Oxaliplatin and raltitrexed combined with leucovorin-modulated 5-fluorouracil i.v. bolus every two weeks: A dose finding study in advanced previously treated colorectal carcinoma

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Summary

Purpose: To determine the maximum tolerated dose of oxaliplatin (L-OHP) given as a two-hour infusion followed by raltitrexed (Tomudex® [TOM]) administered as a 15-min infusion on day 1, and bolus 5-fluorouracil (5-FU) modulated by a fixed dose of levo-folinic acid (LFA) 250 mg/m² on day 2, recycling every two weeks, and to have preliminary evidence of activity of this combination in pretreated advanced colorectal cancer patients.

Patients and methods: Fifty-two patients with advanced colorectal carcinoma previously treated with one (25 cases) or two or more lines of chemotherapy, including irinotecan (26 cases), and/or modulated 5-FU (40 cases) entered this study. Starting doses of L-OHP, TOM, and 5-FU were 85, 2.5 and 750 mg/m², respectively.

Results: Seven dose levels were tested. Neutropenia was the main dose limiting toxicity of the dose escalation (8 of 13 cases). The recommended doses were 130 mg/m² of L-OHP, and 3.0 mg/m² of TOM on day 1, followed by 250 mg/m² of LFA, and 1050 mg/m² of 5-FU on day 2, every two weeks. Severe diarrhoea and stomatitis were rarely reported. Most patients complained of mild peripheral sensitive neurotoxicity, which was related to the cumulative dose of L-OHP. Twelve patients were considered as having a major responses (one complete), and an additional eight patients showed a minor response; the median time to treatment failure was twenty-four weeks.

Conclusions: With this regimen it is possible to give full doses of all three cytotoxic drugs every two weeks. Its activity and its manageable toxicity profile deserve further evaluation in pretreated advanced colorectal cancer patients.

Key words: colorectal carcinoma, dose-finding study, modulated 5-fluorouracil, oxaliplatin, raltitrexed, triplet combination

Introduction

5-fluorouracil (5-FU) is still the mainstay of management for advanced colorectal carcinoma, although its activity is limited to a small proportion of treated patients. Intracellular biochemical modulation of 5-FU by means of folic acid (FA) or methotrexate has been seen to increase its cytotoxicity, but the impact of this approach on survival has been negligible [1, 2]. Therefore, new active drugs or combination chemotherapies for the treatment of these patients are eagerly awaited. Among the new drugs recently tested against colorectal carcinoma, raltitrexed, irinotecan, and oxaliplatin have shown promising activity as single agents, and they are now being intensively investigated in combination chemotherapy.

Raltitrexed (Tomudex® [TOM]) is a novel direct and specific thymidylate synthase (TS) inhibitor, which do not require intracellular modulation and is devoid of non-specific effect on RNA. Administered on a 3-weekly schedule, TOM has shown an overall activity rate in patients with advanced colorectal carcinoma comparable to 'standard' 5-FU + FA regimens in three randomised trials [3–5]. No substantial differences in median survival time (MST) were reported in two of these trials, while in one of them a slightly shorter MST was obtained for patients treated with TOM [5]. Due to its favourable toxicity profile, TOM is a good candidate for combination with other cytotoxic drugs, and with 5-FU. Indeed, preclinical studies in HCT-8 colon carcinoma cell line have demonstrated a synergistic activity between TOM and 5-FU when a 24-hour of exposure to TOM was followed by a short (4-hour) exposure to 5-FU; interestingly, only a marginal synergy was obtained with the same sequence but with a prolonged (5-day) exposure to 5-FU [6]. Moreover, some phase I studies in colorectal cancer patients have shown that a dose of TOM ≥ 2.5 mg/m² administered before 5-FU significantly increases its peak concentration and AUC, regardless of the duration of 5-FU infusion (bolus or 24-hour) [7, 8]. To better investigate the interaction between TOM and 5-FU, our group has conducted a series of in vitro experiments with
three colon cancer cell lines (Lovo, GEO and SW620) and three head and neck cancer cell lines (KB, ZA, HOC313). These were exposed to different concentrations of TOM alone, 5-FU ± LFA, or TOM plus 5FA±LFA, given simultaneously or with a 24-hour interval. A clear synergism between TOM and 5FA + LFA was observed when TOM preceded the short exposure to 5FA + LFA in all tested cell lines, while the reverse sequence or the concomitant exposure reduced the inhibition of cell growth as compared to TOM alone [9]. These results prompted us to perform a dose finding study to assess the maximum tolerated doses (MTDs) of TOM (given a short i.v. infusion on day 1) and LFA-modulated 5-FU (given as i.v. bolus on day 2), recycling every two weeks. We found that TOM (3 mg/m²) can be safely administered before LFA (250 mg/m²) and FU (1050 mg/m²). Interestingly, among the 40 advanced colorectal carcinoma patients admitted to this study (mostly pretreated with fluoropyrimidines) we observed six major (three complete) responses, for an overall activity rate of 15% [10]. It seemed therefore that the administration of TOM prior to 5-FU + LFA was able to overcome the resistance to 5-FU + LFA in a significant proportion of patients.

Oxaliplatin (L-OHP) has been shown to exert a definite activity as single agent in advanced colorectal carcinoma. As first line treatment, L-OHP given at 130 mg/m² has an average activity in 18% (range 12%-24%) of patients [12, 13]. In second line, about 10% of patients previously treated with 5-FU show a response to L-OHP [14]. Preclinical observations suggest that L-OHP has synergistic antitumor activity with 5-FU in murine leukaemia cell cultures transplanted into mice and in human colonic xenografts either sensitive or resistant to 5-FU [15–17]. These findings represented the rationale for combining L-OHP with 5-FU + LFA in the treatment of patients with colorectal carcinoma. However, the best way to combine them is still under investigation. Empirically, in initial clinical studies either a constant (flat) or a chronomodulated infusion for both cytotoxic drugs has been utilised. Both modalities of infusion obtained encouraging response rates in chemonaive patients, and in a comparative trial the chronomodulated infusion performed better than the flat one as well as showing a lower acute toxicity [18]. Also in pretreated patients, a number of flat or chronomodulated schedules every two or three weeks were tested, and objective response rates in 31% and 40% (cumulative data), respectively, were reported [19, 20]. No clinical experience has been reported about the combination of L-OHP and 5-FU given as i.v. bolus. However, a preclinical study recently conducted on four human colorectal cancer cell lines (COLO 205, SW 620, CAL 14, WIDR), which tried to better explore the interaction between L-OHP and 5-FU, with or without the addition of FA, clearly showed that the cytotoxicity of the L-OHP + 5-FU combination was significantly different on all tested cell lines according to the 5-FU exposure type: the short (two-hour) exposure was better than the mixed one (two-hour followed by a seven-fold lower concentration for 20-hour) mimicking the 'De Gramont regimen', and this latter resulted better than the continuous (118-hour) exposure. When the L-OHP + FU/FA combination was analysed, it was demonstrated that the presence of FA significantly enhanced the cytotoxicity of L-OHP + FU, regardless of FU exposure type [21]. The above mentioned findings do not lend support for using infusional 5-FU (either flat or chronomodulated) in combination with TOM or L-OHP, while represent a strong rationale for trying the bolus administration.

On the other hand, also the combination of TOM and L-OHP has recently been investigated. A dose finding trial has been conducted in France, reporting that full doses of both agents (3 mg/m² and 130 mg/m², respectively) could be given together every three weeks [22]. The subsequent phase II study in chemonaive patients with colorectal carcinoma reported with this regimen an impressive overall response rate (40%), suggesting a possible synergism between the two drugs [23].

With these considerations in mind, we decided to perform a disease oriented dose finding study on the combination of L-OHP, TOM and modulated 5-FU in advanced colorectal carcinomas, with the aim of defining the toxicity profile of this new regimen, and to have preliminary evidence of activity in previously treated patients. Since L-OHP has been used both in two- and three-weekly schedule [11], and taking into account our previous experience about TOM and 5-FU biweekly combination [10], also in this study we tried to recycle the treatment every other week, because in this way a more frequent exposure of tumour cells to phase specific drugs like TOM and 5-FU is obtained.

Patients and methods

Patient selection

Candidates for this study were patients affected by histologically proven metastatic carcinoma of the colon or rectum. These patients should have a disease progressing or recurring within 3 months from previous standard chemotherapy used in either the adjuvant setting or to treat metastastic disease. Patients should have at least one bi-dimensional measurable indicator lesion. Other eligibility criteria included an age more than 18 years, the discontinuation of previous chemotherapy for at least 4 weeks, an adequate bone marrow reserve (absolute neutrophil count (ANC) ≥ 1500/mmc, platelet (PLT) count > 100,000/mm², haemoglobin level ≥ 9.5 g/dl, bilirubin serum level ≤ 1.25 x upper normal limit (UNL), ASAT & ALAT ≤ 2.5 x UNL. Exclusion criteria were a performance status ≥ 3 of the World Health Organisation (WHO) scale, the presence of brain metastases, a life expectancy < 12 weeks, uncontrolled metabolic disorders or active infections. Written informed consent was required from each patient before the admission to this trial, that was approved by the Ethical Committee for Biological Research of the National Tumour Institute of Naples.

Patient accrual

At least three patients were entered in each dose level. If one of three patients experienced dose limiting toxicity (DLT), three additional patients were enrolled at the same dose level. The dose escalation was
stopped if ≥2/3 or ≥4/6 patients experienced a DLT. This dose level was identified as the maximum tolerated dose (MTD), and the preceding dose level was recommended for phase II study. DLT was defined as follows: ANC < 500/mm^3 lasting more than seven days, or ANC < 100/mm^3 lasting more than three days; ANC < 500/mm^3 with fever > 38°C; PLT count < 25,000/mm^3, or PLT count < 50,000/mm^3 with bleeding; any WHO grade 3 or 4 non-hematologic toxicity (except alopecia and vomiting); a delay of more than two weeks in treatment recycling.

**Dose escalation plan**

We planned to sequentially increase the doses of all three cytotoxic drugs through seven dose levels. The starting doses were 85 mg/m^2 for L-OHP, 2.5 mg/m^2 for TOM, and 750 mg/m^2 for 5-FU (preceded by a fixed dose of LFA, 250 mg/m^2). Through three following levels, we alternately increased 5-FU and TOM to reach the dose of 1050 mg/m^2 and 3.0 mg/m^2, respectively. In the fifth and sixth levels, L-OHP dose was escalated to 110 mg/m^2 and 130 mg/m^2, respectively, while in last level tested, we tried a further increase of 5-FU to 1200 mg/m^2. Doses were assigned at registration, and no intrapatient dose escalation was permitted.

**Administration of chemotherapy**

L-OHP powder was reconstituted with, and diluted in a 5% dextrose solution (2 litres) administered as a two-hour i.v. infusion, on day 1. TOM was given diluted in 100 ml of saline solution as a short (15 min) i.v. infusion at the end of L-OHP on day 1. On the following day, LFA (diluted in 2 litres of normal saline) was administered as a two-hour i.v. infusion. 5-FU was then given as an i.v. bolus. A standard anti-emetic premedication, including i.v. HT3-receptor antagonists and steroids, was given on the first day of each cycle.

**Recycling rules and doses reduction**

Courses were repeated every two weeks in the presence of ANC ≥1500/mm^3 and PLT count ≥100,000/mm^3, and recovery of any extra-hematologic toxicity. Otherwise, a one to two week delay was allowed. In the presence of WHO grade 4 hematologic toxicity, or in the presence of grade 3-4 non-hematologic toxicity, the subsequent cycles were administered, after recovery of side effects, with a 25% dose reduction of all cytotoxic drugs. In cases of grade 3 neurotoxicity according to the modified Lévi scale (see below), L-OHP was temporarily discontinued, and it could be resumed at 75% of the initial dosage only after the complete recovery of this toxicity.

**Evaluation of toxicity**

For the assessment of acute toxicity, blood cell counts will be performed weekly, and two times a week in cases of grade 4 toxicity. Biochemistry was performed before each cycle. Neurological examination to detect any sign of neurotoxicity was be performed at initial treatment, and at every cycle thereafter. The acute toxicity was classified according to WHO toxicity criteria [24]. Neurotoxicity was graded according to a modified Lévi scale [25] as follows: grade 1 was a peripheral paraesthesia and/or dysesthesia completely disappearing within one week; grade 2 was a peripheral paraesthesia and/or dysesthesia lasting from one to two weeks; grade 3 was peripheral paraesthesia and/or dysesthesia persisting after two weeks; grade 4 was peripheral neurotoxicity with functional impairment.

**Evaluation of activity**

At entry, all patients were submitted to routine chemistry, blood cell count, CEA and CA 19.9 serum level determinations, chest X-ray and abdominal ultrasound scan. Indicator lesion(s) was measured with CT or MNR imaging. Endoluminal recurrent or unresected disease was evaluated with fiberoptic endoscopy. The following criteria were adopted for grading the response: a complete response (CR) was defined as a complete disappearance of all known localizations for at least one month; a more than 50% reduction of the sum of the products of two largest perpendicular diameters of each measurable lesion was require to qualify for a partial response (PR), while a reduction > 25% was classified as minor response (MR). Patients showing an increase > 25% of tumour burden, or appearance of new lesions, were judged in progression of disease (PD), while those that did not meet the criteria for minor response or progressive disease were considered as no change (NC) [24]. To classify the type of response, all initially abnormal tests were repeated after every four cycles of treatment.

The time to treatment failure (TTF) has been calculated from the date of study entry to date of discontinuation of treatment for any cause (progression of disease, death, toxicity or refusal). The survival time for each patient has been calculated from the date of study entry to the date of death or last follow-up. Estimations of TTF and survival were made with the Kaplan–Meier method.

**Results**

**Patient population**

From 28 August 1998 to 12 August 1999, a total of 52 consecutive patients entered into this study. The main characteristics of this case series are reported in Table 1. Many patients had a good performance status, but 27 of them suffered from disease-related symptoms, and 10 had had a significant weight loss. All but one had already received one (48%) or more (50%) lines of chemotherapy, that included 5-FU in 77%, and irinotecan in 50% of the cases. As far as previous treatment is concerned, 28 patients (54%) were considered refractory or resistant because of absence of any response to one (14 patients) or two lines (7 patients) of chemotherapy, or because of appearance of recurrence within 3 months from the discontinuation of chemotherapy (7 patients). Sixteen patients (31%) had one documented site of disease, while twenty-five patients (48%) had two sites, and eleven (21%) of them three or more sites. The most common metastatic site was the liver, followed by the lung and lymph nodes. Fifteen patients also had an unresected primary (3 cases), or a local recurrence after radical surgery (12 cases).

All patients received at least one (range 1–16) course of chemotherapy, with a median number of six courses per patient. All but one patient, who refused further therapy and was lost to follow-up after the first cycle, were evaluated for DLT and cumulative toxicity.

**Dose escalation**

Dose escalation tested seven dose levels (Table 2). Only one case of DLT neutropenia was reported among the six patients entered in the first dose level, and only one case among the six following patients treated with 900 mg/m^2 of 5-FU. In the third level, the increasing dosage of TOM to 3.0 mg/m^2 caused three different episodes of DLT (neutropenia, diarrhoea, and stomatitis, respec-
A total of 322 treatment cycles were administered; the median number of cycles per patient was 6 (range 1–16). Twenty-one patients received at least eight cycles, seven patients received at least nine cycles, and five patients received twelve cycles. Eight patients received fewer than four cycles, due to early progression (2), death (1), refusal (2), or toxicity (3). Twenty patients (38%) underwent a dose reduction: two patients each at first and second dose levels, three patients each at the third and fourth dose level, four patients at the fifth level, six patients at the sixth level and three patients at the seventh level. As a consequence of delays or dose reductions, the mean actually delivered dose intensity (DI) of L-OHP over the first four cycles was 33 mg/m²/wk (78% of the intended one) for the patients entered in the first four dose levels tested (85 mg/m² of L-OHP), while it was 44 mg/m²/wk (68% of the planned) for the patients entered in the last two dose levels (130 mg/m² of L-OHP). The mean DI of TOM (excluding the patients treated with the starting dose of 2.5 mg/m²) was 1.0 mg/m²/wk (70% of the planned one). Finally, for patients entered at the 5-FU dose level of 1050 mg/m², the mean 5-FU DI was 370 mg/m²/wk (70% of planned).

At the 6th dose level tested, which was identified as the MTD, the previous dose level was better evaluated for cumulative toxicity and activity treating a total of 13 patients.

**Study treatment exposure**

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**Acute hematologic toxicity**

Considering all cycles administered at each dose level, neutropenia was the most frequently encountered hae-
matological side effect (Table 3). Indeed, 35 patients (69%) showed during their treatment some reduction of neutrophil count, that was of grade 3 in 11 patients (22%), and of grade 4 in 15 patients (29%). However, neutropenia was usually transient and uncomplicated, and only 4 episodes of neutropenic fever were registered. A mild (no grade 3 or 4) decrease of platelet count was detected in five patients (10%). A mild-moderate anaemia was more frequently observed, affecting 13 patients (25%), but packed red cell transfusions were never required.

Non-hematologic toxicity

Despite the prophylactic administration of HT3-receptor antagonists, nausea or mild vomiting affected 34 patients (67%), while a vomiting requiring repeated doses (after the prophylactic administration) of anti-emetics occurred in 4 patients. Stomatitis or diarrhoea occasionally occurred in 15 and 14 patients, respectively, during their treatment, but only 4 cases each of severe episodes were recorded. Seven (14%) patients complained of some kind of fatigue attributable to therapy, which in one patient caused the refusal of further treatment after four cycles. Two patients suffered from cardiac dysfunction during their therapy: besides the above mentioned episode of arrhythmia occurring after the first cycle in a 69-year-old patient, a ventricular tachycardia occurred in a 57-year-old female after her sixth cycle, causing the discontinuation of treatment. A total of 25 (49%) patients complained of sensitive neurotoxicity caused by L-OHP administration: this side effect appeared as a typical hand and foot paraesthesias and dysaesesthesia triggered by exposition to cold temperature, also occurring among patients entered in the initial dose levels tested, after a mean of 6 (range 2-12) courses of chemotherapy, corresponding to a cumulative L-OHP dosage included between 510 and 780 mg/m² (Table 4). Some patients occasionally reported pharyngeal constriction while drinking cold beverages; in three cases, an acute episode of laryngeal spasm occurred during the L-OHP infusion. Some degree of hair loss was observed from initial dose level tested, and affected 12 patients on the whole, but it was complete in only 1 patient. Mild liver enzyme derangement was occasionally found in two cases. No renal toxicity was recorded.

In the whole series, six patients interrupted the treatment early: one patient was lost to follow-up after the first cycle, another one required the discontinuation of treatment after two cycles because of an allergic skin reaction, while four patients were withdrawn by the attending physician because of occurrence of troublesome toxicity: laryngeal spasm during L-OHP infusion (two patients), severe diarrhoea or neutropenic fever (one case each).

Activity

Although the evaluation of activity was not a primary end point of this study, 46 patients were assessable for

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* One patient was not evaluated.
response after a minimum of 4 cycles of treatment. Indeed, as above reported, six patients received fewer than four cycles, due to refusal (two cases), or to an early discontinuation for toxicity (four cases). Objective responses were observed from initial dose level tested (Table 5). It is worth noting that a CR was obtained in a patient entered at the fourth dose level, who had liver and lung metastases not responding to a previous LFA + 5-FU daily times 5 monthly regimen. The complete disappearance of secondary deposits in both locations was recorded within 14 weeks from the start of treatment, and it persisted after 26+ weeks. Eleven PRs were reported across all dose levels, after seven to thirteen (median 10) weeks of chemotherapy, and lasting from nineteen to fifty-five (median 24) weeks. These major responses were obtained in patients with one site (1 case), two sites (10 cases), or even three sites of disease (1 case). Therefore, a total of 12 patients showed a significant reduction of tumour burden during their treatment, corresponding to an overall activity rate of 26% (95% confidence interval (95% CI): 14%-41%) of adequately treated patients, or of 22% (95% CI: 12%-37%) of the whole series (intention to treat analysis). Furthermore, 8 additional patients, obtained a MR that lasted 17–42 weeks.

Apart from the response obtained in the sole chemonaive patient of this series, all other responses were achieved in patients previously treated with one (10 patients) or two or more (9 patients) lines of chemotherapy. In all these patients, a 5-FU-based chemotherapy had been already used, and 11 of them had been also exposed to irinotecan. Fifteen patients showed a stabilisation of their disease for a minimum time of 10+ (median 23) weeks. As of 31 October 1999, with a median potential follow-up of 43 weeks for the whole series, the median time to treatment failure (TTF) was 24 weeks. Fifteen patients (28%) had a TTF longer than twenty-six weeks. Eighteen patients have died so far; the median survival time is 51 weeks, and the one-year probability of survival is 44%.

### Discussion

The primary objective of this dose finding study was to determine the MTD and the recommended dose of L-OHP combined with TOM and modulated 5-FU administered every two weeks in pretreated colorectal cancer patients. Indeed, in our previous experiences we had already demonstrated that full doses of TOM and modulated bolus 5-FU could be safely given in a biweekly regimen, obtaining an interesting activity in colorectal carcinoma [10, 27]. On the other hand, L-OHP has been extensively investigated in colorectal carcinoma, alone or in combination with infusional 5-FU [11], but no information is available in literature about its addition to bolus 5-FU, although some recent in vitro studies point to explore this regimen [21].

The MTD of this study was identified as to be the dose level 7 (L-OHP 130 mg/m², TOM 3.0 mg/m², and 5-FU 1200 mg/m²), because four of eight patients showed a DLT after the first cycle. The recommended dose for further phase II studies was 130 mg/m² for L-OHP plus 3.0 mg/m² for TOM on day 1, and 1050 mg/m² for 5-FU (preceded by LFA, 250 mg/m²) on day 2. At these recommended doses, the main severe (grade 4) toxicity is neutropenia, affecting 31% of patients. However, neutropenia was usually short-lasting, and only one episode of neutropenic fever was registered. Moreover, 10 of the patients entered at the recommended dose level, who received ≥4 cycles of chemotherapy, had a mean actually delivered dose intensity of L-OHP (44 mg/m²/wk) slightly higher than the one projected with the starting dose level (42.5 mg/m²/wk). This finding may be of clinical relevance, since the achievement of a dose intensity for L-OHP ≥85 mg/m² every two weeks combined with high-dose infusional 5-FU has been recently related to a higher response rate (39% vs. 19%), and to an improved six-month freedom from progression (52% vs. 36%) in pretreated patient with colorectal carcinoma [26].

As far as neutropenia is concerned, its occurrence was probably higher than expected, although we would remember that our patients were heavily pretreated (half of them had received two or more lines of previous chemotherapy). Indeed, severe neutropenia was not a common side effect in chemonaive patients receiving L-OHP as a single agent [11–14], nor chronomodulated with 5-FU over five days [18]. However, grade 3 or 4 neutropenia affected 39% of patients receiving L-OHP (two-hour) on day 1 followed by high-dose leucovorin and 5-FU infusion over 48 hours [19]. On the other hand, we have extensively explored the sequential administration of TOM followed by modulated 5-FU i.v. bolus [10, 27]. Occurrence of neutropenia was not a major problem with this regimen, neither in chemonaive [27], nor in pretreated patients [10]. Therefore, we may hypothesise that the administration of all three drugs together may produce an overlapping toxicity on bone marrow myelopoiesis.

It is worth noting, in our opinion, that the regimen tested in the current trial showed a definite activity in
heavily pretreated patients with colorectal carcinoma. Twelve patients (23%) obtained a major response (1 complete) with this regimen, regardless of the dose level utilised, and an additional eight patients (15%) showed a significant tumour shrinkage that did not qualify for a major response, while a stable disease was seen in fifteen patients, so that a temporary disease control was reached in 67% of patients. Although the follow-up was not long enough to obtain mature survival data, we would stress than the median TTF was around six months. This finding is encouraging, since our study population included many patients considered refractory to 5-FU and/or to irinotecan.

Since the combination of 5-FU and irinotecan will be increasingly used for the treatment of the advanced disease, and is also currently evaluated in the adjuvant setting for surgically resected patients, there is an urgent need to develop alternative, non-cross-resistant regimens for patients that will eventually recur after adjuvant or first line treatment. The capability of L-OHP, added to standard bolus or infusional 5-FU regimen, to obtain further objective responses in patients progressing during first or even second line therapy has already been reported [28, 29]. Also in vitro studies have recently shown that that addition of L-OHP to 5-FU can overcome the resistance to 5-FU of a human colon carcinoma cell line [30]. However, when testing the activity of L-OHP on a colony forming units assay, the growth inhibition of cells either sensitive or resistant to 5-FU or irinotecan was both concentration and time dependent. Indeed, a significant activity was seen only when a concentration ≥ 5 μg/ml of L-OHP, in short (one-hour) or long (14-day) exposure, was used [31], pointing to the clinical relevance of reaching and maintaining in treated patients such a concentration for an adequate time.

On the other hand, TOM seems to show an incomplete cross-resistance with 5-FU, as proved by the 16% overall activity (with 46.5% of patient showing stable disease) yielded in a series of previously treated colorectal cancer patients [32]. Furthermore, also in our previous experience [27], as in those of other authors [7, 8], the toxicity profile of treatment did not worsen when TOM was combined with modulated 5-FU. In addition, there is some evidence that TOM preceding 5-FU may increase its AUC [7, 8], probably through an interference with the DPD activity of the host [10]. Moreover, in vitro experiments have shown that the pre-exposure to TOM may also promote the intracellular 5-FU nucleotide formation by means of an indirect effect on purine biosynthesis, leading to a five to six-fold increase of intracellular level of phosphoribosylpyrophosphate. The same authors have also noted that the addition of folic acid not only did not reverse the synergistic effect but possibly enhanced it [6].

Also in this study we have pursued the biweekly schedule, because it permits a more frequent exposure of tumour cells to phase specific drugs like TOM and 5-FU, and it may also allow increasing the dose intensity of TOM. Indeed, besides the standard regimen [3], there has recently been some interest in exploring other scheduling of TOM: several investigators have tried to increase the dose of TOM [33, 34], or to administer it weekly or biweekly [35, 36]. Some of these trials have already demonstrated that TOM can be given at 3.5 mg/m² [33], or even at 4.0 mg/m² [34], every three weeks, without causing unacceptable toxicity. In weekly regimen, TOM has been safely escalated to 1.5 mg/m², with the main toxicity being only transient transaminases elevation [36].

But a clinical synergism between L-OHP and TOM should also be postulated to explain the impressive overall activity (40%) obtained with such combination in chemo-naive colorectal cancer patients [23]. In this report, full doses of L-OHP (130 mg/m²) and TOM (3.0 mg/m²) were given every three weeks. Based on the results of our present trial, we conclude that these same doses, followed by modulated bolus 5-FU, can be given safely every two weeks. A currently ongoing phase II study will better elucidate the role of this new regimen in colorectal cancer patients already pretreated with 5-FU and irinotecan.

References

11. Raymond E, Chaney SG, Taamna A, Cvitkovic E. Oxaliplatin:


33. Vincent M, Keller O, Maroun J et al. A phase II trial of higher dose (3.5 mg/m²) raltitrexed (Tomudex®) in advanced colorectal cancer. Proc ASCO 1999; 289a (Abstr 1108).


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