

Dose escalating clinical study of high dose infusional 5-fluorouracil and leukovorin (AIO regimen) plus alternate weekly administration of oxaliplatin and irinotecan in patients with advanced tumors of the gastrointestinal tract

I. Gkioulbasanis¹, J. Souglakos¹, N. Vardakis¹, A. Kotsakis¹, Z. Saridaki¹, N. Kentepozidis², A. Polyzos³, S. Giassas², M. Ignatiadis¹, V. Bozionelou¹, C. Christophylakis⁴, V. Georgoulis¹

¹Department of Medical Oncology, University General Hospital of Heraklion, Crete; ²Department of Medical Oncology, "Iaso" General Hospital of Athens; ³Medical Oncology Unit, 1st Department of Propedeutic Medicine, University of Athens, "Laikon" Hospital, Athens; ⁴Medical Oncology Unit, "401" Military Hospital of Athens, Athens, Greece

Summary

Purpose: To determine the dose-limiting toxicities (DLTs) and the maximum tolerated doses (MTDs) of weekly high dose 5-fluorouracil (5FU) continuous infusion and leukovorin (LV) alternatively combined with oxaliplatin and irinotecan in patients with advanced tumors of the gastrointestinal (GI) tract.

Patients and methods: Patients received a fixed dose of LV (500 mg/m²) over 2 h infusion on weeks 1 to 4 and escalated doses of: oxaliplatin (starting dose 65 mg/m²; 120 min i.v. infusion on weeks 1 and 3); irinotecan (starting dose 80 mg/m²; 90 min i.v. infusion on weeks 2 and 4) and 5FU (starting dose 1500 mg/m²; 22 h continuous i.v. infusion, on weeks 1 to 4), in cycles of 5 weeks. DLTs were evaluated during the first cycle.

Results: Twenty-eight patients were treated on 8 dose

levels and all but two patients received the regimen at least as second-line treatment. The DLT level was reached at the oxaliplatin dose of 90 mg/m², irinotecan dose of 110 mg/m², LV dose of 500 mg/m² and 5FU dose of 1750 mg/m²; the recommended MTDs were 85 mg/m² for oxaliplatin, 110 mg/m² for irinotecan, 1750 mg/m² for 5FU and 500 mg/m² for LV. Grade 3 or 4 diarrhea and grade 3 nausea/vomiting were the dose-limiting events. Diarrhea was the most common toxicity of the regimen, occurring in 12 (42.8%) patients. Hematological toxicity was mild and there were no treatment-related deaths.

Conclusion: This weekly regimen showed a favorable toxicity profile and merits further investigation in patients with advanced/metastatic tumors of the GI tract.

Key words: 5-fluorouracil, gastrointestinal tumors, irinotecan, leukovorin, oxaliplatin, phase I

Introduction

Historically, chemotherapy was used for palliation of symptoms in patients with tumors of the GI tract. During the last few years the median overall survival of patients with advanced colorectal cancer (CRC) has

been substantially increased from 12 months to about 21-22 months when all of the available chemotherapeutic agents have been administered [1]. During the same period, the median survival of patients with metastatic tumors of the upper GI tract remains unchanged despite the fact that new active anticancer drugs have been introduced in our armamentarium. Among them, irinotecan and oxaliplatin have proved their activity against a variety of GI tumors.

The 1, 2-diaminocyclohexane (DACH) platinates differ from similar agents such as cisplatin and carboplatin in that they do not present free amino groups linked to platinum, but rather a cyclic, bulky, rigid structure. DACH-platinates combine with DNA to form adducts resistant to DNA repair and replicative bypass. Of the several DACH platinum derivatives, oxaliplatin [trans-1-1,2-diaminocyclohexane-oxalo-

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Author and address for correspondence:

Vassilis Georgoulis, MD, PhD
University General Hospital of Heraklion
Department of Medical Oncology
Voutes, P.O. Box 1352
711 10 Heraklion
Crete, Greece
Tel: +30 2810 392783
Fax: +30 2810 392857
E-mail: georgsec@med.uoc.gr

platinum; LOHP (II)] is the only agent to have successfully reached clinical use [2]. *In vitro* studies in colon cancer cell lines have reported that the combination of oxaliplatin with thymidilate synthase inhibitors (i.e. 5FU) demonstrates a synergistic effect [3,4]. In combination with traditional 5FU/LV regimens, oxaliplatin has shown significant activity against CRC [5] and tumors of the upper GI tract [6-8].

Irinotecan is a hemisynthetic, water soluble derivative of the plant alkaloid camptothecin. After conversion to its active metabolite, SN-38, irinotecan acts by inhibiting the eukariotic enzyme DNA-topoisomerase I [9,10]. This unique mechanism of action of irinotecan opens the opportunity for combinations with other non-cross resistant chemotherapeutic agents. Irinotecan has been proven effective for the treatment of patients with CRC [11,12] and also for the treatment of patients with other malignancies of the GI tract [6,13-15].

Preclinical studies indicated a higher schedule-dependent interaction by exposing HT29 and LoVo cancer cells first to oxaliplatin followed by 5FU, compared with the reverse sequence. It is interesting that this scheduled-dependent interaction was observed in both 5FU-sensitive and 5FU-resistant cells [16]. In addition, other *in vitro* data also suggested increased activity of the combination of SN-38 and 5FU when cells were firstly exposed to SN-38. The German Association of Medical Oncology (AIO), in a multicenter phase I trial in metastatic CRC, demonstrated an overall response rate of 64% using a weekly-times-six schedule of irinotecan (80 mg/m²) and high dose LV (500 mg/m²) followed by infusional high dose (2600 mg/m²) 5FU [17].

The aim of the present study was to develop a dose-dense schedule, which could be administered in a variety of solid tumors (ie: colorectal, gastric, head and neck etc); therefore, a phase I study was conducted in order to define the DLTs and the MTDs of oxaliplatin, irinotecan, which were administered alternatively every other week, combined with weekly infusional high dose LV and 5FU.

Patients and methods

Patients' selection

Patients with histologically confirmed solid tumors of the GI tract were eligible for the study. Other eligibility criteria were: age > 18 years; performance status [World Health Organization (WHO)] 0-2; adequate blood counts (absolute neutrophil count >1500/ μ L, hemoglobin >10 mg/dL and platelets >100000/ μ L); adequate renal (serum creatinine < 2 mg/dL), and he-

patic (total bilirubin < 1.5 mg/dL and SGPT/SGOT < 3 times the upper normal limit) function; pre-existing peripheral neuropathy (National Cancer Institute -NCI) \leq grade 1; life expectancy of at least 3 months; at least 4 weeks have to had been elapsed from prior irradiation which should not exceeded in >25% of the bone marrow. Patients with chronic diarrhea (>3 months), obstruction of the alimentary canal or total colectomy, as well as patients with symptomatic brain metastasis despite central nervous system irradiation were excluded from the study. Finally, patients ought to be free from any severe neurological or psychiatric disease that could affect their compliance. All patients signed written informed consent before study entry. The study was approved by the Ethics and Scientific Committees of our Institution.

Pretreatment evaluation

Patient's evaluation included a detailed medical history and physical examination, a complete blood cell count (CBC) with differential and platelet counts, whole blood chemistry, electrocardiograph, computed tomography (CT) scans of the abdomen and the chest, as well as a chest x-rays within the past month. Other imaging studies were performed according to patient's symptoms and the physician's clinical judgment. Pretreatment evaluation had to be performed within two weeks prior to study enrollment.

Treatment

LV was given at a fixed dose (500 mg/m² over a 2 h i.v. infusion) on weeks 1 to 4. Escalated doses of oxaliplatin (Eloxatin[®]; Sanofi-Aventis, Collegenille, USA), were administered on day 1 of the 1st and 3rd week of the cycle, (starting dose 65 mg/m² with increments of 10 mg/m²) given as a 2 h i.v. infusion in parallel with LV, but using different lines. Irinotecan (Camp-to[®], Pfizer Pharmaceuticals, NY, USA) was administered at escalated doses (starting dose 80 mg/m² with increments of 10 mg/m²) given over a 90 min i.v. infusion on day 1 of the 2nd and 4th week, of the cycle. Irinotecan was administered according to the guidelines used for irinotecan monotherapy, including recommendations for using atropine and loperamide. Escalated doses of 5FU were, then, administered; (starting dose 1500 mg/m² with increments of 250 mg/m²) given as a 22 h continuous i.v. infusion on day 1 of weeks 1 to 4 of the cycle. Treatment was administered every week for 4 consecutives weeks, followed by a 1-week rest, until disease progression, unacceptable toxicity or consent withdrawal. Routine antieme-

tic prophylaxis with a 5-hydroxytryptamine-3-receptor antagonist was used.

During treatment, a CBC was performed weekly and in cases of grade 3-4 neutropenia or febrile neutropenia or thrombocytopenia it was performed daily until hematologic recovery. In addition, patients were clinically assessed and routine biochemical tests were performed before each cycle of treatment. Response to treatment was evaluated after 3 cycles or sooner if clinically indicated. Toxicity was also recorded in every cycle based on the NCI-CTC criteria [18].

Chemotherapy was delayed for 1 week if neutrophils were $<1.5 \times 10^9/L$, platelets $<100 \times 10^9/L$ or in case of persisting severe non-hematological toxicity. Doses of irinotecan and oxaliplatin were reduced by 15% in subsequent cycles in case of grade 4 neutropenia or in case of febrile neutropenia. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was not allowed. Doses of 5FU and irinotecan were reduced by 15% in subsequent cycles in case of grade 3-4 diarrhea and in case of grade 2 or 3 neutropenia combined with grade 2 diarrhea. If grade 2 neurosensory toxicity occurred, the oxaliplatin dose was to be omitted for at least one cycle. Oxaliplatin was omitted from the next cycles in case of grade 3 and 4 neurotoxicity or in case of severe functional impairment. The 5FU dose was reduced by 20% in case of $>$ grade 1 mucositis or dermatitis.

Dose escalation

At least 3 patients were enrolled at each dose level. If a DLT was observed in one of the first 3 patients, then 3 additional patients were enrolled at the same dose level. No intra-patient dose escalation was allowed.

DLTs were assessed during the first chemotherapy cycle with the exception of neurotoxicity that was assessed during the whole treatment period. Any of the following was defined as DLT: any grade 4 hematological toxicity, grade 3-4 neutropenia with temperature $>37.5^\circ C$, grade 3-4 non-hematological toxicity except alopecia and nausea, every treatment delay due to treatment-related toxicity, as well as grade 3 neurotoxicity at any time during treatment. Dose escalation was discontinued and DLT level was reached if at least 50% of the patients treated at that level developed a DLT (e.g. at least 2 of 3 or 3 of 6 patients). The MTD dose level was defined as the first level below the DLT dose level.

Tumor response

Although bi-dimensionally measurable disease was not required in order to enroll patients onto study,

response was assessed according to the RECIST criteria for those who did [19]. Therefore, evaluation of response was performed in patients with measurable disease who had completed at least 2 chemotherapy cycles.

The duration of the response was measured from the first documentation of response to disease progression. The time to tumor progression (TTP) was determined by the interval between the initiation of treatment and the date when disease progression was first documented. Overall survival was measured from the date of registration to the date of death. The follow up time was measured from the date of first treatment administration to the last contact or death.

Results

Patient characteristics

Twenty-eight patients with advanced tumors of the GI tract were enrolled onto the study. Their characteristics are presented in Table 1. The median age was 64 years and the majority of them had a diagnosis of CRC (82%) and were males (61.5%). Twenty-three (82%) of the patients had a PS of 0-1 and all (93%) but two were pre-treated with at least one chemotherapy regimen for metastatic disease. All patients were evaluable for toxicity.

Toxicity

The dose escalation levels, the number of patients enrolled at each dose level and the observed DLTs during the first cycle of treatment are presented

Table 1. Patient characteristics

| <i>Characteristic</i> | <i>Patients</i> | <i>%</i> |
|-----------------------------|-----------------|-----------|
| Number of patients enrolled | 28 | 100 |
| Sex | | |
| Males/ females | 16/12 | 57.1/43.9 |
| Median age, years (range) | 64 (31-76) | |
| Performance status (WHO) | | |
| 0 | 13 | 46.4 |
| 1 | 10 | 35.7 |
| 2 | 5 | 17.9 |
| Primary site | | |
| Colorectal | 23 | 82.1 |
| Stomach | 2 | 7.1 |
| Pancreas | 2 | 7.2 |
| Esophagus | 1 | 3.6 |
| Prior chemotherapy | | |
| Adjuvant | 2 | 7.1 |
| 1 line | 8 | 28.6 |
| 2 lines | 12 | 42.9 |
| ≥ 3 lines | 6 | 21.4 |

enrolled at the 3rd, 7th and 8th dose level; all of the responders were suffering from CRC and the treatment was 3rd line for the complete responder, 2nd line for 2 of the partial responders while the other partial responder received the regimen as 4th line of treatment.

Among the 12 patients with tumor growth control, 3 (25%) were considered as "resistant" to 2 drugs and 6 (50%) to 3 drugs. The median TTP was 4.0 months (range 1.0-14.5) and the median overall survival 13.1 months (range 1.4-37.0). The 1 year survival rate was 52.5%.

Discussion

The present study demonstrates that the alternative administration of oxaliplatin and irinotecan every 2 weeks in combination with weekly high dose LV/5FU in patients with advanced GI tumors is feasible and well tolerated. The MTD of the combination was reached at the dose level of LV 500 mg/m², 5FU 1750 mg/m², oxaliplatin 85 mg/m² and irinotecan 110 mg/m². No patient treated at that dose level developed any grade 3 or 4 toxicity. In addition, the administration of the combination demonstrated a favorable safety profile since the majority of adverse events were mild to moderate in intensity; indeed, the most frequently observed toxicities were grade 2 fatigue and grade 3 diarrhea, while no grade 4 hematological toxicity was reported. The cumulative grade 2 and 3 neurotoxicity was 7.1% and 0%, respectively.

Different schedules of administration of all the active drugs against CRC within the same regimen, some of which were chronomodulated, have been explored in phase I/II studies, in variable treatment combinations [20-25]. Rubio et al. [26] have shown that an every-3-week regimen of weekly bolus 5FU/LV and day-1 oxaliplatin and irinotecan resulted in significant rates of grade 3/4 neutropenia and febrile neutropenia, as well as diarrhea, leading to omission of the day-8 dose of 5FU. Goetz et al. [27] reported that weekly or every 3-weeks addition of oxaliplatin in a weekly regimen of irinotecan and 5FU/LV was associated with similar types and frequencies of toxicities. On the contrary, Roth et al. [28] using an every-5-week regimen of alternating weeks of oxaliplatin (days 1 and 15) and irinotecan (days 8 and 22) given together with weekly 24 h infusional FU/LV (days 1, 8, 15, and 22) reported a lower incidence of neutropenia (20%) and febrile neutropenia (7%), while diarrhea, the main non-hematological toxicity, was 23%. Additionally, Cals et al. [29] reported a phase I study with an alternating regimen of oxaliplatin and irinotecan combined with 24 h

infusional 5FU without LV. The recommended phase II doses were consequently different in this study. In the last 2 studies with a quite similar design the observed toxicity profile is practically comparable with that observed in the present study.

Although response to treatment was not a primary endpoint, the observed 16% objective response rates could be considered as promising in this particular group of patients who were heavily pretreated, since 64% of them had already received at least 2 lines of chemotherapy prior to enrollment. It is interesting to note that, based on the classical clinical criteria, 2 of the responders had resistance to irinotecan and 5FU and the other 2 patients to irinotecan, oxaliplatin and 5FU. It is unclear whether the use of higher doses of oxaliplatin, irinotecan or 5FU may account for the observed efficacy of the regimen since 2 out of 4 patients achieving an objective response were treated with lower doses (within the 2nd and the 3rd dose level).

The combination of irinotecan, oxaliplatin and 5FU/LV gave the highest objective response rates in the chemotherapy-naïve patients with advanced CRC [20]. An Italian phase II trial exploited the increased antitumor activity of the above triplet combination to render resectable initially unresectable metastatic CRC [30]. Moreover, the activity of subsequent second-line treatment in patients who received all of the known active chemotherapy drugs upfront was not impaired [31]. Finally, the combination of irinotecan, oxaliplatin and 5FU/LV has also been shown to be active as front-line treatment of patients with metastatic gastric carcinoma [32].

In conclusion, the administration of irinotecan and oxaliplatin alternating every other week combined with high dose infusional 5FU/LV could be an interesting therapeutic option for pretreated patients with CRC, especially taking into account its excellent toxicity profile. In addition, the combination of this regimen with monoclonal antibodies which target EGFR or VEGF will be of great interest.

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