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ORIGINAL RESEARCH

Three Weekly Irinotecan and Bolus 5-Fluorouracil Combination in the First Line Treatment of Advanced Gastric Cancer A Single Institution Experience

Dr Mohamed Mesmoudi[a], MD, Pr Tarek Mahfoud[b], MD, Pr Samir Ahid[c], MD, Dr Nabil Ismaili[d], Dr Saber Boutayeb[c], Pr Hassan Errihani[e].

[a] Department of medical oncology, Regional Oncology Center, Tangier, Morocco.
[b] Department of Medical Oncology, Military Hospital Mohammed V, Rabat, Morocco
[c] Department of biostatistics, Mohamed V University, Rabat, Morocco.
[d] Department of Medical Oncology, Mohammed VI University Hospital, Marrakech, Morocco.
[e] Department of medical oncology, National institute of oncology, Rabat, Morocco.

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ABSTRACT
Background: The goal of this study is to determine the efficacy and toxicity of a non-platinum based chemotherapy combination using irinotecan associated to bolus 5-FU as first line treatment in advanced gastric cancer. **Materiel and methods:** Retrospective analysis of a population of patients treated for metastatic and locally advanced gastric cancer with irinotecan and 5-FU as upfront chemotherapy. **Results:** Thirteen patients were enrolled. The median age was 56 years. Seven patients were males and six were of females. Ten patients had a metastatic disease and three patients had a locally advanced disease. Patients received a total number of 43 cycles of chemotherapy. Overall response rate was 38,4%, median time to progression (TTP) was 3 months, and median overall survival was 4 months. Three patients (23,1%) presented grade 3 /4 neutropenia complicated with an infectious episode with fever in two cases, three patients (23,1%) required blood transfusion for a grade 4 anemia, and one patient (7,6%) was hospitalized for a severe episode of diarrhea. **Conclusion:** Three weekly irinotecan and bolus 5-FU is an interesting combination as first line treatment of advanced gastric cancer; designed clinical trials are needed to confirm the activity of this combination.

KEY WORDS: Advanced gastric cancer, Irinotecan, Bolus 5-FU, First line treatment.

Corresponding author:
Dr Mohamed Mesmoudi, Department of medical oncology, Regional Oncology Center, Tangier, Morocco.
E-mail: mohamedmesmoudi@yahoo.fr.

INTRODUCTION
Irinotecan (CPT11) is a camptothecin analog that acts on cells by inhibiting DNA topoisomerase-I through one of its metabolites, namely SN-38, it is widely used in the treatment of metastatic colorectal cancer, and its use is limited by severe toxicities such as neutropenia and delayed-type diarrhea [1].
In 1994, Futatsuki et al reported that CPT11 showed activity against advanced gastric cancer with a generally reversible toxicity [2], consequently the drug was tested with different combinations in patient pretreated for advanced gastric cancer, and in 2001, Blanke et al reported the first phase II trial of upfront chemotherapy based on CPT 11 and 5-FU combination in the treatment of 36 patients presenting an advanced gastric carcinoma; the response rate (RR) was 22%, median time to progression (TTP) was 4.4 months, and median survival time (MS) was 7.6 months [3]. Wang et al reported a pooled analysis of clinical trials in the first line treatment of advanced gastric cancer and proved that CPT11 containing combinations are superior to non CPT11 containing combinations in term of time to treatment failure with no significant toxicity [4]. Basing on this background, and looking to avoid the systemic hydration needed for cisplatin

administration, we have opted for a treatment based on the association of CPT11 and bolus 5-FU.
The aim of this study is to report a retrospective analysis of the population of patients treated with the described combination of chemotherapy.

MATERIALS AND METHODS

We reviewed the clinical records of all patients with advanced gastric cancer who have been treated with irinotecan associated to 5-FU from January 2007 to January 2010. Selected patients were those with histologically confirmed gastric adenocarcinoma and a metastatic or a locally advanced disease. Patients treated up front with chemotherapy based on CPT 11 and 5-FU were included. Evaluation of tumor response was performed using response evaluation criteria in solid tumors (RECIST). Tumor measurement was performed based on the reports from physical examination and CT scan, serum tumor markers were not used in the evaluation of response. Median time to progression (TTP) was measured from the initiation of treatment until the progression of disease, death from any cause or to the date of last follow-up. Median survival time (MS) was measured from the initiation of treatment to the date of death or to the date of the last follow-up. Toxicity was evaluated in accordance with the National Cancer Institute Common Toxicity Criteria (NCI-CTC).Statistical analyses were performed using SPSS software (Version 17).

RESULTS

Patient Characteristics

13 patients were enrolled, the median age was 56 year (range, 38–81 year), 7 patients were males and six were of females (53,8% and 46,2% respectively). Five patients (38,4%) had an ECOG performance status (PS) of 2.
All patients had measurable tumor lesions at the initiation of chemotherapy, ten patients (76,9%) had a metastatic disease and three patients (23,1%) had a locally advanced disease. Peritoneum (46,2%) and liver (38,4%) were the most common metastatic sites, three patients (23,1%) had lung metastases, one patient had supraclavicular metastatic lymphadenopathy, and one woman had a Krukenberg tumour. One case (7,6%) had more than 3 organs involved by gastric cancer metastasis, and four cases (30,8%) had two organs involved.

Characteristics	Number (%)
Gender	
Male/Female	7/6 (53,8/46,2)
Median age	56 years (38-81)
ECOG PS	
0-1/2	8/5 (61,6/38,4)
Histological type	
Dissociated cell carcinoma/ Non dissociated cell carcinoma	7/6 (53,8/46,2)
Metastatic/Locally advanced	10/3 (76,9/23,1)
Number of involved organs	
1	5 (38,4)
2	4 (30,8)
≥3	1 (7,6)
Total	10 (76,9)
Organ involvement	
Liver	5 (38,4)
Peritoneum	6 (46,2)
Lung/Pleura	3 (23,1)
Ovary	1 (7,6)
Distant lymph nodes	1 (7,6)

Table 1: Patient's characteristics (N=13).
ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Drug delivery and objective responses (Table 2)

The treatment schedule used for all patients was: CPT11 (270 mg/m2 in a 2-h infusion) on day 1, associated to Leucovorine (20mg/m2) and bolus 5-FU (375 mg/m2) each delivered on day 1 to 5. Treatment cycles were repeated every 21 days. Atropine was routinely administered at a dose of 1mg. All patients were treated until disease progression or occurrence of unacceptable toxicity. Forty three treatment cycles were delivered with a median of 3 cycles per patient (range, 1–6). Dose reduction was required in five patients (38,4%). All patients were assessable for treatment response.
The overall response rate was 38,4%, one patient (7,6%) achieved a complete response (CR), and 4 patients (30,8%) achieved a partial response (PR). Two patients (15,4%) had stable disease (SD).

	N	%
CR	1	7,6
PR	4	30,8
SD	2	15,4
PD	6	46,2
ORR	5	38,4
Total	13	100

Table 2: Response rate in the study group.

Survival: (Figure 1 and 2)

The median time to progression (TTP) was 3 months (95% CI: 1,8- 4,1 months). After failure to respond to 5-FU/CPT11, six patients received second-line chemotherapy; cisplatine-based chemotherapy in 5 patients (cisplatin/5-FU), and oxaliplatin/capecitabine combination in one case.
As of the reference date of the final analysis, all patients had died of their disease. The median survival time (MS) was 4 months (95% CI: 2.6- 5,3 months).

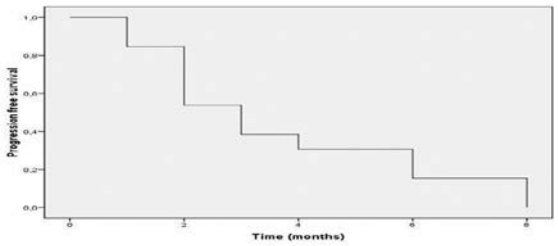

Figure 1: Time to disease progression in the study group.

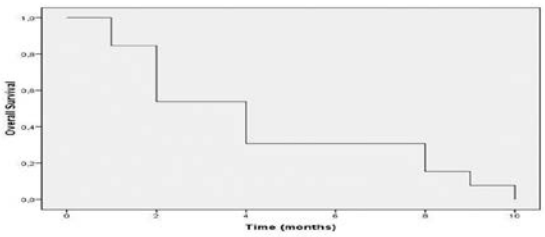

Figure 2: Overall survival in the study group.

Toxicity (Table 3)

Thirteen patients received a total of 43 treatment cycles, the most common hematologic adverse events were anemia followed by neutropenia and thrombocytopenia (76,9%, 38,4%, and 23,1% respectively), grade 4 neutropenia was observed in 3 cases (23,1%) and febrile neutropenia occurred in two cases (15,4%). Non-hematologic toxicities consisted particularly in diarrhea, stomatitis and emesis; diarrhea was noted in seven patients (53,8%), and one patient was hospitalized for a severe episode of diarrhea with dehydration, mild stoamtitis was noted in five patients (38,4%), vomiting was observed in 8

cases (61,6%), two patients (15,4%) developed a hand-foot syndrome, and hepatic disorders was observed in two cases (15,4%). No treatment-related deaths occurred.

CR, complete response ; N: number of patients; ORR, Overall response rate; PD, progressive disease; PR, Partial response; SD, stable disease.

	All events N(%)	Grade 3/4 events N(%)
Hematologic toxicities (n=13)		
Anemia	10 (76,9)	3 (23,1)
Neutropenia	5 (38,4)	3 (23,1)
Thrombocytopenia	3 (23,1)	-
Febrile neutropenia	2 (15,4)	2 (15,4)
Non hematologic toxicities (n=13)		
Diarrhea	7 (53,8)	1 (7,6)
Stomatitis	5 (38,4)	-
Hand-Foot syndrom	2 (15,4)	-
Nausea	10 (76,9)	-
Vomiting	8 (61,6)	2 (15,4)
Hepatic disorders	2 (15,4)	-

Table 3: Toxicity profile. N: number of patients who presented the event. n: total number of patients.

DISCUSSION

Irinotecan associated to continuous infusion of 5-FU is a standard combination in the treatment of metastatic colorectal cancer and have demonstrated efficacy in the management of advanced gastric cancer in upfront treatment. Dank et al was the first to report in a randomized phase III trial that there is no significant difference in term of survival between first line chemotherapy based on irinotecan / 5-FU (IF) and cisplatine / 5-FU (CF), time to progression was respectively 5 months versus 4,2 months (p=0,08), and overall survival was respectively 9 months versus 8,7 months, furthermore, IF combination was more well tolerated than CF.[5]

In phase II trials different schedules of Irinotecan/5-FU combination were used as a first line treatment in advanced gastric cancer (Table 4), one observation from these trials is the use of 5-FU as a continuous infusion apart from the study of Blanke et al that used 5-FU as bolus injections.[3]

In the recent prospective phase III study of the French Intergroup, the Leucovorin / 5FU/Irinotecan combination (FOLFIRI) has been demonstrated to be superior to Epirubicin/ Cisplatine/Capecitabine combination in term of time to treatment failure. [12] A survival benefit was reported previously to this study in a meta-analysis of ten randomized trials using different combination with irinotecan as first line therapy. [13]

In our context, economic and demographic particularities are two major difficulties limiting the use of 5-FU as a continuous infusion and in our institution the treatment schedule was adapted to better fit the whole context and to overcome its limits, therefore, we opted for a treatment schedule based on three weekly bolus 5-FU and CPT11 combination. Thirteen patients with advanced gastric cancer were treated following this schedule as a first line palliative chemotherapy, and in the retrospective analysis of this population that we report here the overall response rate was 38,4%, the median time to progression was 3 months, and the median overall survival was 4 months. Toxicity was generally mild and no treatment related death was observed. Hematologic adverse effects and diarrhea were the most frequent, and hospitalization was required in two cases for febrile neutropenia, and one episode of severe diarrhea, furthermore, blood transfusion was required in three cases of severe anemia.

Author(Year)	Trial*	Protocol	Patient(n)	RR %	TTP	OS
Kim *et al (2010) [6]*	Phase II	Modified FOLFIRI	44	38,6	4,9	10,3
Park *et al (2008) [7]*	Phase II R	ILF	45	42	4,8	10,7
Rosati *et al (2007) [8]*	Phase II	Folfiri	50	36	8	14
Moehler *et al (2005)[9]*	Phase II R	IF	56	43	4,5	10,8
Pozzo *et al (2005) [10]*	Phase II R	IF	59	42,4	6,5	10,7
Bouché *et al (2004)[11]*	Phase II R	Folfiri	45	40	6,9	11,3
Blanke *et al (2001)[3]*	Phase II	IFL	36	22	4,4	7,6

Table 4 : Results of phase II clinical trial testing irinotecan /5-FU combination as first line treatment of advanced gastric cancer.

Folfiri: Leucovorine (LV) 100 mg/m^2 (2-hour intravenous infusion) followed by 5-FU 400 mg/m^2 (bolus) and 5-FU 600 mg/m^2 (22-hour continuous infusion) on therapeutic days 1 and 2 plus Irinotecan 180 mg/m^2 (1-hour infusion) on day 1; **IF**: Irinotecan 80 mg/m^2 IV , folinic acid 500 mg/m ^{2} IV, and a 22-h infusion of 5-FU 2000 mg/m^2 IV, weekly for 6 weeks with a 1-week rest; **IFL** : Irinotecan 125 mg/m ^{2} IV followed immediately by Leucovorine 20 mg/m^2 IV. and 5-FU 500 mg/m^2 IV, all given weekly for four weeks followed by a two-week rest; **ILF**: irinotecan 150 mg/m^2 on day 1, leucovorin 20 mg/m^2 and a 22-h infusion of 5-FU 1000 mg/m^2 on days 1 and 2 every 2 weeks; **modified Folfiri:** irinotecan 150 mg/m^2 on day 1 and LV 20 mg/m^2 followed by 5-FU 400 mg/m^2 (bolus) and 5-FU 600 mg/m^2 (22 h continuous infusion) on days 1 and 2 every 14 days**; n:** number of patients; **OS:** median overall survival; **R**: Randomized trial **; RR:** Response rate**; TTP:** median time to progression.
*In randomized trials, only the results of the arms containing CPT11/5-FU combination are reported.

In term of response rate, our findings are generally similar to the rates reported in the literature, and in term of safety adverse events were generally well managed. However, in term of survival our findings don't match the average survival benefit of 6 months that was reported with the use of chemotherapy when compared to best supported care [14], these results can be interpreted by the number of patients with worsening performance status who were included in our study (38,4% had an ECOG PS of 2) and the lower median number of treatment cycle received (3 cycles per patient), otherwise, statistical bias consisting of the limited number of cases reported and the retrospective report could explain these findings.

CONCLUSION

Three weekly irinotecan and bolus 5-FU is an interesting combination in first line treatment of advanced gastric cancer; designed clinical trials are needed to confirm the activity of this combination.

AUTHORS' CONTRIBUTIONS

MM was involved in the analysis of the data, the literature research and wrote the manuscript, TM helped with the analysis of the data, NI helped with the analysis of data, the modifications and revision of the manuscript, , SB helped with the literature research and the collect of the data, SA was involved in the analysis of the data and helped write the manuscript, HE approved the treatment schedule, analyzed the data, and revised the manuscript. All authors read and approved the final manuscript.

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Declared none.

PATIENT CONSENT
Oral consent for study participation was obtained from the subjects, and the study protocol was approved by the institutional review boards of the National Institute of Oncology in Rabat.

COMPETING INTERESTS
The authors declare no competing interests.

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