ORIGINAL RESEARCH PAPER

Oncology

SAFETY OF BEVACIZUMAB IN ELDERLY MOROCCAN PATIENTS WITH METASTATIC COLORECTAL CANCER

KEY WORDS: mCRC, elderly, Bevacizumab, safety

Rachid Tanz*	medical oncology department, military hospital Mohamed V, hay Riad, 10000, Rabat, Morocco faculty of medicine and pharmacy, Rabat, Morocco *Corresponding Author
Tarik Mahfoud	medical oncology department, military hospital Mohamed V, hay Riad, 10000, Rabat, Morocco
Aziz Bazin	medical oncology department, military hospital Mohamed V, hay Riad, 10000, Rabat, Morocco
Ilyas El Alami	medical oncology department, military hospital Mohamed V, hay Riad, 10000, Rabat, Morocco
Mohamed Reda Khmamouch	medical oncology department, military hospital Mohamed V, hay Riad, 10000, Rabat, Morocco
Choukri El Mhadi	medical oncology department, military hospital Mohamed V, hay Riad, 10000, Rabat, Morocco
Mehdi Toreis	medical oncology department, military hospital Mohamed V, hay Riad, 10000, Rabat, Morocco
Hassan Errihani	national institute of medical oncology, Rabat, Morocco
Mohamed Ichou	medical oncology department, military hospital Mohamed V, hay Riad, 10000, Rabat, Morocco

ABSTRACT

Background: Colorectal cancer is the most frequent digestive cancer. The incidence and mortality of CRC increases in elderly patients. Bevacizumab improves survival of mCRC patients at the price of particular toxicity profile that can be increased in an elderly population generally having comorbidities. The aim of this study was to evaluate the safety of use of Bevacizumab in elderly Moroccan patients with mCRC in real life.

Material and methods: This was a retrospective observational study conducted in medical oncology unit of military hospital Mohamed V of Rabat. The study was conducted in a general patient population, including elderly patients, with mCRC who had been treated on first line Bevacizumab based chemotherapy between December 2009 and May 2014.

The primary objective was to assess the safety profile of Bevacizumab in elderly patients in combination with chemotherapy as first-line treatment of mCRC.

We analyses the safety of Bevacizumab for patients older than 65 years, which is a widely accepted age cutoff point for the definition of elderly.

Results: forty-seven patients were included in this study. The most frequent observed adverse event was hypertension in 19% of our patients followed by Proteinuria(14%), Thrombotic diseases (10%) ,Serious bleeding events (2%) and Fistulae (2%). There was no case of Ischemic heart disease or Perforations in our serie.

Conclusions: Despite the low statistical power of our study, the use of Bevacizumab in older Moroccan patients does not seem to bring an excess of toxicity compared with published reports. These results must be confirmed in most important studies.

Background:

Metastatic Colorectal cancer (mCRC) remains one of the most frequent and the most lethal cancers elderly patients (1). mCRC remains incurable disease, even if prognosis has been improved with survival exceeding three years due especially to the use of targeted therapies such as Bevacizumab.

Despite the high frequency of this cancer, elderly patients are generally excluded from big trials and those included are totally different from patients observed in clinical practice of all days because of too stringent inclusion criteria. (2)

Bevacizumab is a vascular endothelial growth factor-specific angiogenesis. Its addition to standard chemotherapy regimens improve response rate and survival in mCRC. (3) Bevacizumab has a particular toxicity pro file: (hypertension, heart failure, myocardial infarction, venous and arterial thrombo-embolism, bleeding; gastro intestinal perforation; fistula; Delayed wound healing; and proteinuria...)(4) All these adverse events can be increased in an elderly population generally having others co morbidities.

In the aim to evaluate in real life the tolerability of the use of Bevacizumab in elderly Moroccan patients with mCRC we conducted this study.

Material and methods:

This was a retrospective observational study conducted in medical oncology unit of military hospital Mohamed V of Rabat. The study was conducted in elderly patients, with mCRC who had been treated on first line regimen with Bevacizumab and chemotherapy combination between December 2009 and May 2014.

The primary objective was to assess the safety of Bevacizumab in patients older than 65 years who received Bevacizumab in combination with first-line treatment of mCRC.

Bevacizumab was used at the dose of 5 mg/kg/2 weeks in 5-FU-based regimens (FOLFIRI, FOLFOX OR LV5FU2) or at 7.5 mg/kg/3 weeks with capecitabine +/- oxaliplatin regimens.

We reported all serious adverse events (SAEs) observed with Bevacizumab. All cases of hypertension, heart failure, myocardial infarction, venous and arterial thrombo-embolism, bleeding; gastro intestinal perforation; fistula; Delayed wound healing; and proteinuria were reported. AEs were graded according to National

Cancer Institute Common Terminology Criteria for Adverse Events version 3.

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

Results

Between December 2009 and May 2014 fourty-seven Moroccan patients were included in this study. Epidemiological characteristics of this population are described in Table 1.

The principal adverse events observed with Bevacizumab in elderly Moroccan patients are summarized in Table 2.

Discussion

Bevacizumab is a vascular endothelial growth factor-specific angiogenesis. Its addition to standard chemotherapy regimens improve response rate and survival in mCRC. (3) Bevacizumab has a specific toxicity pro file: (hypertension, heart failure, myocardial infarction, venous and arterial thrombo-embolism, bleeding; gastro intestinal perforation; fistula; Delayed wound healing; and proteinuria.(4) All these adverse events can be increased in an elderly population generally having others co morbidities.

Hypertension was the most frequent adverse event observed in our study. This complication does not seem to be related to the duration of treatment with Bevacizumab and its real pathogenesis is not completely understood. (5) In a meta-analysis of eight randomized trials the use Bevacizumab was associated with a fourfold higher risk for hypertension compared to control arm. (6) Older age seems to be a risk factor for the development of hypertension induced by Bevacizumab as has been reported in a retrospective study that found a higher incidence of hypertension in patients aged >75 years versus 65–75 (29 vs. 11% respectively). (7) In our study, nine patient of 47 (19%) developed this complication.

In our study proteinuria was the second more frequent side event with 14% of grades 1 or 2 , however no grade 3 or 4 has been reported. In a systematic review published by Zhu et al. (8) The overall incidence of proteinuria induced by Bevacizumab use was between 21% and 63%. Authors concluded that use of Bevacizumab lead to a significant risk of developing proteinuria and hypertension and they insisted on the importance of early detection and treatment of these adverse events to improve the tolerance of Bevacizumab.

An analysis of two phase II studies conducted specially in a population of elderly patients (with age ≥ 70 years old) suggests that both hypertension and proteinuria are associated with the duration of Bevacizumab treatment. (9)

Bevacizumab is known to increase the risk of arterial thromboembolisms (ATEs) with a higher incidence in patients older than 75 years. (10) In a published report about a large population of patients receiving Bevacizumab for mCRC, ATEs were more frequent in patients older than 80 years compared with those younger than 65 years (4.3 Vs. 1.5%). (11) In our sample the incidence of arterial thromboembolic events seems to be higher than those reports, however the small size of our study do not allow us to conclude .

The contribution of Bevacizumab to venous thrombo-embolic events (VTEs) remains controversial. A meta-analysis conducted by Nalluri et al. found an increased risk of VTE with use of Bevacizumab (12). However, These results are to be weighed These results are to be weighed because of a criticizing methodology of this study.(13) Moreover in another publication there was no increased risk of VTE with Bevacizumab use in combination with chemotherapy compared with chemotherapy alone. (14) In a pooled analysis of 10 randomized studies about 6055 patients there were no statistically significant increases in the incidences of VTEs with Bevacizumab. In this report, older age, poorer performance status, VTE history, and baseline oral anticoagulant use seems to increases risk of VTE. (15)

Serious bleeding events (SBEs) were one of serious concern about Bevacizumab use. In the BRITE (Bevacizumab Regimens: Investigation of Treatment Effects and safety) study the incidence of SBEs was 2.6% in case of use of Bevacizumab in combination with first-line chemotherapy for mCRC. (16) Patients with rectal cancer had twice time risk of SBEs compared to those with colic primary. Our results are comparable to this study, and the only case reported is about a patient with rectal cancer and prior radiation therapy.

The risk of ischemic heart disease with Bevacizumab may be particularly important in elderly patients with others cardiac risk factors. However the implication of Bevacizumab in the development of ischemic heart disease remains controversial.

In a meta-analysis published by Chen Xl. et al. about of 4617 patients from 7 randomized controlled trials, Bevacizumab was associated with higher risk of cardiac ischemia in mCRC. (17) In contrast, another large study no association between Bevacizumab and cardiac death or cardiomyopathy or congestive heart failure was noted. However patients with cardiac comorbidity were less likely to receive Bevacizumab ($P < 0.0001$). (18)

In our study despite the risk of thrombotic events and hypertension, no patient was detected with cardiac ischemia or cardiomyopathy.

Gastrointestinal perforations were first reported in the pivotal trial conducted by Hurwitz et al. (19) with six cases in the Bevacizumab group (1.5%) versus no one in patients treated with chemotherapy alone. In this randomized phase 3 study patients aged over 65 years was particularly at risk of development incidence of gastrointestinal perforation compared to younger patients(1.5% versus 0%). Data from an observational study in a large community study showed that risk of gastrointestinal perforations was superior in patients with unresected primary tumor compared with those with resected primary tumors (3.6% versus 1.2% respectively). (20)

Bevacizumab is associated with increased risk postoperative fistulae specially in mCRC. (21) In a published phase III trial Bevacizumab use in adjuvant setting in colorectal cancer lead to a five times higher risk of wound complications in patients treated compared to chemotherapy alone (1.7% v 0.3%). In this study overall rate of grade 4 and 5 toxicities was higher in elderly regardless of treatment arm. (22)

Despite the low statistical power of our study, the use of Bevacizumab in older Moroccan patients does not seem to bring a excess of toxicity. In fact in the subgroup analysis of the Phase III BICC-C there was no significant relation between tolerability of Bevacizumab and age of included patients.(23) Moreover a subgroup analysis of another randomized Phase III (CAIRO-2 trial) did not showed any difference of the incidence of greater toxicities (grades 3 and 4) between three age groups (≤75, 70–75, and ≥75 years). Despite the fact that older patients had a significant higher rate of early treatment discontinuation for unacceptable toxicity than younger patients, no evaluation of Bevacizumab-specific toxicity was reported. (24) In a pooled analysis conducted by Cassidy et al (25) including more than 3000 patients, Bevacizumab-associated adverse events in the elderly population were not more frequent than those observed in younger patients. In other report, the subgroup analysis of elderly patient in The SEER database found no difference adverse event incidence rates with use of Bevacizumab. (26)

Declarations

-Ethics (and consent to participate):

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

-Consent to publish

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

Table 1 : demographic characteristics

Characteristic	Frequency
• N • Males	47 35
Age at treatment initiation Median (min-max)	71 (66- 81 years)
Localization, n (%) • Colon • Rectum	 31(65) 16 (34)
History of thromboembolism, n (%) **History of hypertension,** n (%)	1 (2) 8 (17)
Primary metastatic, n (%)	30 (64%)
Site of metastaticdisease, n (%) • Liver • Peritoine • Lung • Other	 39 (82) 22 (46) 15 (31) 2 (4)
Number of metastatic sites, n % • 1 to 2 • >2	 12 (25) 35 (74)
Chemotherapyregimens, n (%) • Oxaliplatinbased • Irinotecanbased • 5 FU/Capec mono	 16 (34) 12 (25) 19 (40)
PS at bevacizumab initiation, n (%) • 0 • 1 • 2-3	 2 (4) 38 (80) 7 (14)
Nombre beva cycle () • Median (min- max)	 12 (2- 24)

Table 2: the results of principal adverse events with bevacizumab in elderly patients

Adverse events	Results n (%)
Hypertension	9 (19)
Proteinuria	7 (14)
Thrombotic diseases • Arterial • Venous	3 (6.38) 2 (4.25)
Serious bleeding events	1 (2)
Ischemic heart disease	0 (0)
Gastrointestinal events • Perforations • Fistulae	0 1 (2)

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