Foreword

UFT/LV: a novel concept in the chemotherapy of metastatic colorectal cancer

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Fluorouracil is one of the most widely used drugs for the systemic treatment of metastatic colorectal cancer. Over the past 45 years, treatment with intravenous (IV) fluorouracil has involved bolus schedules, continuous infusions using permanent venous-access devices or portable infusion pumps, and biochemical modulation with folinic acid [1]. However, there has also been considerable research into the use of oral fluorouracil prodrugs. Recent research has focused on the development of an orally administered fluorouracil prodrug, that has equivalent efficacy and improved tolerability compared with IV fluorouracil, and offers patients a more convenient and preferential mode of administration.

Tegafur is a prodrug of the antineoplastic agent fluorouracil, and is coadministered with uracil so as to enhance the cytotoxicity of the fluorouracil generated from tegafur [2,3]. Phase I/II studies demonstrated the efficacy and safety of oral tegafur-uracil (UFT), with evidence of increased antitumour activity when combined with oral leucovorin (LV) [4–7].

The encouraging response rates and acceptable safety profile shown with UFT plus LV initiated two large, randomised phase III studies of this combination versus IV fluorouracil plus LV (Mayo regimen) in patients with previously untreated metastatic colorectal cancer [8,9]. Dosing schedules comprised UFT at 300 mg/m^2/day and LV 75–90 mg/day divided in 3 daily doses for 28 days every 35 days, or IV fluorouracil 425 mg/m^2/day and LV 20 mg/kg/day for 5 days every 28 [8] or 35 days [9].

The primary endpoint was survival in one phase III trial [8] and, as demonstrated by the hazard ratio of 0.964 (95.6% confidence interval [CI]: 0.826–1.125) for the IV to oral chemotherapeutic regimens, survival in both treatment groups was equivalent. In the other phase III trial [9], the primary endpoint was time to progression. Although there was a statistically significant difference in favour of 5-FU/LV, this difference was only 9 days. Of note, disease assessments were performed at different timings in the two treatment arms due to the different duration of chemotherapy (5 weeks cycle UFT/LV and 4 weeks cycle of 5-FU/LV). Data also confirmed equivalence between treatments in tumour response, duration of response and time to response.

With regard to tolerability, UFT/LV demonstrated a significantly improved safety profile over IV fluorouracil/LV. Patients treated with UFT plus LV had significantly less myelosuppression, resulting in fewer episodes of febrile neutropenia and documented infections. Substantial safety benefits were also found with UFT/LV in the reduction of non-haematologic toxicities. The incidence of diarrhoea, nausea and vomiting, stomatitis, and mucositis was significantly less frequent with UFT/LV than IV fluorouracil/LV. Also, in both studies severe stomatitis and mucositis were significantly less prevalent in patients who received oral therapy. The lower incidence of these events in the UFT/LV treatment arm was reflected in the reduced need for concomitant anti-infectives and antiemetic medication, and fewer hospitalisations. Hand–foot syndrome (palmar–plantar erythrodysesthesia) was uncommon in either treatment group, but fewer cases were reported in patients treated with UFT/LV than IV fluorouracil/LV.

Overall these data indicate that UFT/LV provides effective and well tolerated first-line chemotherapy in advanced colorectal cancer. The substantially improved safety profile was achieved while maintaining an efficacy equivalent to that of conventional IV fluorouracil/LV.

Considerable progress has been made in recent years in the treatment of advanced colorectal cancer, as shown by improvements in survival rates, tumour response and better control of disease-related symptoms. As the role of chemotherapy in the management of metastatic disease is developed, a number of issues remain to be fully elucidated, including:

- choice of first- and second-line treatment regimen
- use of combination versus sequential therapy
- choice of infused 5-FU, or oral fluoropyrimidines
- extent of treatment duration
- patient suitability for combination therapy as first-line treatment
- role of chemoradiation therapy
- role of maintenance or intermittent chemotherapy.

Further to information from clinical trials, our knowledge of the use of chemotherapy can be widened from experiences within clinical practice. During a round table meeting in Nice, October 2002, a group of delegates presented case studies and discussed their use of UFT/LV in patients with advanced colorectal cancer.

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