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Efficacy of Bevacizumab versus Epidermal Growth Factor Receptor Inhibitors for Ras Wild Type Metastatic Colorectal Cancer: A Real-World Data Analysis from a Tertiary Care Institution

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Abstract

Introduction: A combination of chemotherapy regimen and biologics in patients with RAS wild-type (wt) metastatic colorectal cancer (mCRC) resulted in improvements in survival. However, the optimal choice of initial biologic therapy in previously untreated patients remains challenging. **Aim**: The objective of this study is to compare the efficacy and safety outcomes of first-line epidermal growth factor receptor (EGFR) inhibitors versus vascular endothelial growth factor (VEGF) inhibitors in patients with RAS wtmCRC. **Methods:** A retrospective analytical study of patients with RAS wtmCRC who received first-line chemotherapy with either bevacizumab or panitumumab/cetuximab was conducted at the department of medical oncology of Hassan II University Hospital of Fez, Morocco, over a period of 4 years (June 2015 to June 2019). Endpoints included overall survival (OS), progression-free survival (PFS) and overall response rate (ORR). **Results:** 85 patients were included: 48.2% (n = 41) received cetuximab or panitumumab and 51.7% (n = 44) received bevacizumab, in association with first-line chemotherapy. Median OS and PFS did not differ significantly between patients having received bevacizumab and cetuximab or panitumumab treatment. ORR was significantly higher with first-line treatment with EGFRi. The proportion of patients with treatment-related grade 3 or higher, adverse events was similar between treatment groups. **Conclusion:** Our study showed no sig-

nificant difference in survival between the addition of cetuximab/panitumumab vs bevacizumab to first-line chemotherapy as initial biologic treatment in RAS-wt mCRC patients.

Subject Areas

Oncology

Keywords

Colorectal Cancer, Advanced Disease, First-line, Biologics, Survival

1. Introduction

The combination of monoclonal antibodies with conventional polychemotherapy further improve survival of mCRC patients and are currently standard first-line treatments. These molecules act by targeting circulating VEGF and the receptor of EGFR. Current targeted therapies available for first-line treatment include bevacizumab, a humanized monoclonal antibody directed against VEGF, and panitumumab or cetuximab, monoclonal antibodies that targeted EGFR. At the present time, no biomarker has been proven to predict the efficacy of bevacizumab. RAS mutations (50% - 55%), BRAF mutations (8% - 10%), and HER2 amplification (2%) represent negative predictive markers for anti-EGFR therapy, and, consequently, its use is limited to RAS wild-type, and BRAF and HER2 negative patient population.

Recently, primary tumor sidedness is being proven to play a role in the selection of biologics. Guidelines, such as the European Society for Medical Oncology, and National Comprehensive Cancer Network recommend that an anti-EGFR antibody is used in left-sided but not right-sided tumors for KRAS and BRAF wild patients.

In this study, we aimed to evaluate the efficacy of first-line chemotherapy in combination with a VEGF inhibitor versus EGFR inhibitors in patients with RAS-wt mCRC.

2. Methods

This is aretrospective study conducted at the department of medical oncology, Hassan II University Hospital of Fez, Morocco, over a 4-year period from June 2015 to June 2019. Patients with pathologically-documented RAS-wtgenotype mCRC treated with first-line chemotherapy with either cetuximab/panitumumab or bevacizumab were included. The choice of either the mFOLFOX-6/CAPOX or FOLFIRI/XELIRI chemotherapeutic regimen was made by the patient and physician. Patients who had undergone less than two cycles of targeted therapy were excluded. Demographic, clinical, treatment, effectiveness, and toxicity data were abstracted from clinical and administrative recorded.

The endpoints were OS, defined as the time from the start of first-line treatment to death or last follow-up; progression-free survival (PFS), defined as the time from initiation of first-line treatment to disease progression on first-line or death; and objective response rate (ORR), defined as the proportion of patients with complete or partial response as best response according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria (version 1.1). Safety was evaluated by the proportion of patients with grade ≥ 3 adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE).

Descriptive statistics were used for the characteristics of these tumors using mean+/– standard deviation for continuous variables and frequencies for categorical variables. Survival was calculated by the Kaplan-Meier method. The significance level for all tests was set at 0.05. Statistical analysis of the results was performed using SPSS version 26.

The study was approved by the Institutional Ethics Committee. Due to its retrospective nature, the requirement for informed consent was waived for this study.

3. Results

85 patients were included. Of these, confirmed KRAS wt tumors received bevacizumab (51.7%, n = 44) or cetuximab/panitumumab (48.2%, n = 41) in association with standard first-line chemotherapy. 74.1% (n = 63) of patients had oxaliplatin based regimen (mFOLFOX-6 or CAPOX), and 25.9% (n = 22) of patients had irinotecan (FOLFIRI7XELIRI) based chemotherapy. The mean age of patients was of 64 years [extremes: 31 - 78]. 18.8% of patients were aged 70 or older. The study population was predominantly men (67%, n = 57). The majority of patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores of 0 to 1 (77.6%, n = 66). The majority of tumors were located in the left colon (75.3% of cases, n = 64) and 24.7% (n = 21) in the right colon. With regard of primary tumor extension, 31.7% (n = 27) of patients had T4 disease; N2 and N3 lymph node metastasis were observed in 41.1% (n = 35) and 38% (n = 32) of cases respectively. Metastatic lesions in our study interested: liver (75.2%, n = 64), peritoneum (28.2%, n = 24), and lung (25.8%, n = 22). The majority of our patients had more than one metastatic site at the time of the diagnosis (81.1%, n = 69). After a median follow-up of 20.6 months, median overall survival was 30 months (95% CI 15.9to 44 months) in the chemotherapy-EGFR-I group versus 21 months (95% CI 14.6 to 27.3 months) in the chemotherapy-bevacizumab group p = 0.79 (**Figure 1**). Median progression-free survival was 9.4 months (95% CI 6.3 to 11.6 months) in the chemotherapy-EGFR-I and 11 months (95% CI 8.4 to 15.6 months) in the chemotherapy-bevacizumab group with p = 0.062 (**Figure 2**).

Response rates were significantly higher with chemotherapy-EGFR-I compared to chemotherapy-Bevacizumab (52.7% versus 40.3%, p = 0.039).

96% of patients reported at least 1 adverse event. The overall incidence of grade 3 to 4 adverse events (AEs) was similar between the 2 groups. Toxic effects

that were lower than grade 3 were distinct with acneiform rash predominating for cetuximab/panitumumab and hypertension predominating for bevacizumab. The rate of arterial thrombotic events was not statistically higher than 5% on either regimen.

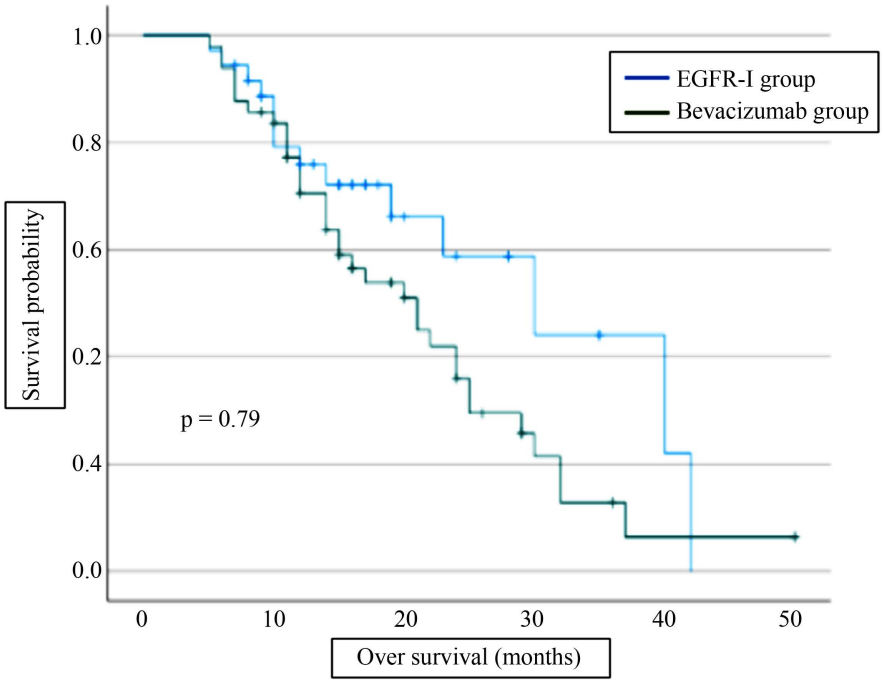

Figure 1. Differences in OS between the two targeted therapies.

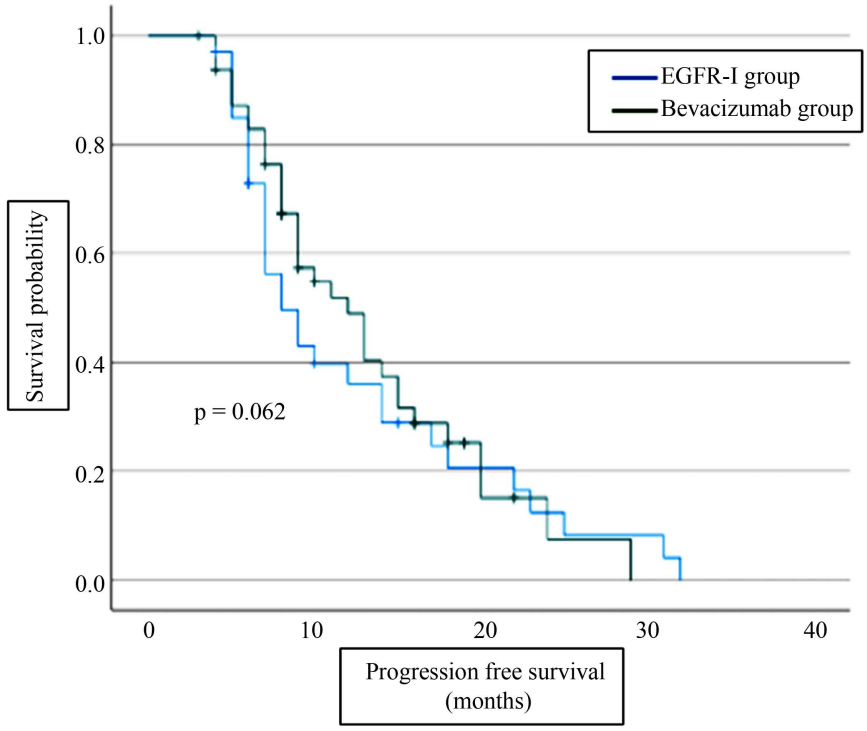

Figure 2. Differences in PFS between the two targeted therapies.

4. Discussion

In this real-world study involving patients with advanced or metastatic KRAS-wt CRC, there was no significant difference in OS and PFS with treatment using EGFR-I versus Bevacizumab added to the standard chemotherapeutic regimens. In contrast, we observed a significantly higher ORR in patients treated with an EGFR-I during first-line treatment.

EGFR and VEGF inhibitors are both monoclonal antibodies sharing equal importance in mCRC treatment. Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor-A (VEGF-A), a member of a family of VEGF receptor-activating ligands. In CRC, RAS gene mutations upregulate VEGF expression and promote tumor angiogenesis [1]. Thus, a VEGF inhibitor may be effective in either mutant or wild-type RAS CRC. However, EGFR is upstream of RAS, and RAS gene mutations could activate the downstream signaling cascade independent of EGFR. Although EGFR is blocked, its downstream pathway remains active. Thus, EGFR inhibitors exhibit treatment benefits exclusively in wild-type RAS mCRC. Therefore, the relative benefit of starting with bevacizumab versus an anti-EGFR agent as the initial biologic agent to be added to the chemotherapy backbone for RAS-wtmCRC remains a major unanswered question [2] [3] [4].

The benefit of adding bevacizumab to a variety of fluoropyrimidine, irinotecan and oxaliplatin-containing regimens used for first-line therapy has been established in several large randomized phase III trials. However, the modest benefit observed in terms of survival comes at a cost of treatment-related side effects including bleeding, bowel perforation, and thromboembolic events [5]. Retrospective analyses of the randomized trials demonstrated that the benefit of bevacizumab was observed irrespective of KRAS mutational status. The backbone cytotoxic chemotherapy seems immaterial in terms of efficacy with the addition of bevacizumab [6]. For anti-EGFR therapies, panitumumab and cetuximab are the two EGFR mono-clonal antibodies currently approved for the treatment of metastatic colorectal cancer. Initial randomized trials showed only modest benefit of EGFR-I containing regimens in unselected population by RAS mutation status. The margin of improvement associated with the addition of EGFR-I was widened when all patients with KRAS outside of exon 2 and NRAS mutations were excluded [7].

Therefore, the absence of proven biomarker could predict the response to anti-VEGF therapy, choosing between biologics in first-line remainschallenging in RAS-wt mCRC.

Bevacizumab or EGFR monoclonal antibodies cetuximab and panitumumab can be used as companion targeted therapy, and on the basis of the threetrials that have directly compared Bevacizumab versus Cetuximab, many clinicopathologic features have been identified as predictive markers of benefit of one or the other [8] [9] [10].

In addition to RAS mutations (50% - 55% of patients), tumors with mutually

exclusive BRAF mutations (8% - 10%), and HER2 amplification (2%) may not benefit from EGFR-I. Secondly, it has been proposed that tumor sidedness may help in the selection of the optimal first-line target agent. A meta-analysis of these three trials directly comparing first-line cetuximab versus bevacizumab found that patients with RAS wild-type left-sided colorectal tumors had a significantly greater survival benefit from anti-EGFR treatment than from anti-VEGF treatment when added to standard chemotherapy (HR 0.71, 95% CI 0.58 - 0.85). By contrast, for patients with right-sided tumors, there was a trend toward longer survival with bevacizumab-based therapy (HR 1.3, 95% CI 0.979 - 1.74) [11].

In our study, association between tumor sidedness with a differential benefit according to target agent could not be studied due to the low number of patients with right-sided tumors.

The results of our study provided further real-world evidence on the use of EGFG-I and bevacizumab in RAS-wt mCRC. However, our study had several limitations: its retrospective nature, the small sample size in subgroups which limit the ability to statistically compare any possible interaction with the antibodies, and the bias regarding treatment selection, which depended on the physician's choice.

5. Conclusion

Among patients with RAS wild type, untreated advanced or metastatic colorectal cancer, there was no significant difference in survival between the addition of cetuximab vs bevacizumab to chemotherapy as initial biologic treatment. Further research is still needed to confirm whether anti-EGFR or anti-VEGF represents a better choice when combined with different chemotherapy regimens and to identify predictive markers of treatment efficacy.

Conflicts of Interest

The authors declare to have no conflict of interest.

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