Capecitabine in the treatment of rectal cancer

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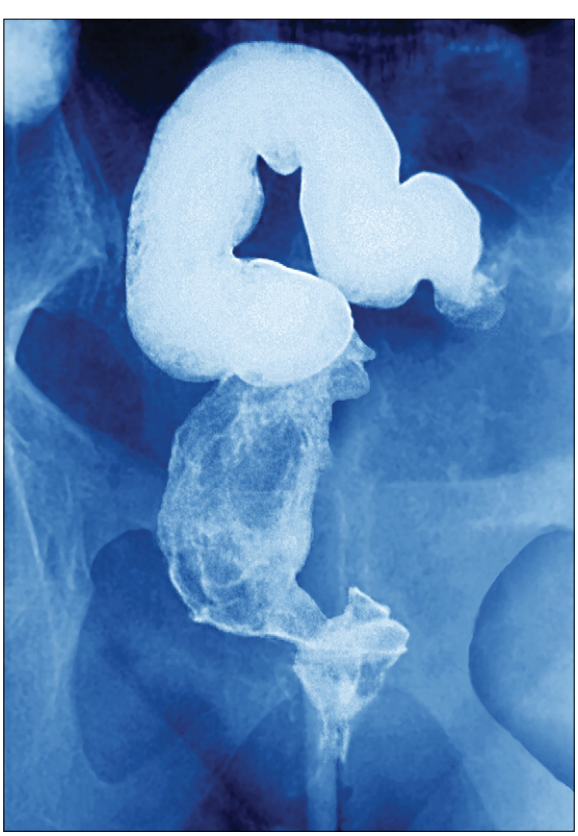
The fluorouracil prodrug capecitabine was developed as an oral substitute for intravenous fluorouracil in the 1990s. Since then, many phase 2 and 3 trials have investigated capecitabine in different tumour types and stages, at various doses, and as a single agent or multiagent therapy.[1,2] Most phase 3 trials that compared the two drugs reported that capecitabine was at least as effective as fluorouracil, and capecitabine was approved by the US Food and Drug Administration (FDA) for treatment of metastatic breast cancer in 1998, for metastatic colorectal cancer in 2001, and as adjuvant therapy for colon cancer in 2005.

Fluorouracil-based chemoradiation is standard treatment for many solid tumours, and substituting fluorouracil with capecitabine is attractive because of the ease of administration and mimicking of a continuous infusion.[3] Capecitabine has been assessed in several phase 1 and 2 trials of adjuvant or neoadjuvant chemoradiotherapy for rectal cancer, as monotherapy or in combination with oxaliplatin, irinotecan, or targeted therapies; however, until now, capecitabine was never formally compared with fluorouracil in a randomised trial.[1] In *The Lancet Oncology*, Hofheinz and colleagues[4] report results of their trial testing non-inferiority for overall survival with capecitabine versus fluorouracil, as part of neoadjuvant chemoradiotherapy and as single-agent adjuvant systemic therapy. Overall survival with capecitabine was non-inferior to fluorouracil, and, in fact, slightly better at 5 years. These findings mirror those of the large X-ACT trial[5] of adjuvant capecitabine in colon cancer, which led to FDA approval in 2005. The results of these two trials[4,5] seem to warrant replacement of fluorouracil with capecitabine for adjuvant therapy of rectal cancer. Substitution of capecitabine for fluorouracil in combination regimens is also logical, and is being assessed in ongoing trials of rectal cancer registered with ClinicalTrials.gov.



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Although use of adjuvant systemic therapy in rectal cancer is widespread, the evidence base for this approach is not as strong as in colon cancer,[6] which can raise the question of how solid the evidence for a specific treatment should be.[7] The post-hoc exploratory finding of improved survival with capecitabine over fluorouracil in the present study adds to the large body of circumstantial evidence supporting a benefit for adjuvant therapy in rectal cancer.

Hofheinz and colleagues' study began in 2002 as a trial to assess postoperative chemoradiation, but was changed in 2005 to include patients receiving preoperative chemoradiation, after publication of the German CAO/ARO/AIO-94 study[8] showed improved local control with neoadjuvant chemoradiotherapy. This amendment presented some methodological difficulties, since the two cohorts could not be directly compared. Whereas in the adjuvant cohort the inclusion of stage II–III disease was based on histological staging, inclusion in the neoadjuvant cohort was necessarily based on clinical staging. In the CAO/ARO/AIO-94 trial, such clinical staging meant that 18% of patients had stage I disease.[8] Therefore, better survival might be expected in the neoadjuvant compared with adjuvant cohort of the present trial; however, the reverse was true. This is an intriguing result and might be related to lower compliance with adjuvant chemotherapy after preoperative chemoradiation and surgery.

In the neoadjuvant cohort, capecitabine chemoradiation provided a better response than fluorouracil chemoradiation; there were more pathological complete responses and more downstaging. This does not necessarily translate into better local control, because with optimum total mesorectal excision after chemoradiotherapy the number of local recurrences should already be very low. Better local control could, however, be beneficial with the current interest in organ-saving treatment of rectal cancer.

It is anticipated that the results of the NSABP R-04 trial (NCT00058474), expected at the end of 2013, will show, in accordance with the present study, that capecitabine is at least as effective as fluorouracil for neoadjuvant chemoradiotherapy, confirming capecitabine as the basis for systemic therapy in the treatment of colorectal cancer. Future trials should focus on the role of chemoradiotherapy in organ-saving treatment, and on improving the cure of micrometastatic disease, possibly by treating earlier in a neoadjuvant setting.

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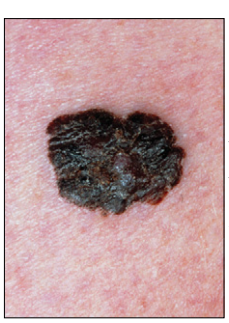
We declare that we have no conflicts of interest.

1 Hirsch BR, Zafar SY. Capecitabine in the management of colorectal cancer. *Cancer Manag Res* 2011; **3:** 79–89.
2 Bang YJ. Capecitabine in gastric cancer. *Expert Rev Anticancer Ther* 2011; **11:** 1791–806.
3 Rich TA, Shepard RC, Mosley ST. Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. *J Clin Oncol* 2004; **22:** 2214–32.
4 Hofheinz R-D, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol* 2012; **13:** 579–88.
5 Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005; **352:** 2696–704.
6 Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. *Ann Oncol* 2010; **21:** 1743–50.
7 Glimelius B. Adjuvant chemotherapy in rectal cancer—an issue or a nonissue? *Ann Oncol* 2010; **21:** 1739–41.
8 Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351:** 1731–40.

Finally, a substantial role for radiotherapy in melanoma

Does adjuvant radiotherapy have a well-defined role in the definitive management of high-risk malignant melanoma? For decades, the answer to this question has been murky and contentious.[1] Early reports gave conflicting results, but the data were clouded by variability in target field sizes, radiation doses, and fractionation schemes. In *The Lancet Oncology*, Bryan Burmeister and colleagues[2] present an important intergroup randomised trial showing that adjuvant nodal basin radiotherapy, when used carefully and systematically, significantly improved regional lymphatic control for high-risk patients compared with no further treatment after lymphadenectomy (20 relapses among 109 patients in the adjuvant radiotherapy group *vs* 34 among 108 patients in the observation group, hazard ratio [HR] 0·56, 95% CI 0·32–0·98; p=0·041). They show that widely accepted risk stratification measures, such as the number and size of involved nodes and the presence of extracapsular disease, might be used to identify patients at high risk of regional lymphatic failure, and that the treatment of these patients with a radiation dose of 48 Gy in 20 fractions will significantly improve local control. Although Burmeister and colleagues showed a significant improvement in risk of local relapse within the affected nodal basins, unfortunately, overall survival did not differ significantly (59 *vs* 47 deaths, HR 1·37, 95% CI 0·94–2·01; p=0·12). Toxic effects were generally mild and manageable, much the same as in previous studies.

Where do we go from here, and how do we build on this work? Many new, promising targeted pharmaceuticals and immunomodulating compounds with clear activity against melanoma have been introduced.[3] These compounds were developed on the basis of a wealth of preclinical data for melanoma cell-cycle regulatory circuits, signal transduction control, and immune system activation signals.[4] Some of this work relates specifically to the identification of mutations that activate oncogenes that are present in a large proportion of melanoma specimens and—perhaps more importantly—the synthesis and testing of small molecule inhibitors of these aberrant gene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