

Letters to the Editor

UFT/leucovorin and oxaliplatin alternated with UFT/leucovorin and irinotecan in metastatic colorectal cancer

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Sir,

In the January 26, 2004 issue, Petrioli *et al* (2004) reported a small phase II study of 41 patients with metastatic colorectal cancer treated with UFT/leucovorin and oxaliplatin or UFT/leucovorin and irinotecan alternatively. The overall response (58.5%), median progression-free survival (8.8 months) and median overall survival (17.3) months are comparable to those of previous reported combinations including either oxaliplatin or irinotecan (de Gramont *et al*, 2000; Douillard *et al*, 2000; Saltz *et al*, 2000), but with no grade 4 toxicity. Nevertheless, this study is questionable by many aspects. The first point to discuss is the inevitable selection bias illustrated by the favourable general status and the wide predominance (93%) of patients with 1 or 2 metastatic sites. Many baseline characteristics have not been precised such as albumin, lactate dehydrogenase, alkaline phosphatases, or carcinoembryonic antigen levels. Metastasectomy has been performed in about 20% of cases despite very low-dose intensities. This secondary surgery introduces a major confusing factor since prolonged survival and probably cure rates of about 20% can be obtained (Elias *et al*, 1998). Above all, there is a major recruitment bias since 85% of the patients have had been operated for a primary tumour, favouring the early detection of metastases, leading to the selection of patients with low tumour burden and, consequently, to a potential advantage in terms of therapeutic efficacy and tolerance. However, the dose intensities of irinotecan

and oxaliplatin are only 36 and 17 mg m⁻² in this study vs 90 and 50 mg m⁻², respectively, in the FOLFIRI and FOLFOX6 regimens and up to 100 and 65 mg m⁻² in the recent intensified FOLFIRI-3 (Mabro *et al*, 2003) and FOLFOX7 versions (Maindrault-Goebel *et al*, 2001). UFT also is administered at a dose which is that recommended for combination with a full dose of irinotecan (Alonso *et al*, 2001; Mackay *et al*, 2003). Given the rarity of diarrhoea under oxaliplatin, higher doses of UFT might be combined with this agent (Kim *et al*, 2002).

In fact, the aim of the study may be discussed since efficacy should be privileged in such selected patients potentially candidates to secondary surgery. Possibly, more patients might have benefited from this approach with heavier regimens, taking into account progresses in surgery allowing the treatment of patients with liver and lung metastases (Mineo *et al*, 2003). The question of the selection of resistant clones by low doses also must be addressed. The evaluation of response to either oxaliplatin or irinotecan is extremely difficult with the alternated regimens. Consequently, second-line chemotherapy should have been a dilemma since the investigators had to use mitomycin. This study contributes to demonstrate that, at present, the neoadjuvant approach should be clearly distinguished from palliative chemotherapy. There is also a need for rapid integration of biological predictive factors of response (Etienne *et al*, 2002; Arango *et al*, 2003; Fallik *et al*, 2003; Mariadason *et al*, 2003).

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Reply: UFT/leucovorin and oxaliplatin alternated with UFT/leucovorin and irinotecan in metastatic colorectal cancer

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Sir,

We would like to thank Dr Alliot for his comments concerning our study of metastatic colorectal cancer patients treated with UFT/LV + L-HOP alternated with UFT/LV + CPT-11 (Petrioli *et al*, 2004).

In relation to the baseline characteristics of the enrolled patients, it was pointed out in the Discussion that 'the performance status and the percentage of chemo-naïve patients suggested a better than average group with regard to efficacy and toxicity'. As far as metastatic sites are concerned, a selection bias is common to small phase II studies. It is also worth pointing out that most of the metastatic colorectal cancer patients enrolled in clinical trials have ≤2 metastatic sites (as in our study population). Furthermore, patients undergoing surgery for colorectal cancer are unlikely to have metastatic sites other than the liver, lung and peritoneum, and those having three or more metastatic sites are unlikely to have a performance status that would allow their enrolment in a chemotherapeutic protocol. Finally, phase II studies do not usually report baseline CEA, albumin and LDH levels because these have little prognostic value in the case of patients

with advanced disease (Douillard *et al*, 2000; Saltz *et al*, 2000; Souglakos *et al*, 2002; Zeuli *et al*, 2003).

In relation to the low level of toxicity, it should be remembered that this was also due to the advantage of oral chemotherapy: that is, unlike boluses and continuous infusions, the treatment can be discontinued when toxicity arises and before it worsens (Twelves and Cassidy, 2002).

About 20% of our patients underwent postchemotherapy surgery for residual metastases, thus confirming the efficacy of the proposed chemotherapy protocol. However, postchemotherapy surgery led to a major advantage in terms of global survival in very few cases (9%).

The fact that 85% of our patients underwent primary tumour surgery is said to be a major recruitment bias, but we would like to point out that this percentage is the same or lower than that reported in the majority of studies of metastatic colorectal cancer (Van Cutsem *et al*, 2001; Twelves *et al*, 2001; Schilsky *et al*, 2002; Falcone *et al*, 2002).

As mentioned in the Discussion, low dose intensities of L-HOP and CPT-11 can be expected when using an alternating chemotherapy regimen. Nevertheless, the results of the study are supported by other studies of alternating chemotherapy in patients with metastatic colorectal cancer, suggesting that prolonged tumour exposure to a fluoropyrimidine plus full doses of L-HOP

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