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Editorial

Second Line Treatment Options in Advanced Colorectal Cancer

J.M. Stewart, M.J. Millward and J.R. Zalcberg

Division of Haematology and Medical Oncology, Peter MacCallum Cancer Institute, Locked Bag #1, A'Beckett Street, Melbourne 3000, Australia

TOMUDEX, A new direct inhibitor of thymidylate synthase (TS), has now been approved in several countries including the U.K. and Australia, for the first line treatment of advanced colorectal cancer. Its activity is based on the results of a large multinational phase II trial [1], in which an objective response rate of 26% was reported, as well as two randomised studies conducted in Europe, South Africa and Australia. In those two trials (study 003 and study 12) objective response rates of 18.6 and 19.3% were observed, but more importantly, tomudex was equivalent to 5-FU (5-fluorouracil) and LV (leucovorin) in terms of survival and time to progression [2, 3]. In addition, both studies demonstrated the palliative benefits of tomudex, as well as a more favourable toxicity profile compared with 5-FU/leucovorin (5-FU/LV). In fact, a recent analysis of the toxicities observed in the first European and Australian randomised study (study 003) are of interest, in that female gender and increased age predicted for significantly increased grade 3 or 4 leucopenia and mucositis in patients receiving 5-FU/low-dose (LD) LV but not in those receiving tomudex [4]. This raises the consideration that relative to 5-FU/LDLV, tomudex may well be the drug of choice in older patients and particularly in older women.

However, despite the results observed in the two previously mentioned randomised studies, tomudex was significantly inferior to 5-FU/LDLV in a third randomised study conducted in North America [5]. The explanation for those differing results is difficult to understand, although full publication of this study may provide greater insight into these findings.

In this issue, Farrugia and colleagues (pp. 987–991) [6] provide some evidence that second line chemotherapy with an infusional 5-FU-based regimen (with or without mitomycin C) after first line therapy with tomudex, is an ineffective approach in advanced colorectal cancer. They report an analysis of the outcome of second line chemotherapy in 50 out of 98 evaluable patients who had received first line tomudex. The majority of patients (22) received 5-FU-based therapy (20 received infusional 5-FU combined with mitomycin C in four cases). Disappointingly, only one objective response was seen in a patient treated with infusional 5-FU and mitomycin C out of a total of 19 evaluable patients, with no responses seen when other regimens were used.

The authors suggested that, on theoretical grounds, the mechanism by which resistance to tomudex results in subsequent resistance to infusional 5-FU may be due to increased TS levels within the tumour. However, the available data concerning the importance of TS in 5-FU resistance are not clear cut. Investigators within the ECOG retrospectively assessed the prognostic importance and significance (with respect to response) of TS expression in an analysis of 120 patients entered on three phase III intergroup cancer studies (two adjuvant studies, one advanced disease study) for which tissue samples were available. Preliminary analysis of the data for patients with advanced disease showed a significant correlation between response to 5-FU-based chemotherapy and high TS levels [7]. In contrast, in a British study in which immunostaining for TS levels was performed on the primary colorectal tumours of 134 patients, presenting for palliative chemotherapy predominantly with 5-FU-based regimens, no correlation was found between the TS values and clinical endpoints such as time from diagnosis to relapse or response to chemotherapy for disseminated disease [8]. With a variety of techniques now reported as a means of measuring TS levels in tumour tissues [9] and the conflicting results reported herein, standardisation of the measurement of TS levels and a prospective analysis of the role of this enzyme in predicting outcome will be required before this prognostic marker can be applied in understanding resistance to this class of drugs.

In the subsequent resistance of colorectal tumours to 5-FU-based schedules, the importance of other mechanisms of resistance to tomudex, such as impaired drug uptake into cells by the reduced folate carrier (RFC) or its reduced polyglutamation [10], also need to be considered. This is particularly relevant where the regimen involves the use of leucovorin, which is also transported into tumour cells via the RFC and requires polyglutamation. Pre-clinical studies in human colorectal cancer (HCT-8) sublines [11] have suggested that the mechanism of action of 5-FU is schedule-dependant, with bolus 5-FU working mainly through incorporation into

Correspondence to J.R. Zalcberg.
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RNA and infusional 5-FU through the inhibition of TS. Therefore, at least on theoretical grounds, the use of either infusional 5-FU or tomudex can be associated with a number of related changes in cells, so that in future studies, measurement of critical parameters determining drug activity may be a useful way of clarifying potential means of bypassing these resistance mechanisms.

Although Farrugia and colleagues have not documented TS levels in their paper, this group has been involved in the assessment of TS as well as molecular and/or biochemical markers as determinants of response [12]. For instance, in a preliminary report examining predictors of response and toxicity in patients with advanced colorectal cancer treated with tomudex, pre-treatment levels of folylpolyglutamyl synthetase (FPGS), TS mRNA, TS protein and p53 and post-treatment, polyglutamated drug levels and TS levels were measured, thus demonstrating the feasibility of such an approach [12].

As all patients with advanced colorectal cancer receiving first line tomudex will ultimately progress or relapse, the study by Farrugia and colleagues [6] is important, as it is the first to analyse the activity of 5-FU-based therapy as second line therapy after the use of tomudex. Using response criteria alone, the authors concluded that single agent infusional 5-FU is not effective in this setting. In fact only 19 of the 50 patients receiving second line therapy were evaluable for response with infusional 5-FU (+/− MMC) giving a response rate of 5.3% (1/19) but with 95% confidence limits of 0.13 to 26%. Given that infusional 5-FU plus mitomycin C (which does not act via TS) has been reported to be more active than infusional 5-FU alone in a randomised trial [13], the single objective response to this schedule in this study, albeit anecdotal, is of interest. However, it needs to be stressed that response criteria should not be the only ones used to assess the benefit of second line chemotherapy in this setting. The failure to address a variety of other endpoints including quality of life, physical symptoms, etc. leaves the readers without the means to assess fully the clinical benefit of second line chemotherapy in this group of patients.

Clearly, the role of the increasing number of promising new drugs as second line therapy is best explored in prospective, randomised trials after evidence of some activity in the phase II setting. For example, CPT-11 appeared to have some activity in patients resistant to 5-FU, with response rates of 15–22% [14] being reported in phase II studies. More recently [15], there has been the suggestion of a survival benefit associated with CPT-11 when patients with progressive metastatic colorectal caner after 5-FU-based therapy were randomised to CPT-11 or best supportive care (BSC). However, alternative endpoints such as improvements in physical symptoms and/or quality of life (QOL) would be acceptable evidence of the benefit of treatment in this setting.

The combination of oxaliplatin and 5-FU has also shown promise. In one study, response rates of 46% in 46 patients previously treated with 5-FU/LV and 43% in 22 patients refractory to 5-FU/LV were reported [16]. Unlike other platinum compounds, oxaliplatin has not been associated with nephrotoxicity and causes minimal myelosuppression. Whether this will translate into tangible benefits in the setting of a randomised trial remains unclear. We await phase III data with appropriate QOL as well as survival endpoints.

More recently, phase I trials have explored the combination of CPT-11 and oxaliplatin, given the synergistic effect seen in pre-clinical studies and lack of overlapping toxicities. These trials have demonstrated the feasibility of combining these two drugs and the activity of the combination in patients who had progressed during or after 5-FU-based therapy [17, 18].

In considering the reverse scenario, the place of tomudex in patients who have previously received 5-FU, has also not been clearly defined. *In vitro* data suggest incompletely overlapping activity spectra [19] and additional pre-clinical data suggest that this may be dependent on the specific 5-FU schedule. For example, tomudex appeared to be active in cell lines rendered resistant to 5-FU with a 1 h 5-FU schedule but not with a 24 h schedule [20]. Johnston and colleagues demonstrated sensitivity to 5-FU in two human cell lines resistant to tomudex despite expressing markedly elevated TS levels [21]. However, the only available clinical data is from a US-based phase I study of tomudex in 32 previously treated patients, most of whom had initially received 5-FU-based therapy for advanced colorectal cancer. This study did not identify any evidence of anti-tumour activity. In a small subset of patients, high intratumoral TS levels were identified in the primary tumours [22].

A more definitive study of the role of tomudex in metastatic colorectal cancer after prior 5-FU-based therapy was recently completed by ECOG. This study compared patients (in a non-randomised design) who had received no previous treatment with those who had received a prior 5-FU-based regimen with leucovorin or a 5-FU-based regimen without leucovorin. This study, which included the measurement of TS levels, will hopefully provide some information about the potential cross-resistance between 5-FU and tomudex as well as clinical rationale for phase I studies of tomudex and 5-FU in combination.

For the practicing clinician wishing to use first line tomudex, the appropriate regimen for second line therapy is still not clear. This paper suggests that infusional 5-FU is not the answer. However, to address this formally, there need to be prospective randomised trials with appropriate QOL endpoints, in which CPT-11 alone (subject to a more detailed analysis of the toxicity and benefits of the recent study of CPT-11 [15] versus BSC) should arguably be the control arm.

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