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Raltitrexed + irinotecan as second-line chemotherapy in elderly patients with advanced colorectal cancer

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ABSTRACT

Aims and Background: Irinotecan is a standard option for relapsed/refractory advanced colorectal cancer. Combination with raltitrexed and irinotecan at lower than MTD doses should preserve disease stabilisation while decreasing toxicity. Patients and Methods: From January 2004 to April 2009, we analyzed, retrospectively, our data on irinotecan + raltitrexed, fixed doses, as a second-line chemotherapy in elderly patients (>70 years) with advanced colorectal cancer after failure of oxaliplatin based chemotherapy twenty-three patients were evaluated. Irinotecan 350 mg + raltitrexed 2.6 mg were given every 3 weeks. Tumo *r* measurements were obtained after every third course of therapy. Toxicity was assessed weekly using the National Cancer Institute Common Toxicity Criteria, version 2. Results: The median number of treatment courses received per patient was 4 (range, 1 - 8). All patients were assessable for toxicity and 21 for response. The most frequently observed severetoxicities were diarrhea (grade 2, 13%) No cases of significant neutropenia occurred. Objective partial responses were observed in 3 patients (13%). An additional 10 patients (43%) had stable disease as their best response. To date, 12 patients have progressed with a median time-to-progression of 4.3 months and a median survival of 8.3 months. Conclusions: A three weekly irinotecan + raltitrexed administration can induce tumor control in elderly patients with advanced colorectalcancer that has progressed during or shortly after oxaliplatin-based chemotherapy. The diarrhea by irinotecan, seems mitigated by coadministration of a smaller dose of raltitrexed

Keywords: Colorectal; Elderly; Irinotecan; Second-Line; Unresectable

1. INTRODUCTION

Irinotecan (CPT-11), a DNA topoisomerase I inhibitor, has demonstrated antitumor activity as a single agent in the second-line treatment of advanced colorectal cancer (ACC) [1,2]. In Europe, the drug was developed as a 3-weekly regimen (350 mg/m^2 every 3 weeks), whereas in the USA, a weekly regimen (100 - 125 mg/m^2/week for 4 consecutive weeks out of 6) wasevaluated 3 - 5. In patients with 5-fluorouracil (5-FU)-refractory disease, these phase II trials demonstrated objective response rates of 12% to 15% and median survivals of 8 to 9 months. However, the major toxicities encountered with these regimens were grade 3 for diarrhea, neutropenia, nausea and vomiting, and alopecia. Several randomized studies have studied the optimal regimen for single-agent CPT-11. In the first study, CPT-11 was administered weekly (125 mg/m^2), once every 2 weeks (250 mg/m^2) or once every 3 weeks (350 mg/m^2), or as a continuous infusion (10 mg/m^2/day, 14-day continuous infusion every 3 weeks). It was concluded that the 3-week and 2-week regimens showed better tolerance and induced higher response rates than the weekly regimen 6. In another study, CPT-11 schedules of weekly (125 mg/m^2) and of once every 3 weeks (350 mg/m^2) demonstrated similar efficacy and quality of life. However, the 3-week regimen was associated with a significantly lower incidence of severe diarrhea 7. By adding raltitrexed to 3 weekly irinotecan, diarrhea and neutropenia were decreased. By lowering the dose to the lowest one active for both drugs, we hoped to avoid the neutropenia associated with three weekly irinotecan, whilst maintaining an easy outpatient regimen conceived for elderly patients risk. Due to the physiological reduction of functional organ reserve and the presence of comorbid conditions, elderly patients are often excluded from clinical trials. These subjects frequently suffer from tumor-related symptoms and need some kind of palliative treatment. In clinical practice, they often receive inadequate and untested treatments [9, 10]. The aforementioned trials did not obtain exhaustive

information on the CPT-11 activity and tolerability in this subset of patients. From January 2004 to April 2011, we retrospectively collected our data on elderly patients with ACC responding to defined selection criteria and treated with irinotecan + raltitexed as second-line treatment following 5-FU/oxaliplatin-based therapy.

2. PATIENTS AND METHODS

2.1. Patient Selection

Patients with the following inclusion criteria were considered for retrospective analysis: histologically confirmed ACC; age 70 years; performance status PS) 2 (Eastern Cooperative Oncology Group); at least one bidimensionally measurable lesion; disease progression during or within 6 months of 5-FU/oxaliplatin-based chemotherapy for advanced disease; radiotherapy acceptable if it was completed 3 weeks before the start of CPT-11 chemotherapy and not including the only site of measure able disease; adequate hematologic reserve and hepatic and renal function, documented by WBC 3000 mm^3, absolute neutrophil count 1500 mm^3, hemoglobin level 9.0 g/dL, platelets 100,000 mm^3, serum bilirubin 1.5 mg/dL, AST (SGOT) 3x and 5x upper level of institutional normal if liver metastases were present), and serum creatinine 2.0 mg/dL. Patients with metastatic involvement of the CNS, a psychiatric disorder that could interfere with treatment compliance, significant concurrent infection or concurrent or previous malignancy, or significant cardiac disease were excluded.

2.2. Staging, Response and Toxicity Evaluation

Retrospectively analyzed patients were assessed according to usual clinical practice including a complete medical history and a general physical examination. Tumor staging was assessed by a two-view chest X-ray, upper abdomen ultrasound and, when appropriate, diagnostic scans (*i.e*., computed tomography, magnetic resonance imaging, or bone scan). Complete blood cell counts with platelet and differential counts were obtained weekly during chemotherapy. Serum chemistries were repeated at least once every course. Physical examination, tumour marker levels (CEA and Ca 19.9) and radiologic tumour parameter assessment were obtained every 3 cycles of treatment. The World Health Organization (WHO) criteria were used for the definition of response, response duration, time to progression (TTP), and survival1. 1) Decreased tumour marker levels were considered useful for monitoring therapy in patients whose CEA and CA 19-9 had been elevated at baseline, but were not used to evaluate the response. All adverse reactions were recorded before each chemotherapy course. Toxicities were scored according to the standard National Cancer Institute common toxicity criteria, version. 2) The worst experienced grade was recorded for each patient and type of toxicity.

2.3. Statistical Methods

Duration of response was calculated from the first documentation of response to disease progression or last examination. TTP was determined by the interval from the beginning of therapy to the date when disease progression was first documented. Survival was measured from the date of registration to the date of death. Patients dying before completion of restaging were defined as "progressed" on the date of death.

Overall survival from the date of the beginning of 5-FU/oxaliplatin-based first-line chemotherapy was also calculated.

3. TREATMENT

The analysis was conducted in one centre. Patients received irinotecan 350 mg (1 h infusion) + raltitrexed 2.5 mg (15 min infusion) on days 1 repeated every 3 weeks. Corticosteroids and granisetrons were delivered before each chemotherapy infusion to prevent emesis. Primary prophylaxis with Granulocyte Colony-Stimulating Factor (GCSF) was not allowed. On days 1 the minimum requirements for chemotherapy administration were a neutrophil count of 1500 mm^3, a platelet count of 100,000 mm^3, a hemoglobin level 9.0 g/dL, and no sign of organ toxicity (excluding alopecia).

For the patients who experienced hemoglobin levels <10 g/dL, the recombinant human erythropoietin was admitted. Loperamide, 2 mg orally every 2 hr, was recommended in the event of delayed diarrhoea and discontinued 12 h after the last liquid stool. If diarrhoea was not under control after 48 hr, other supportive measures, including hospitalization for iv rehydration, were prescribed. In case of appearance of grade 3 - 4 diarrhoea, a 20% dose reduction was chosen for the subsequent courses. Treatment was administered until evidence of disease progression, unacceptable toxicity or patient refusal.

4. RESULTS

4.1. Patient Demographics

Twenty-three patients treated in the involved institution were analyzed. Their characteristics are shown in **Table 1**. The median age of patients was 75 years (range, 70 - 89), and 10 patients (43%) were 75 years old or older. Patients generally had widespread disease, with the most frequent distant sites including liver, lung, and peritoneum. Six patients (26%) had received prior radiotherapy.

Table 1. Main characteristics of the study patients.

Characteristics	All patients (%)
No. of patients	23 (100)
Gender	
Male	11 (48)
Female	12 (52)
Age (yr)	
Median	75
Range	70 - 79
Primary site	
Colon	15 (65)
Rectum	8 (35)
Site of metastases	
Liver	15 (65)
Local (recurrent)	5 (22)
Lung	5 (22)
Peritoneum	4 (17)
Lymph nodes	2 (9)
Bone	2 (9)
Involved sites	
1	14 (61)
2	7 (30)
>2	2 (9)
ECOG performance status	
0	11 (48)
1	12 (52)
Previous therapy	
Surgery	23 (100)
First-line chemotherapy	23 (100)
Radiotherapy	4 (17)

4.2. Treatment Duration

A total of 114 cycles of treatment were administered, with a median of 4 cycles per patient (range, 1 - 8). Four patients (17.3%) received less than three cycles because of disease progression, 2 patients (8.6%) received less than three cycles because of adverse events.

Nevertheless, all of the patients evaluated were considered assessable for efficacy and toxicity. There were no cases of significant delay or dose reduction due to neutropenia.

The median relative dose intensity value was 95%.

4.3. Tumor Response and Survival

In our analysis, the overall response rate was 13%.The median duration of response was 4.1 months (range, 3 - 7+). In addition, 10 patients (43.4%) maintained stable disease, and another 10 patients (43.4%) had disease progression. The median follow-up for alive patients was 10.4 months. At the time of analysis, the median TTP was 4.3 months (range, 1 - 8+) and the median survival was 8.3 months (range, 1 - 16+). Excluding those patients not truly assessable, the response rate reached was 14.2%. The overall median survival from the beginning of the first-line chemotherapy exceeded 18 months.

5. SAFETY

The main severe hematologic toxicity was neutropenia, which was grade 3 in 30.4% and no grade 4 toxicity. Diarrhoea was the main non-hematologic toxicity, but grade 2 diarrhoea occurred in 13% of patients. One patient reported severe diarrhoea not responsive to rescue Anemia, fatigue, and alopecia were frequent toxicities.

Table 2. Results.

	Total no. (%)
Patients entered	23 (100)
Patients assessable	21 (97)
Response	
CR	- (0)
PR	3 (13)
SD	10 (43.4)
PD	10 (43.4)
Response rate	13.0
Median duration, months	
Response rate	4.1
Range	3 - 7+
TTP	4.3
Range	1 - 8+
Survival, months	8.3
Range	1 - 16+

CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; TTP, time to progression.

Table 3. Different authors on second line irinotecan (or combinations) after oxaliplatin.

author	year	1st	2nd	number	RR	PFS (months)	reference
Tournigand	1999	folfox	folfiri	34	6	4	21
Maindrault	2000	folfox	folfiri	22	20	not	24
Louvet	2007	folfox	pem/iri	44	14	not	23
Sorbye	2007	folfox	folfiri	59	7	4.1	25
Recchia	2004	folfox	folfiri	35	20	7.1	27
Marbro	2004	folfox	Folfiri-3	65	17	4.1	26
our series	2009	xelox	Tom-iri	23	13	4.2	

No thromboembolic phenomena occurred. No treatment high-dose loperamide administration. This required hospital admission related death was reported. The incidence of any cholinergic symptom was significantly low (2 patients, 8.6%).

6. DISCUSSION

The treatment of elderly patients is an emerging issue. Although irinotecan monotherapy is recognized as the treatment of choice in second-line therapy (after failure of 5-FU) in ACC, unfortunately only a few studies have evaluated its feasibility in elderly patients. Most of the trials enrolled patients with a cut-off age ranging from 60 - 65 years, probably not representative of a real elderly population. Nevertheless, a higher rate of adverse events was detected in a CPT-11 study in patients 65 years compared with patients younger than 65 years (rate of grade 3 and 4 diarrhoea, 39% and 19%, respectively) [5], although this has not been confirmed in other studies [12,13]. The dose-limiting toxicities for CPT-11 are delayed diarrhea and neutropenia [14,15]. However, toxicity patterns depend on the CPT-11 schedule. Grade 3 - 4 diarrhea occurred in 36% of the patients treated on a weekly basis and in 19% of those treated once every 3 weeks (P = 0.002) in the trial of Fuchs *et al.* [7], providing comparative data on the efficacy, tolerability, and effect on quality of life between the schedules. A higher treatment-related mortality rate was noted among patients receiving weekly CPT-11 (5.3%) than among those given the every-3-weeks schedule (1.6%), although this difference was not statistically significant. In the weekly group, at least three of five treatment-related deaths were caused by diarrhoea and dehydration. In contrast, grade 3 - 4 neutropenia appeared slightly more frequent in the every 3 weeks schedule (34% vs 29%), but this difference was not statistically significant. On the other hand, the randomized phase II study of Schoe maker *et al.* [6] reporting severe neutropenia in 34% of the patients treated once every 3 weeks and in 25% of those treated weekly , also supports the idea that these differences in toxicity profile are probably related to the administration schedule rather than the dose per cycle. Adding raltitrexed to three weekly irinotecan proved to decrease diarrhoea. In our study, we used lower doses of both drugs, while maintaining its efficacy; in comparison to other second line regimens.

The objective response rate (13%) is consistent with those reported in the analysis of pooled data from 455 patients from European studies and 304 patients from American studies [4,18,19]. The median TTP of 4.3 months and the median survival of 8.3 months are similar to those of the aforementioned pooled data analysis (**Table 3**). Interestingly, we observed that the overall median survival from the beginning of the first chemtherapy exceeded 18 months. These data prompted us to use a second-line chemotherapy in the elderly after first-line failure. This finding suggests that it is important to make all drugs that have well-demonstrated clinical activity in ACC available to all patients to guarantee maximal benefit of systemic therapy for survival, as mentioned in the analysis of Grothey *et al.* [19]. Actually, this schedule should be prospectively used as a skeleton of active and lower dose of chemotherapy to which targeted treatments should be added.

The advent of several biologic agents such as cetuximab and bevacizumab, which demonstrated to be beneficial and tolerable without adding supplementary toxicity has revolutionazed the management of metastatic colon cancer. Determining a chemotherapeutic basis to whom these drug can be added will become a major issue, especially in elderly patients. However, it is important to bear in mind that our patients were a subpopulation of elderly patients characterized by a good general condition. Therefore, these data cannot be extrapolated to the

elderly population in general, but must be confirmed by randomized prospective studies.

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