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DESPITE THE availability of 5-fluorouracil (5-FU) for four decades, the issues of optimal scheduling and the role of biochemical modulation of 5-FU remain controversial. As 5-FU has been the most active drug available for the treatment of colorectal cancer until recently, the potential enhancement of the efficacy of 5-FU by biochemical modulation and/or manipulation of the schedule has remained a major clinical research priority. Sobrero and Herrmann have presented opposing views on the impact of biochemical modulation of 5-FU [1, 2]. Both authors have focused on colorectal cancer as there is insufficient evidence to draw any conclusions in other tumour types.

In the adjuvant setting, there has not been any direct comparison of unmodulated and modulated 5-FU. However, unmodulated 5-FU has not been demonstrated to be an effective adjuvant treatment, perhaps related to the relative dose intensity of the 5-FU regimens used [3]. In contrast, 5-FU and folinic acid improves survival in stage III carcinoma of the colon and 5-FU combined with folinic acid or levamisole has become standard adjuvant therapy for patients with stage III disease [4, 5].

It is in the advanced disease setting that the arguments about the benefits of modulated 5-FU compared with unmodulated 5-FU have continued over the last 10 years. As both authors have pointed out, the controversy revolves around the benefits of adding either folinic acid or methotrexate to 5-FU as the addition of interferon has not been shown to be beneficial [6]. We propose to concentrate primarily on the role of folinic acid and 5-FU, as this combination, rather than 5-FU and methotrexate, has been adopted as standard chemotherapy for advanced colorectal cancer by many centres around the world. Nevertheless, a meta-analysis found that the addition of methotrexate results in an improved response rate and a small improvement in survival [7], although interpretation of these trials is confounded by the use of different regimens with variable intervals between the two drugs and the use of folinic acid for methotrexate rescue.

Randomised trials have primarily addressed the role of folinic acid in the context of bolus schedules of 5-FU. A meta-analysis found improved response rates without any improvement in survival when 5-FU and folinic acid combinations were compared with 5-FU alone [8]. The meta-analysis included different schedules and doses of both 5-FU and folinic acid. The North Central Cancer Treatment Group (NCCTG) trial, which was the only trial at that time to have demonstrated a survival advantage for the combination, was not included in the analysis, although it was estimated that its inclusion would not have altered the conclusions of the statistical overview [9]. The recently published results of a large Swiss Group for Clinical Cancer Research (SAKK) trial

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confirm the findings of the NCCTG trial demonstrating an improved survival as well as response rate with bolus 5-FU and low dose folinic acid daily for 5 days every 4–5 weeks [10]. It has been suggested that the survival advantage seen in the NCCTG trial may relate to the inclusion of a large number of better prognosis patients without measurable disease [2], but this is not supported by the SAKK trial in which 90% of patients had measurable disease. In addition to the SAKK trial, there have been a number of other trials reported since the meta-analysis, some showing a survival benefit [11, 12], whilst others have not [13, 14]. An updated meta-analysis would be worthwhile. The majority of trials that have used the same dose of 5-FU in both arms have demonstrated at least an improvement in response rate in the combined arm, supporting the biological concept that biochemical modulation with folinic acid improves the efficacy of 5-FU. The counter argument that higher doses of 5-FU alone can give similar results does not negate the fact that biochemical modulation has a clinical effect, although it may call into question the clinical utility of biochemical modulation with folinic acid. Trials that have used higher doses of 5-FU in the control arm than in the folinic acid arm have not demonstrated any significant differences in response rates or other outcome measures tested, although there was more haematological toxicity noted in the unmodulated 5-FU arms in these trials [15, 16]. In general, 5-FU and folinic acid regimens are associated with more mucositis and/or diarrhoea, although the differences are less marked in the trials that had more dose intensive 5-FU alone control arms. It is of interest that in the SAKK trial, patients suffering $\geq$ grade 2 mucositis or diarrhoea in either the 5-FU alone or the 5-FU + folinic acid treatment arms had longer survivals [10]. The available data on the dose intensity of 5-FU support the importance of 5-FU dose and if bolus 5-FU is given without folinic acid, higher doses of 5-FU may be optimal.

A recently published meta-analysis concluded that unmodulated continuous infusion 5-FU is superior to unmodulated bolus 5-FU in terms of response rate and is associated with a slight increase in overall survival [17]. Although it has been argued on theoretical grounds that folinic acid may be more effective at modulating a continuous infusion of 5-FU than bolus 5-FU via inhibition of thymidylate synthase [18], this is not supported by the limited available clinical data [14]. As discussed by Herrmann [2], in a series of phase 2 trials performed by Spanish investigators using a weekly 48 h infusion of 5-FU, the addition of folinic acid did not appear to be beneficial. Interestingly, this group has recently demonstrated that this intermittent infusional 5-FU schedule without folinic acid results in a higher response rate but no improvement in survival when compared with bolus 5-FU and low-dose folinic acid given daily for 5 days every 4–5 weeks [19].

In the absence of a definite survival advantage, the impact on quality of life parameters should be a major consideration when choosing between 5-FU with or without folinic acid. An improved response rate without evidence of improved palliative benefit or survival is of dubious clinical significance. The NCCTG trial reported improved performance status, weight gain and symptomatic relief in the 5-FU and low-dose folinic acid arm [9]. The SAKK trial confirmed that the addition of folinic acid to 5-FU resulted in improved symptom control, but did not find any improvement in performance status and significant weight gain was in fact more frequent in the control arm [10]. The Laufman trial, which did not find a significant difference in response rates, also did not find any differences in quality of life parameters [20]. These limited data would support the concept that an improved response rate is probably a prerequisite for identifying a chemotherapy regimen that results in improved symptom control in advanced colorectal cancer, acknowledging that some patients with stable disease may also derive symptomatic benefit. However, it cannot be assumed that response will always translate into a significant palliative benefit, and, hence, it cannot necessarily be considered a surrogate measure of clinical improvement. Global quality of life measures will also be influenced by other factors such as the toxicity of the respective regimens. There are inadequate data to draw any firm conclusions about differences in overall quality of life between intensive bolus 5-FU regimens compared with standard combinations of 5-FU and folinic acid.

As this debate demonstrates, several issues regarding the optimal use of 5-FU remain unresolved. However, the time for further elucidating the benefits or otherwise of modulated bolus 5-FU relative to dose intensive bolus 5-FU as a single agent in advanced colorectal cancer has surely passed. It is time to explore other treatment approaches that may improve patient outcomes in advanced colorectal cancer. The relative merits of hybrid regimens, oral 5-FU analogues that can pharmacologically mimic continuous infusion 5-FU, and the combination of irinotecan or oxaliplatin with 5-FU or with new thymidylate synthase inhibitors such as raltitrexed, are under investigation and show considerable promise. Also under investigation are a range of emerging biological approaches and the role of molecular markers that may predict response to specific treatments. The available evidence does not allow one to be dogmatic about the choice of the control arm for randomised trials evaluating these new treatments, although bolus 5-FU with folinic acid or one of several regimens involving a continuous infusion of 5-FU would be reasonable options. Whilst individual clinicians may feel that the risk/benefit ratio may favour unmodulated, dose intensive, bolus 5-FU, it is unlikely that unmodulated bolus 5-FU would be perceived by the wider oncology community to be an acceptable control arm for clinical trials.

There are many lessons to be learned from the clinical investigation of 5-FU and folinic acid regimens. Future clinical trials in advanced colorectal cancer need to have sufficient sample sizes to detect realistic differences in survival and/or clinical benefit. A meta-analysis that includes several small and often limited clinical trials using different schedules and/or doses of drugs is unlikely to provide definitive answers, and cannot replace larger well-designed randomised trials, in which assessment of palliative benefit and quality of life has been incorporated into the initial trial design.

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