Thymidine Phosphorylase (TP) Activation: Convenience Through Innovation

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The management of patients with metastatic colorectal cancer most commonly involves treatment with 5-fluorouracil (5-FU), administered with or without leucovorin (LV) as an i.v. bolus or protracted infusion. Protracted infusion schedules have demonstrated superior efficacy compared with bolus regimens [1], but are associated with greater inconvenience and cost. Complications can also arise from the use of indwelling catheters [2].

The oral fluoropyrimidines have been developed to avoid some of these problems. Among the most promising of the oral agents is capecitabine (Xeloda®), a novel fluoropyrimidine carbamate that mimics continuous-infusion 5-FU. Capecitabine is metabolized to 5-FU via a three-step enzymatic cascade, the third step of which is mediated by thymidine phosphorylase (TP). TP, also known as platelet-derived endothelial cell growth factor, is correlated with poor prognosis, fast malignant growth, aggressive invasion potential, and anti-apoptotic properties. Preclinical studies have shown that TP is significantly more active in tumor tissue than in adjacent healthy tissue [3]. Capecitabine exploits the higher intratumoral concentrations of TP to achieve tumor-selective generation of 5-FU, resulting in increased concentrations of 5-FU in the tumor [4]. This tumor selectivity potentially reduces systemic exposure to 5-FU, improving efficacy and enhancing tolerability.

Capecitabine has demonstrated considerable single-agent activity as first-line treatment for metastatic colorectal cancer. Data from two large, randomized, phase III clinical trials demonstrated that capecitabine results in a significantly superior tumor response rate compared with i.v. 5-FU/LV (Mayo Clinic regimen) and equivalent time to disease progression and overall survival [5]. Capecitabine also demonstrated an improved safety profile compared with i.v. 5-FU/LV. On the basis of these trials, capecitabine has recently been approved in Europe, the U.S., Canada, and numerous other countries for the first-line treatment of metastatic colorectal cancer.

Another important advance in the treatment of colorectal cancer has been the introduction of two new agents, irinotecan and oxaliplatin. Irinotecan monotherapy is now an established treatment for patients with colorectal cancer that has progressed with prior 5-FU-based therapy [6, 7]. More recently, phase III trials have shown that the addition of irinotecan to bolus or infused 5-FU/LV in the first-line setting results in significantly improved survival [8, 9]. The addition of oxaliplatin to 5-FU/LV has also been shown to increase activity in both the first- and second-line settings [10-13], and the use of oxaliplatin, particularly in Europe, is widespread.

As an oral fluoropyrimidine with high single-agent activity and a favorable safety profile, capecitabine potentially provides a more effective, convenient, and better-tolerated alternative to 5-FU/LV in these combination regimens. Phase I/II trials have already evaluated capecitabine in combination with oxaliplatin and irinotecan, with encouraging results. In addition, capecitabine is being investigated in combination with radiotherapy in rectal cancer. There is a strong preclinical rationale for exploring this combination, as TP activity in the tumor is upregulated by irradiation. Phase I and II trials have shown that the combination is feasible, and capecitabine may have the potential to replace i.v. 5-FU as a combination partner for radiotherapy in the treatment of rectal cancer [14].

This supplement provides an in-depth review of a large, European meeting in which leading experts gathered to discuss the state-of-the-art in the treatment of colorectal cancer [15]. Topics covered include the clinical trial data of irinotecan and oxaliplatin, the different strategies for incorporating these novel agents into clinical practice, and the
REFERENCES