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Colorectal cancer

Prospective evaluation of fluorouracil chemotherapy based on the genetic makeup of colorectal cancer

J M Carethers

Evaluation of 5-fluorouracil chemotherapy and survival, based on mismatch repair (MMR) status, indicates that patients with MMR proficient colorectal tumours benefit from 5-fluorouracil treatment while patients with MMR deficient tumours do not

The current gold standard for treating patients with advanced colon cancer is chemotherapy with 5-fluorouracil (5-FU) based regimens.¹ This standard is based on compelling clinical trials utilising 5-FU and levamisole, and demonstrating a survival benefit for patients with TNM stage III (Dukes-Aston Collier stage C) colon cancer.²⁻⁴ Although there is no set standard for treating stage II patients, some stage II patients do receive 5-FU chemotherapy, albeit the natural history of this stage of colon cancer is reasonably favourable at more than 70% five year survival.¹ Patients with rectal cancer may receive neoadjuvant or adjuvant chemotherapy for stage II or III disease, as treatment in both of these stages of tumour benefit patient survival.¹ Stage I patients with colorectal cancer do not receive 5-FU as their prognosis is excellent with removal of the tumour, and stage IV patients may receive 5-FU for palliation. Overall, determination for use of 5-FU based chemotherapy is completely based on the stage of the colorectal cancer in the patient at presentation.

The past decade has brought a fruitful understanding of the genetic and

biological behaviour of colorectal cancer, and our knowledge is still growing in this aspect. Colorectal cancer is a genetic disease, with changes in the genome of the tumour cell that are favourable for the tumour's growth and remote spread. Taking knowledge learned from hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) in which a germline mutation occurs in genes that encode proteins for DNA mismatch repair (MMR), it was discovered that approximately 15% of sporadic colorectal cancers lack intact MMR due to the epigenetic inactivation of the MMR protein *hMLH1* without genetic mutation.⁵ Sporadic colorectal cancers can thus be categorised into two groups: those that express all components of the MMR system) and those that are MMR deficient (that is, cancers that lack a component of the MMR system, such as *hMLH1*, and exhibit microsatellite instability, a marker for loss of MMR function). Intact DNA MMR will repair DNA polymerase mistakes to maintain the fidelity of replicating DNA. Additionally, the MMR system can recognise certain chemotherapeutic agents that intercalate or get incorporated

into DNA, and may be an important trigger to execute cell death.⁶⁻⁹ With MMR deficiency, repair of polymerase mistakes are lacking and affected cells accumulate mutations that may drive tumorigenesis.^{3, 10} Importantly, MMR deficiency may prevent the recognition of DNA damaging chemotherapy to initiate cell killing by that agent.^{8, 11, 12}

There are differences in the biological behaviour of MMR deficient tumours compared with MMR proficient tumours. MMR deficient tumours are more likely to be located in the proximal (right) colon, and on histology are more likely to demonstrate the presence of mucin, have a surrounding lymphoid reaction, and be of poor histological grade.³ Despite this poor histological grade, there is some evidence that patients with MMR deficient tumours have a more favourable prognosis for survival. This has been particularly shown in patients with MMR deficient tumours who were under the age of 50 years,¹³ but extends to older ages as well in some studies.^{14, 15} Pooling multiple studies confirmed the relationship between MMR deficiency and patient survival, with a combined hazard ratio for overall survival associated with MMR deficiency of 0.65 (95% confidence interval 0.59-0.71).¹⁶

The fact that patients with MMR deficient tumours may have a better prognosis over patients with MMR proficient tumours confounded some original studies examining 5-FU chemotherapy and benefit, with most lacking the appropriate control group for comparative purposes.¹⁷⁻¹⁹ Indeed, these reports appeared to indicate that 5-FU adjuvant chemotherapy was beneficial for patients with MMR deficient colorectal cancer, but without control groups it was not clear if the survival benefit was derived from the chemotherapy or from the presence of the MMR deficient tumour itself. Two

retrospective studies addressed this conundrum by including patients who had MMR deficient tumours and who did not receive 5-FU chemotherapy. One study of 204 sporadic stage II and III colorectal cancer patients showed a significant survival advantage for patients with MMR proficient tumours after receiving 5-FU adjuvant chemotherapy, while patients with MMR deficient tumours showed no difference in survival.²⁰ The other retrospective study of 570 sporadic stage II and III patients enrolled in prior randomised trials of 5-FU chemotherapy demonstrated a survival benefit in patients with MMR proficient tumours, but not in patients with MMR deficient tumours.²¹ Similarly, stage III patients with Lynch syndrome do not demonstrate a five year survival benefit with 5-FU treatment over untreated patients.²² Taken together, these results suggest that 5-FU based chemotherapy does not prolong survival in patients with MMR deficient colorectal cancers. The findings from these retrospective studies also suggest that the genetic makeup of the tumour may predict the response to 5-FU, as patients with MMR proficient tumours gain survival with 5-FU treatment. Because of the lack of large prospective data, and the rarity of determining the MMR status of tumours in clinical practice, there has been caution in recommending an implementation for change in the approach to 5-FU treatment based on the MMR status of colorectal cancers.

In this issue of *Gut*, Jover and colleagues²³ present the first prospective data on the use of 5-FU based chemotherapy dichotomised by a patient's tumour MMR status (see page 848). In this nested prospective cohort from the large EPICOLON study investigating the prevalence of Lynch syndrome in Spain, the authors enrolled 754 patients with colorectal cancer from 10 medical centres (out of a total of 25 centres) in which adjuvant chemotherapy was administered according to current standard clinical practice. Oncologists treating the patients were blinded to the tumour MMR status. Two hundred and six (27.3%) patients died, 66 (8.8%) patients had MMR deficient tumours (based on one mononucleotide microsatellite marker and immunohistochemistry for two MMR proteins), and seven of these had Lynch syndrome. This cohort had more females with MMR deficient colorectal tumours, and despite the blind prospective nature of the study, more patients with MMR proficient tumours received chemotherapy. To determine whether the MMR status affected 5-FU response, the authors closely examined the 505

patients with stage II or III colorectal cancer, in which 251 patients received 5-FU chemotherapy. Consistent with previous data,^{20, 21} stage II and III patients treated with 5-FU chemotherapy had improved overall survival (87.3% v 74.7%; $p = 0.0001$). However, as indicated from the retrospective studies,^{20, 21} better overall survival segregated to patients with MMR proficient tumours (87.1% v 73.5%; $p = 0.0001$) that did not extend to patients with MMR deficient tumours (89.5% v 82.4%; $p = 0.4$). Identical findings were found if the data were analysed for disease free survival.²³ Thus this prospective trial evaluating 5-FU chemotherapy and survival based on MMR status confirms data obtained from the retrospective studies, and indicates that patients with MMR proficient colorectal tumours benefit from 5-FU treatment while patients with MMR deficient tumours do not.

The concept of using biological information from tumours to determine treatment approaches is not new as this is routinely done for breast cancers (among others), and testing for the hormonal receptor status of these tumours has become routine. Because a number of studies have indicated that immunohistochemistry of MMR proteins is a good surrogate for determining the MMR status of colorectal tumours,^{24, 25} this testing, which can be done by any pathology laboratory service, needs to become commonplace as studies such as the one highlighted in this issue of *Gut* determine that this information will guide the most optimal care of patients. This study, in combination with the strong retrospective information, suggests that a revision of the guidelines for adjuvant chemotherapy should be considered for patients with MMR deficient colorectal cancers, and surgery may be the only therapy needed for those with stage II or III MMR deficient tumours. This would add important tumour biological data to staging information in the algorithm for treating colorectal cancer.

How does tumour MMR deficiency cause resistance to 5-FU? Current evidence points towards the MMR proteins themselves recognising 5-FU that gets incorporated into DNA.^{11, 12} Thus with MMR deficiency, there is no MMR binding or recognition of the incorporated 5-FU molecules, and no subsequent triggering for tumour cell demise. Investigation into other chemotherapeutic agents that may circumvent this mechanism for patients with MMR deficient tumours should be pursued. Some compounds that induce toxicity on colorectal cancer cells may work independently of DNA MMR, and many of these drugs, such as irinotecan and

oxaliplatin, will need further evaluation to exploit them as independent treatments for patients with MMR deficient colorectal cancer.^{26, 27} The prospective study by Jover and colleagues²³ helps cement the need to re-evaluate the current chemotherapeutic approach for patients with MMR deficient tumours.

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Correspondence to: Dr J M Carethers, GI Section, 111D, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA; jcarethers@ucsd.edu

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Budd Chiari syndrome

Prognosis in Budd Chiari syndrome after re-establishing hepatic venous drainage

D-C Valla

Treatment of Budd Chiari syndrome by interventional radiology has good medium term survival for patients with all forms of disease severity

Budd Chiari syndrome (BCS), the entity resulting from an obstructed hepatic venous outflow tract,^{1,2} is a so-called ultra rare disease³: the estimated incidence was approximately 1 per 2.5 million per year in France or Japan in the 1990s.⁴ This rarity explains why classical randomised trials could not be performed in the past. Trials cannot be foreseen in the near future either, even though excellent collaborations have been developed in European countries, nationwide, and at an international level (see <http://www.envie-project.org/origin.html>). The report by the Birmingham group⁵ in this issue of *Gut* should be analysed in the context of the rarity of this disease (see page 878).

The authors retrospectively analysed the outcome of patients with primary BCS treated percutaneously with repermeation (hepatic vein or inferior vena cava angioplasty, with or without stenting) or transjugular intrahepatic portosystemic shunting (TIPS). They included 29 patients referred between 1985 and 1999, and 32 patients referred between 1999 and 2004. This is the largest series of BCS patients treated with interventional radiology in a single Western centre. There are several reports on large series from China^{6–8} and India⁹ where, unlike Western countries, there is a

large predominance of inferior vena cava occlusion. Inferior vena cava occlusion differs from pure hepatic vein occlusion in many aspects.¹⁰

The authors made considerable efforts to circumvent the usual limitations in treatment evaluation of rare diseases. Firstly, as above mentioned, they included a remarkably large number of cases, given the ultra rarity of the disease. Secondly, although the study focused on a particular treatment modality, all other modalities were available at this referral centre. Thirdly, they stratified the analyses according to prognostic indices that have been well validated in several Western studies. Fourthly, the findings were placed in the perspective of other contemporary cohorts where interventional radiology had not been as extensively used. Unfortunately, there is no accepted statistical tool to compare survival in small samples of different patient populations, even after adjustment for established prognostic indices.

The results were impressive, as actuarial survival in the entire cohort at one and five years was 94% (95% confidence interval (CI) 88–100%) and 87% (95% CI 78–96%), respectively. These survival rates can be contrasted with those from another British study

dating back to the early 1970s, which illustrates the natural history of BCS: one and five year survival rates were 68% and 10%, respectively.¹¹ These results are even more comforting when one remembers that most BCS patients are young adult females generally not exposed to lifestyle related risk factors except for the contraceptive pill—a demographic group where expected life duration is long. There are several possible reasons for such an improvement: earlier diagnosis, recognition of asymptomatic cases, better general supportive care, or true efficacy of specific treatments for venous obstruction. Whatever the reasons, the authors have to be congratulated for this achievement.

The authors opted for evaluation of a therapeutic modality: “all interventional radiology”. This option is in line with their progressive elaboration of an algorithm for treatment, based on their unique experience.¹² The algorithm was applied to patients seen after 1999. According to this algorithm, patients were treated with angioplasty whenever a short length stenosis on the hepatic veins or inferior vena cava was identified. Such short length stenoses were specifically looked for using ultrasound by world leading experts in hepatic vascular radiology and percutaneous recanalisation. In the other patients, TIPS was performed whenever medical therapy alone failed to control manifestations. Opting for an evaluation of “all interventional radiology” led to pooling of patients treated with percutaneous recanalisation or with TIPS, which is sensible for the purpose of increasing the number of patients. Even with a large number of patients available for enrolment, testing the full strategy in a randomised trial would be difficult as it is unclear what should be the comparator.

There are limitations, however, in evaluating the proposed algorithm. Although 61 patients were analysed, only 32 were deliberately managed according to this algorithm (that is, those referred after 1999). The 29 other