



LOW DOSE WEEKLY IRINOTECAN PLUS BEVACIZUMAB AS FIRST LINE CHEMOTHERAPY FOR METASTATIC COLORECTAL CANCER WITH POOR PERFORMANCE STATUS ECOG 3 AND 4

Oncology

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ABSTRACT

Background: Colorectal cancer is the most frequent digestive cancer. Use of chemotherapy and targeted therapy had clearly improved prognostic of metastatic disease. However there are no standard of care for management of patients with poor performance status who are generally excluded from pivotal trials. We conducted this study with the aim to evaluate efficacy and toxicity of low dose weekly Irinotecan plus Bevacizumab regimen in this setting.

Material and methods: This was a retrospective observational study conducted in medical oncology unit of military hospital Mohamed V of Rabat between January 2010 and December 2014. The study was conducted in patients with mCRC and poor performance status ECOG 3 and 4. The primary objective was to assess the safety and the efficacy low dose weekly Irinotecan plus Bevacizumab in patients with PS 3 or 4 who received this combination in first-line treatment of mCRC.

Assessment of tumor response was granted by comparative measurement of target lesion size as RECIST1.1 criteria. Treatment was administered until evidence of disease progression, unacceptable toxicity, death or patient refusal. Adverse events were graded according to classification of the National Cancer Institute Common Toxicity Criteria version 4.0.

Results: Between 1 January 2010 and 31 December 2014, eleven patients were included in this study. Therapeutic evaluation showed a rate of disease control of 72.72%, with 27.27% of partial response and 45.45% with stabilization. The median of overall survival of our patients was 7 month. No complete response could be obtained. No grade 3/4 toxicities were noted in our patients. Most common adverse events were Diarrhea, Fatigue and hematological toxicities.

Conclusions: Despite the low statistical power of our study, the use of low dose weekly Irinotecan plus Bevacizumab in poor performance mCRC patients seems to be effective and well tolerated in this setting and its place deserves to be studied in a larger study.

KEYWORDS

mCRC, poor performance, Bevacizumab, weekly Irinotecan.

Background:

Colorectal cancer is the third most common cancer in men and the second in women worldwide (1,2). Metastatic colorectal remains incurable disease (3). Polychemotherapy with the combination of a Fluoropyrimidine with Oxaliplatin or Irinotecan increases survival and response rate (4,5). Addition to chemotherapy of biological agents such Bevacizumab or anti-EGFR drugs improve prognosis with median survival beyond 2 years (6,7). However there is no standard approach to manage patients with poor performance status who have been generally excluded from pivotal trials.

In real life, mCRC patients with poor PS are often seen in clinical practice. Management of those patients represents a real challenge to oncologists due to the lack of evidence based data. According to our institutional protocol those patients are treated on first line regimen with Bevacizumab and low dose weekly Irinotecan. We conducted this study with the aim to evaluate efficacy and toxicity of low dose weekly Irinotecan plus Bevacizumab regimen in this setting.

Patients and methods

This was a retrospective observational study conducted in medical oncology unit of military hospital Mohamed V of Rabat between January 2010 and December 2014. The study was conducted in patients with mCRC and poor performance status.

Patients included in this study were 18 years or older, with histologically confirmed colorectal cancer, radiological evidence of metastatic disease and PS 3 and 4 measured using the Eastern Cooperative Oncology Group (ECOG) classification who were treated according institutional protocol on first line regimen with Bevacizumab and low dose weekly Irinotecan.

The primary objective was to assess the safety and the efficacy Bevacizumab and low dose weekly Irinotecan in patients with PS 3 or 4 who received this combination in first-line treatment of mCRC.

Bevacizumab was used at the dose of 5 mg/kg/2 weeks and Irinotecan at the dose of 80 mg/m²/d on days 1, 8 and 14 repeated every 4 weeks. Antiemetics and growth factors were used as needed. A biological assessment was requested systematically before each cycle, including complete blood count, serum electrolytes, liver function and renal function tests. Adverse events were graded according to classification of the National Cancer Institute Common Toxicity Criteria version 4.0.

Assessment of tumor response was granted by comparative measurement of target lesion size as RECIST1.1 criteria.

Treatment was administered until evidence of disease progression, unacceptable toxicity, death or patient refusal.

Statistical analysis was performed using SPSS software version 18.0. Differences were considered as significant for p-value under 0.05.

Results

Between 1 January 2010 and 31 December 2014, eleven patients were included in this study. Epidemiological characteristics of this population are described in Table 1.

Therapeutic evaluation showed a rate of disease control of 72.72%, with 27.27% of partial response and 45.45% with stabilization. The median of overall survival of our patients was 7 month. No complete response could be obtained. Results are summarized in Table 2.

No grade 3/4 toxicities were noted in our patients. Most common adverse events were Diarrhea, Fatigue and hematological toxicities. Principal adverse events are described in Table 3.

Discussion

Colorectal cancer is the third most common cancer in men and the second in women worldwide (1,2). Metastatic colorectal remains incurable disease (3). polychemotherapy with the combination of a Fluoropyrimidine with Oxaliplatin or Irinotecan increases survival and response rate (4,5). Addition to chemotherapy of biological agents such Bevacizumab or anti-EGFR drugs improve prognosis with median survival beyond 2 years (6,7). There is no standard approach to manage patients with poor performance status who have been always excluded from pivotal trial.

In real life, mCRC patients with poor PS are often seen in clinical practice. Management of those patients represents a real challenge to oncologists due to the lack of evidence based data. Balance between benefits and risks of treatments is a real concern of physicians.

In a metaanalysis published in 2009 (8), polychemotherapy leads to a better outcome compared to monochemotherapy in a population of mCRC patients with PS 2. However in this study rate of grade 3 and 4 toxicity was high and patients with more compromised PS (3 and 4) were not represented. The authors concluded that the benefit of modern chemotherapy for mCRC is present in young and fit patients but also in elderly and those with poor PS.

In our institution the use of first line chemotherapy using weekly Irinotecan plus Bevacizumab was based on several observations. Indeed there no standard treatment for mCRC patients with poor health conditions however low dose weekly Irinotecan has been reported to be effective and well tolerated as second line chemotherapy in elderly patients with mCRC (9). Bases on the literature the benefit of the combination of Bevacizumab to chemotherapy in this population of patients still clearly established (10). In a published phase II study (11) combination of Bevacizumab and Capecitabine was effective and had favorable toxicity profile in a population of elderly mCRC.

Chemotherapy with low dose weekly Irinotecan plus Bevacizumab seems to be effective. The rate of disease control in our study was 72.72%, with 27.27% of partial response and 45.45% with stabilization. The median of overall survival of our patients was 7 month.

Similar results was reported in a previous study (12) with a median of overall survival of 6.8 months for ECOG PS of 3 and 4. In this report median overall survival of patients with PS 3 and 4 treated by best supportive care without chemotherapy was only 2.3 months confirming the benefit of chemotherapy of this population of patients. However This study had some limitations compared with study.

In this report patients was treated by modified bolus fluorouracil and oxaliplatin regimen (mFLOX) or fluoropyrimidine monotherapy. In fact a meta-analysis (13) analyzing Individual data of 1,219 patients included in six randomized trials comparing the administration of fluorouracil by continuous intravenous infusion versus the bolus administration in patients with advanced colorectal cancer showed the superiority of continuous infusion in terms of tumor response and overall survival with a different profile of tolerance between the two schedules of administration (less hematologic toxicity in continuous infusion but more hand-foot syndrome compared with bolus).

Moreover None patient in this study benefited from the addition of biological agents such Bevacizumab. Indeed there no established

standard about the benefits from the combination of Bevacizumab to standard chemotherapy in patients with poor PS, however in a recently published meta-analysis (14) including data from 782 patients adding Bevacizumab to first-line fluoropyrimidine mono-chemotherapy significantly improved progression-free and overall survival in unfit and elderly patients with mCRC, with a manageable safety profile and no unexpected toxicities. Thus patients with poor PS should not be excluded from a possible benefit of Bevacizumab. In our sample the overall tolerance of Bevacizumab was good with no major toxicities.

Toxicity of oncological treatments is a major concern in general population and especially in those with poor general condition. In our study tolerability of low doses weekly Irinotecan with Bevacizumab was acceptable with no grade 3 and 4 toxicities. In the study conducted by Crosara Teixeira M. et al. (12) the use of mFLOX regimen appears potentially toxic in such fragile population with a rate of grade 3/4 toxicities about 22%.

Our study is limited by the low statistical power of our study and the retrospective design. however the lack of randomized trial specially dedicated to mCRC patients with poor PS and the efficacy and the good tolerance of our proposed regimen, make us believe that our study adds Provides valuable information about the management such specific population.

Conclusion

Despite the low statistical power of our study, the use of low dose weekly Irinotecan plus Bevacizumab in poor performance mCRC patients seems to be effective and well tolerated in this setting and its place deserves to be studied in a larger study.

List of abbreviations

ECOG : Eastern Cooperative Oncology Group
PS: performance status
mCRC: metastatic colorectal cancer
RECIST: Response Evaluation Criteria In Solid Tumors
mFLOX :modified bolus fluorouracil and oxaliplatin regimen
EGFR: Epidermal Growth Factor receptor

Declarations

-Ethics (and consent to participate):

This study was approved from ethics the committee of military hospital of Rabat

-Consents

written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.

All patients gave their consent for participation in this study and for the publication

-Competing interests

All authors declare not have any competing interests in the manuscript.

-Authors' contributions

All authors had equally contribute to this work

-Availability of data and materials

Not applicable

-Acknowledgments

Not applicable

Table 1: Characteristics of the study patients

Characteristics	N	%
Nombre of patients	11	100
Genre		
Male	8	72.72
Female	3	27.27
Age		
median	63	
Range (years)	(48 – 75)	
Primary site		
Colon	7	63.63
Rectum	4	36.36

Site of metastases		
Liver	10	90.90
Lung	5	45.45
Peritoneum	7	63.63
Lymph nodes	7	63.63
Bones	0	00.00
ECOG performance status		
3	8	72.72
4	3	27.27

Table 2: results

	N	%
Response		
Complete response	0	00.00
Partial response	3	27.27
Stabilisation	5	45.45
Progressive disease	3	27.27
Survival		
Median months	7	
Range	(4 – 12)	

Table: 3 adverse events

	N	%
Adverse events		
Grade 1	10	90.90
Grade 2	7	63.63
Grade 3	0	00.00
Grade 4	0	00.00
Diarrhea	9	81.81
Nausea/vomiting	7	63.63
Alopecia	4	36.36
Fatigue	9	81.81
Neutropenia	8	72.72
Anemia	9	81.81
Thrombocytopenia	7	63.63

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