

Irinotecan and mismatch repair deficiency

We read the recent publications of Ychou et al. [1, 2] on ‘adjuvant’ irinotecan-based chemotherapy in high-risk localized colorectal cancer (CRC) and after resection of liver-confined metastatic disease with great interest. In contrast to the improved outcome provided by oxaliplatin-based adjuvant treatment of early-stage disease, there is now a body of evidence showing that the addition of irinotecan to 5-fluorouracil (5-FU)/Leucovorin does not provide a benefit in this setting [1, 3]. The authors are to be congratulated for reporting the largest randomized trial of adjuvant treatment after resected colorectal liver metastases. Such trials have been historically difficult to accrue and it has been hard to show an overall survival benefit with either systemic or regional treatment in this setting. On the basis of data, we are now pretty sure that the conclusion from the localized disease setting—only combination of 5-FU with oxaliplatin confers an advantage over 5-FU alone—can also be applied to liver-confined resectable CRC as has already been common practice in most centers.

It is a commonly uttered wish that future clinical trials should stratify patients according to their particular risk as well

as biomarkers predicting response to treatment. Resectable metastatic CRC would lend itself to such a strategy as the postoperative recovery period leaves several weeks to do the ‘molecular homework’. Despite groundbreaking work in colon cancer assessing the role of topoisomerase I, thymidylate synthase and excision repair cross-complementation group in predicting response to irinotecan, 5-FU and oxaliplatin, respectively, practice-changing trials are still at large. DNA mismatch repair (MMR) defects, in contrast, are easily assessed by immunohistochemistry and may provide important information regarding efficacy of irinotecan [4]. We are interested to know whether Ychou et al. assessed tumor tissue for DNA MMR defects or microsatellite instability (MSI). Patients who can undergo curative resection of liver metastases have an outcome that lies somewhere between that for patients with stage IIIB–IIIC disease. MMR status may, therefore, be of relevance for this group. We acknowledge that MMR loss is an uncommon event in sporadic advanced CRC (<10%) [5] and recent data from a large adjuvant trial for early-stage disease have shown that MSI, a surrogate for MMR protein loss, was less common in stage III and was not independently prognostic of outcome (relapse-free survival and overall survival) [6]. However, there are little data on the potential role of MMR loss as a biomarker post-liver resection and chemotherapy trials in this setting are lacking. One of the difficulties inherent to accrual for adjuvant trials is likely explained by the reluctance of patients and physicians alike to consider a surgery-alone arm after liver resection. The validation of biomarkers such as MMR loss, even in small subsets of patients, may make a surgery-alone arm more attractive, improve accrual and may identify a population who will benefit most from adjuvant therapy. In concordance with the authors, we also feel that ‘considerations for tailoring combination therapies in the adjuvant treatment of liver-limited CRC to patients who will receive most benefit will need to be integrated into future trials’. Response to oxaliplatin-based treatment may also be different in tumors that harbor MMR defects [7].

D. G. Power^{1*} & J. Feilchenfeldt²

¹Department of Medicine, Gastrointestinal Oncology Division, Memorial Sloan Kettering Cancer Center, NY, USA, ²Department of Oncology, Zurich University Hospital, Zurich, Switzerland
(*E-mail: drdgpower@gmail.com)

disclosure

The authors have no conflict of interest to declare.

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