4179-4187.
2. Moore JO, George SL, Dodge RK, et al. Sequential multiagent chemotherapy is not superior to high-dose cytarabine alone as postremission intensification therapy for acute myeloid leukemia in adults under 60 years of age: Cancer and Leukemia Group B Study 9222. *Blood.* 2005;105(9):3420-3427.
3. Buchner T, Berdel WE, Haferlach C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol.* 2009;27(1):61-69.
4. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med.* 2009;361(13):1249-1259.
5. Petersdorf S, Kopecky K, Stuart RK, et al. Preliminary results of Southwest Oncology Group Study S0106: an International Intergroup Phase 3 randomized trial comparing the addition of gemtuzumab ozogamicin to standard induction therapy versus standard induction therapy followed by a second randomization to postconsolidation gemtuzumab ozogamicin versus no additional therapy for previously untreated acute myeloid leukemia [abstract]. *Blood.* 2009;114(22):790a.
6. Rowe JM, Tallman MS. Intensifying induction therapy in acute myeloid leukemia: has a new standard of care emerged? *Blood.* 1997;90(6):2121-2126.
7. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood.* 2000;96(13):4075-4083.
8. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood.* 1998;92(7):2322-2333.
9. Byrd JC, Mrozek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood.* 2002;100(13):4325-4336.
10. Grimwade D, Hills RK. Independent prognostic factors for AML outcome. *Hematology Am Soc Hematol Educ Program.* 2009:385-395.
11. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med.* 2008;358(18):1909-1918.
12. Pagel JM, Gooley T, Estey E, Wood B, Appelbaum FR. Impact of pre-transplant minimal residual disease assessed by flow cytometry on outcome following myeloablative hematopoietic cell transplantation for patients with AML-CR1 [abstract]. *Blood.* 2008;112(11):3253a.
13. Appelbaum FR. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia when a matched related donor is not available. *Hematology Am Soc Hematol Educ Program.* 2008:412-417.
14. Marcucci G, Maharry K, Radmacher MD, et al. Prognostic significance of, and gene and microRNA expression signatures associated with, CEBPA mutations in cytogenetically normal acute myeloid leukemia with high-risk molecular features: a Cancer and Leukemia Group B Study. *J Clin Oncol.* 2008;26(31):5078-5087.
15. Wouters BJ, Lowenberg B, Erpelinck-Verschueren CA, van Putten WL, Valk PJ, Delwel R. Double CEBPA mutations, but not single CEBPA mutations, define a subgroup of acute myeloid leukemia with a distinctive gene expression profile that is uniquely associated with a favorable outcome. *Blood.* 2009;113(13):3088-3091.
16. Tallman MS, Rowlings PA, Milone G, et al. Effect of postremission chemotherapy before human leukocyte antigen-identical sibling transplantation for acute myelogenous leukemia in first complete remission. *Blood.* 2000;96(4):1254-1258.
17. Cahn JY, Labopin M, Sierra J, et al. No impact of high-dose cytarabine on the outcome of patients transplanted for acute myeloblastic leukaemia in first remission: Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Br J Haematol.* 2000;110(2):308-314.
18. Appelbaum FR, Clift RA, Buckner CD, et al. Allogeneic marrow transplantation for acute nonlymphoblastic leukemia after first relapse. *Blood.* 1983;61(5):949-953.
19. Blume KG, Beutler E, Bross KJ, et al. Bone-marrow ablation and allogeneic marrow transplantation in acute leukemia. *N Engl J Med.* 1980;302(19):1041-1046.
20. Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol.* 2005;23(9):1969-1978.
21. Estey E. Treatment of refractory AML. *Leukemia.* 1996;10(6):932-936.
22. Rowe JM, Li X, Cassileth PA, et al. Very poor survival of patients with AML who relapse after achieving a first complete remission: the Eastern Cooperative Oncology Group Experience [abstract]. *Blood.* 2005;106(11):162a.
23. Tallman MS, Kim HT, Paietta E, et al. Acute monocytic leukemia (French-American-British classification M5) does not have a worse prognosis than other subtypes of acute myeloid leukemia: a report from the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2004;22(7):1276-1286.
24. Rowe JM, Kim H, Cassileth PA, et al. Adult patients with acute myeloid leukemia who achieve complete remission after one or two cycles of induction have a similar prognosis: a report on 1,980 patients registered to six studies conducted by the Eastern Cooperative Oncology Group [published online ahead of print July 13, 2010]. *Cancer.* doi: 10.1002/cncr.25263.
25. San Miguel JF, Martinez A, Macedo A, et al. Immunophenotyping investigation of minimal residual disease is a useful approach for predicting relapse in acute myeloid leukemia patients. *Blood.* 1997;90(6):2465-2470.

26. Cilloni D, Renneville A, Hermitte F, et al. Real-time quantitative polymerase chain reaction detection of minimal residual disease by standardized WT1 assay to enhance risk stratification in acute myeloid leukemia: a European LeukemiaNet study. *J Clin Oncol*. 2009;27(31):5195-5201.
27. Gale RE, Green C, Allen C, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood*. 2008;111(5):2776-2784.
28. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453-474.
29. Krauter J, Heil G, Hoelzer D, et al. The role of consolidation therapy in the treatment of patients up to 60 years with high-risk AML [abstract]. *Blood*. 2005;106(11):172a.
30. Moore J, Nivison-Smith I, Goh K, et al. Equivalent survival for sibling and unrelated donor allogeneic stem cell transplantation for acute myelogenous leukemia. *Biol Blood Marrow Transplant*. 2007;13(5):601-607.
31. Kiehl MG, Kraut L, Schwerdtfeger R, et al. Outcome of allogeneic hematopoietic stem-cell transplantation in adult patients with acute lymphoblastic leukemia: no difference in related compared with unrelated transplant in first complete remission. *J Clin Oncol*. 2004;22(14):2816-2825.
32. Shaw BE, Gooley TA, Malkki M, et al. The importance of HLA-DPB1 in unrelated donor hematopoietic cell transplantation. *Blood*. 2007;110(13):4560-4566.
33. Ringden O, Pavletic SZ, Anasetti C, et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood*. 2009;113(13):3110-3118.
34. Weisdorf DJ, Nelson G, Lee SJ, et al. Sibling versus unrelated donor allogeneic hematopoietic cell transplantation for chronic myelogenous leukemia: refined HLA matching reveals more graft-versus-host disease but not less relapse. *Biol Blood Marrow Transplant*. 2009;15(11):1475-1478.
35. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol*. 2010;28(11):1878-1887.
36. Rowe JM. Optimal induction and post-remission therapy for AML in first remission. *Hematology Am Soc Hematol Educ Program*. 2009;396-405.
37. Levi I, Grotto I, Yerushalmi R, Ben-Bassat I, Shpilberg O. Re: Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a meta-analysis. *J Natl Cancer Inst*. 2004;96(13):1038-1039, author reply 1039-1040.
38. Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med*. 1998;339(23):1649-1656.
39. Burnett AK, Goldstone AH, Stevens RM, et al. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties. *Lancet*. 1998;351(9104):700-708.
40. Cassileth PA, Lee SJ, Litzow MR, et al. Intensified induction chemotherapy in adult acute myeloid leukemia followed by high-dose chemotherapy and autologous peripheral blood stem cell transplantation: an Eastern Cooperative Oncology Group trial (E4995). *Leuk Lymphoma*. 2005;46(1):55-61.
41. Rowe JM, Sun Z, Cassileth PA, et al. Treatment-related mortality and relapse rate from time of initiation of post-remission therapy for patients receiving allogeneic transplantation, autologous transplantation or intensive chemotherapy: a report from the Eastern Cooperative Oncology Group (ECOG) [abstract]. *Blood*. 2008;112(11):49a.
42. Ciceri F, Labopin M, Aversa F, et al. A survey of fully haploidentical hematopoietic stem cell transplantation in adults with high-risk acute leukemia: a risk factor analysis of outcomes for patients in remission at transplantation. *Blood*. 2008;112(9):3574-3581.
43. Wagner JE. Should double cord blood transplants be the preferred choice when a sibling donor is unavailable? *Best Pract Res Clin Haematol*. 2009;22(4):551-555.
44. Cassileth PA, Sylvester LS, Bennett JM, Begg CB. High peripheral blast count in adult acute myelogenous leukemia is a primary risk factor for CNS leukemia. *J Clin Oncol*. 1988;6(3):495-498.
45. Appelbaum FR, Kopecky KJ, Tallman MS, et al. The clinical spectrum of adult acute myeloid leukaemia associated with core binding factor translocations. *Br J Haematol*. 2006;135(2):165-173.
46. Yanada M, Matsuo K, Emi N, Naoe T. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a meta-analysis. *Cancer*. 2005;103(8):1652-1658.
47. Suciu S, Mandelli F, de Witte T, et al. Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMAAML-10 trial. *Blood*. 2003;102(4):1232-1240.
48. Lin P, Chen L, Luthra R, Konoplev SN, Wang X, Medeiros LJ. Acute myeloid leukemia harboring t(8;21)(q22;q22): a heterogeneous disease with poor outcome in a subset of patients unrelated to secondary cytogenetic aberrations. *Mod Pathol*. 2008;21(8):1029-1036.
49. Paschka P, Marcucci G, Ruppert AS, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B Study. *J Clin Oncol*. 2006;24(24):3904-3911.
50. Care RS, Valk PJ, Goodeve AC, et al. Incidence and prognosis of c-KIT and FLT3 mutations in core binding factor (CBF) acute myeloid leukaemias. *Br J Haematol*. 2003;121(5):775-777.
51. Stone RM. Prognostic factors in AML in relation to (ab)normal karyotype. *Best Pract Res Clin Haematol*. 2009;22(4):523-528.
52. Cairoli R, Grillo G, Beghini A, et al. C-Kit point mutations in core binding factor leukemias: correlation with white blood cell count and the white blood cell index. *Leukemia*. 2003;17(2):471-472.
53. Pollard JA, Alonzo TA, Gerbing RB, et al. Prevalence and prognostic significance of KIT mutations in pediatric patients with core binding factor AML enrolled on serial pediatric cooperative trials for de novo AML. *Blood*. 2010;115(12):2372-2379.
54. Rowe JM. Closer to the truth in AML. *Blood*. 2009;113(18):4129-4130.
55. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1235-1248.
56. Abou-Jawde RM, Sobecks R, Pohlman B, et al. The role of post-remission chemotherapy for older patients with acute myelogenous leukemia. *Leuk Lymphoma*. 2006;47(4):689-695.
57. Walter RB, Kantarjian HM, Huang X, et al. Effect of complete remission and responses less than complete remission on survival in acute myeloid leukemia: a combined Eastern Cooperative Oncology Group, Southwest Oncology Group, and M. D. Anderson Cancer Center Study. *J Clin Oncol*. 2010;28(10):1766-1771.
58. Rowe JM. Consolidation therapy: what should be the standard of care? *Best Pract Res Clin Haematol*. 2008;21(1):53-60.
59. Goldstone AH, Burnett AK, Wheatley K, Smith AG, Hutchinson RM, Clark RE. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. *Blood*. 2001;98(5):1302-1311.
60. Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood*. 2001;98(5):1312-1320.
61. Rowe JM, Neuberg D, Friedenberg W, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. *Blood*. 2004;103(2):479-485.
62. Büchner T, Berdel WE, Schoch C, et al. Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia. *J Clin Oncol*. 2006;24(16):2480-2489.
63. Forman SJ. What is the role of reduced-intensity transplantation in the treatment of older patients with AML? *Hematology Am Soc Hematol Educ Program*. 2009;406-413.
64. Appelbaum FR. Optimising the conditioning regimen for acute myeloid leukaemia. *Best Pract Res Clin Haematol*. 2009;22(4):543-550.
65. Ringden O, Labopin M, Ehninger G, et al. Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. *J Clin Oncol*. 2009;27(27):4570-4577.
66. Koreth J, Aldridge J, Kim HT, et al. Reduced-intensity conditioning hematopoietic stem cell transplantation in patients over 60 years: hematologic malignancy outcomes are not impaired in advanced age. *Biol Blood Marrow Transplant*. 2010;16(6):792-800.
67. Shimoni A, Hardan I, Shem-Tov N, Yerushalmi R, Nagler A. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: long-term follow-up. *Leukemia*. 2010;24(5):1050-1052.
68. Estey E, de Lima M, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood*. 2007;109(4):1395-1400.
69. Godley LA, Larson RA. Therapy-related myeloid leukemia. *Semin Oncol*. 2008;35(4):418-429.
70. Borthakur G, Estey AE. Therapy-related acute myelogenous leukemia and myelodysplastic syndrome. *Curr Oncol Rep*. 2007;9(5):373-377.
71. Preisler HD, Early AP, Raza A, et al. Therapy of secondary acute nonlymphocytic leukemia with cytarabine. *N Engl J Med*. 1983;308(1):21-23.
72. Goldstone AH, Burnett A, Avivi I, Hills R, Wheatley K. Secondary acute myeloid leukamia always predicts worse outcome than de novo AML, regardless of cytogenetics or age. AML 10,11,12 MRC trials *Blood*. 2002;100(11):322a.
73. Kern W, Schoch C, Haferlach T, et al. Multivariate analysis of prognostic factors in patients with refractory and relapsed acute myeloid leukemia undergoing sequential high-dose cytosine arabinoside and mitoxantrone (S-HAM) salvage

therapy: relevance of cytogenetic abnormalities. *Leukemia.* 2000;14(2):226-231.

74. Estey EH. Treatment of relapsed and refractory acute myelogenous leukemia. *Leukemia.* 2000; 14(3):476-479.
75. Giles F, Verstovsek S, Garcia-Manero G, et al. Validation of the European Prognostic Index for younger adult patients with acute myeloid leukaemia in first relapse. *Br J Haematol.* 2006;134(1): 58-60.
76. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation during untreated first relapse of acute myeloid leukemia. *J Clin Oncol.* 1992;10(11):1723-1729.
77. Brown RA, Wolff SN, Fay JW, et al. High-dose etoposide, cyclophosphamide, and total body irradiation with allogeneic bone marrow transplantation for patients with acute myeloid leukemia in untreated first relapse: a study by the North American Marrow Transplant Group. *Blood.* 1995;85(5):1391-1395.
78. Keating MJ, Kantarjian H, Smith TL, et al. Response to salvage therapy and survival after relapse in acute myelogenous leukemia. *J Clin Oncol.* 1989;7(8):1071-1080.
79. Rowe JM, Mazza JJ, Hines JD, et al. Mitoxantrone and etoposide in patients with relapsed and refractory acute nonlymphocytic leukemia. *Haematol Blood Transfus.* 1990;33:326-329.
80. Thalhammer F, Geissler K, Jager U, et al. Duration of second complete remission in patients with acute myeloid leukemia treated with chemotherapy: a retrospective single-center study. *Ann Hematol.* 1996;72(4):216-222.
81. Hiddemann W, Martin WR, Sauerland CM, Heinecke A, Buchner T. Definition of refractoriness against conventional chemotherapy in acute myeloid leukemia: a proposal based on the results of retreatment by thioguanine, cytosine arabinoside, and daunorubicin (TAD 9) in 150 patients with relapse after standardized first line therapy. *Leukemia.* 1990;4(4):184-188.
82. Rees JK, Gray RG, Swirsky D, Hayhoe FG. Principal results of the Medical Research Council's 8th acute myeloid leukaemia trial. *Lancet.* 1986; 2(8518):1236-1241.
83. Herzig RH, Lazarus HM, Wolff SN, Phillips GL, Herzig GP. High-dose cytosine arabinoside therapy with and without anthracycline antibiotics for remission reinduction of acute nonlymphoblastic leukemia. *J Clin Oncol.* 1985;3(7):992-997.
84. Capizzi RL, Davis R, Powell B, et al. Synergy between high-dose cytarabine and asparaginase in the treatment of adults with refractory and relapsed acute myelogenous leukemia: a Cancer and Leukemia Group B Study. *J Clin Oncol.* 1988; 6(3):499-508.
85. Carella AM, Carlier P, Pungolino E, et al. Idarubicin in combination with intermediate-dose cytarabine and VP-16 in the treatment of refractory or rapidly relapsed patients with acute myeloid leukemia: the GIMEMA Cooperative Group. *Leukemia.* 1993;7(2):196-199.
86. Karanes C, Kopecky KJ, Head DR, et al. A phase III comparison of high dose ARA-C (HIDAC) versus HIDAC plus mitoxantrone in the treatment of first relapsed or refractory acute myeloid leukemia Southwest Oncology Group Study. *Leuk Res.* 1999;23(9):787-794.
87. Vogler WR, McCarley DL, Stagg M, et al. A phase III trial of high-dose cytosine arabinoside with or without etoposide in relapsed and refractory acute myelogenous leukemia: a Southeastern Cancer Study Group trial. *Leukemia.* 1994;8(11): 1847-1853.
88. van Prooijen HC, Dekker AW, Punt K. The use of intermediate dose cytosine arabinoside (ID Ara-C) in the treatment of acute non-lymphocytic leukaemia in relapse. *Br J Haematol.* 1984;57(2): 291-299.
89. Ho AD, Lipp T, Ehninger G, et al. Combination of mitoxantrone and etoposide in refractory acute myelogenous leukemia: an active and well-tolerated regimen. *J Clin Oncol.* 1988;6(2):213-217.
90. Harousseau JL, Cahn JY, Pignon B, et al. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia: the Groupe Ouest Est Leucemies Aigues Myeloblastiques (GOELAM). *Blood.* 1997;90(8):2978-2986.
91. Appelbaum FR, Rowe JM, Radich J, Dick JE. Acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program.* 2001;62-86.