Evaluating the Optimal Sequence of Treatment With EGFR Inhibitors and Bevacizumab in RAS Wild-Type Metastatic Colorectal Cancer

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Abstract

Background

Epithelial growth factor receptor inhibitors (EGFRi) and bevacizumab are the two main target therapies available for first-line treatment of RAS wild-type (wt) metastatic colorectal cancer (mCRC). However, the optimal sequencing of these agents remains unclear. In this study, we aimed to evaluate the optimal sequence with EGFRi and bevacizumab in first- and second-line treatment.

Methods

This was a retrospective cohort study with RAS wt mCRC patients identified by extended RAS analysis between 2013 and 2020 at a comprehensive cancer center. All patients had to be treated with a sequence of systemic treatment that included an EGFRi and bevacizumab in first and second line, in either order. Two groups were defined according to treatment sequence: first-line EGFRi followed by second-line bevacizumab (cohort A) or the reverse sequence (cohort B). Primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival with first-line treatment (PFS1), progression-free survival with second-line treatment (PFS2), objective response rate (ORR), and serious adverse events (grade ≥ 3). Survival was estimated using the Kaplan-Meier method, and survival differences between groups were compared using the log-rank test. Univariate analyses were performed using Cox proportional hazard model.

Results

A total of 124 patients were included (93 in cohort A and 31 in cohort B). There were no statistical significant differences in median OS (A: 34.9 months vs B: 29.2 months; p=0.590), PFS1 (A: 13.1 months vs B: 8.2 months; p=0.600), and PFS2 (A: 7.4 months vs B: 5.5 months; p=0.110) between groups. No significant differences were also found between treatment sequences in subgroups defined by age, gender, primary tumor location, sidedness, timing of metastasis, number of metastatic sites, multimodal therapy, primary tumor resection, and first-line chemotherapy backbone. ORR was significantly higher with first-line treatment with EGFRi (A: 55.9% vs B: 22.6%; p=0.001). At the final follow-up, the proportion of patients with SAEs was similar between treatment sequences (p=0.827).

Discussion

Our study showed no impact of the treatment sequence with EGFRi and bevacizumab in the survival of RAS wt mCRC. However, patients treated with first-line EGFRi had significantly higher response rates, thus favoring its use in patients with symptomatic tumors and borderline resectable metastasis. Prospective trials are warranted to define the optimal sequence of treatment in RAS wt mCRC patients.

Categories: Oncology
Keywords: oncology, sequence, egfr inhibitors, bevacizumab, metastatic colorectal cancer

Introduction

According to the most recent data from GLOBOCAN, colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death worldwide [1]. In 2020, there were more than 1.95 million new CRC cases and 935,000 CRC-related deaths in the world [1]. Approximately 25% of the patients with CRC present with metastatic disease at diagnosis and 40-50% will develop metastasis during follow-up [2]. With the development of multimodal therapies and increasing use of targeted agents, median overall survival (mOS) of metastatic colorectal cancer (mCRC) has improved to more than 30 months in selected studies [3].

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Current molecular targeted therapies, available for first-line treatment, include bevacizumab, which targets the vascular endothelial growth factor (VEGF), and cetuximab or panitumumab, which targets the epithelial growth factor receptor (EGFR) [4]. While there are no validated predictive molecular biomarkers of response to bevacizumab, RAS mutations (exons 2-4 of KRAS and NRAS) represent a negative predictive marker for anti-EGFR therapy, and, consequently, its use is limited to RAS wild-type (wt) population [5-7].

The optimal target agent for first-line treatment of RAS wt patients has not been established [3,8]. The FIRE-3 and CALGB/SWOG 80405 trials compared the efficacy of first-line chemotherapy with either cetuximab or bevacizumab but provided conflicting results [3,8]. The first trial did not meet its primary endpoint of objective response rate (ORR) but showed an overall survival (OS) benefit for cetuximab, contrasting with the second one that showed similar progression-free survival (PFS) and OS in both treatment groups [3,8]. A possible explanation may be the impact of subsequent later-line therapies and the sequence of targeted therapies [9]. Retrospective analysis has suggested that the prior use of bevacizumab may impair the effect of cetuximab or panitumumab, thus favoring EGFR inhibitors (EGFRi) as the optimal choice for first-line treatment [9-12]. However, this was not uniformly replicated in other studies [13,14].

In this study, we aimed to evaluate the optimal sequence of treatment with EGFRi and bevacizumab in patients with RAS wt mCRC.

**Materials And Methods**

**Study design and participants**

This was a retrospective cohort study that included all consecutive RAS wt mCRC patients submitted to extended RAS analysis between January 2013 and December 2020 at a comprehensive cancer center in Portugal (Portuguese Oncology Institute of Porto). Eligibility criteria were as follows: (i) histologically confirmed diagnosis of CRC; (ii) confirmed KRAS (exons 2-4) and NRAS (exons 2-4) wt genotype; (iii) sequential first-line treatment with an EGFRi (cetuximab or panitumumab) followed by second-line bevacizumab, or the reverse sequence, in combination with chemotherapy; and (iv) documented disease progression between first and second line. 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 records.

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

**Study outcomes**

The primary endpoint was OS, defined as the time from the start of first-line treatment to death or last follow-up. Secondary endpoints were progression-free survival 1 (PFS1), defined as the time from initiation of first-line treatment to disease progression on first line or death; progression-free survival 2 (PFS2), defined as the time from initiation of second-line treatment to disease progression on second 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). The cut-off date for the analysis was August 31, 2021.

**Statistical analysis**

Patients were categorized into two cohorts according to sequence of treatment received: first-line EGFRi followed by bevacizumab (cohort A) and first-line bevacizumab followed EGFRi (cohort B). Categorical variables were summarized as frequencies and percentages. Continuous variables were presented as median, minimum, and maximum. Comparison between groups of continuous variables was performed using the Mann-Whitney U test, and the association of categorical variables and ORR was assessed using the chi-square test or the Fisher’s exact test. Survival analysis was performed using the Kaplan-Meier method and survival differences were compared with log-rank test. Univariable Cox regression analysis was used to calculate differences in survival for selected subgroups. A p-value of less than 0.05 was considered statistically significant. Data analysis was performed using the R software v4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Patient characteristics and treatment**

In total, 710 medical records of patients with RAS wt mCRC were reviewed. After applying all the inclusion and excluding criteria, 124 patients were included for the analysis: 93 patients (75.0%) received a first-line anti-EGFR followed by second-line bevacizumab (cohort A) and 31 patients (25.0%) received the reverse treatment sequence (cohort B) (Figure 1).
Patients and disease characteristics are summarized in Table 1. Median age at diagnosis was 57.7 years (24.0-74.0). Most patients were female in cohort A (66.7%) and male in cohort B (54.8%) (p=0.055). Compared with cohort B, cohort A had a significantly higher proportion of patients with synchronous metastatic disease (A: 61.3% vs B: 38.7%; p=0.047). In addition, more patients in cohort A had metastasis limited to the liver (48.4% vs 16.1%; p=0.003). Both groups had mainly left-sided tumors (82.8% vs 80.6%; p=0.790), a non-mucinous histology (97.8% vs 90.3%; p=0.099), and low grade of differentiation (46.2% vs 45.2%; p=0.464). No significant imbalances were detected for the proportion of BRAF-V600E mutations (7.5% vs 19.4%; p=0.091) and microsatellite instability (5.4% vs 12.9%; p=0.345).

| Baseline patient characteristics | Overall (n=124) | Cohort A (anti-EGFR/bevacizumab) (n=93) | Cohort B (bevacizumab/anti-EGFR) (n=31) | p-Value |
|---------------------------------|----------------|----------------------------------------|---------------------------------------|---------|
| Age at diagnosis, median (range), years | 57.5 (28.0-74.0) | 57.0 (30.0-74.0) | 59.0 (28.0-74.0) | 0.876 |
| Gender                          |                |                                        |                                       |         |
| Male                            | 48 (38.7%)     | 31 (33.3%)                             | 17 (54.8%)                           | 0.055 |
| Female                          | 76 (61.3%)     | 62 (66.7%)                             | 14 (45.2%)                           |         |
| ECOG PS                         |                |                                        |                                       |         |
| 0-1                             | 124 (100.0%)   | 93 (100.0%)                            | 31 (100.0%)                          | -       |
| Primary tumor location          |                |                                        |                                       |         |
| Colon                           | 75 (60.5%)     | 56 (60.2%)                             | 19 (61.3%)                           | 1.000 |
| Rectum                          | 49 (39.5%)     | 37 (39.8%)                             | 12 (38.7%)                           |         |
| Tumor sidedness                |                |                                        |                                       |         |
| Right sided^a                   | 22 (17.7%)     | 16 (17.2%)                             | 6 (19.4%)                            | 0.790 |
| Left sided^b                    | 102 (82.3%)    | 77 (82.8%)                             | 25 (80.6%)                           |         |
| Histology                       |                |                                        |                                       |         |
| Adenocarcinoma, NOS             | 119 (96.0%)    | 91 (97.8%)                             | 28 (90.3%)                           | 0.099 |
| Mucinous adenocarcinoma         | 5 (4.0%)       | 2 (2.2%)                               | 3 (9.7%)                             |         |
### TABLE 1: Baseline patient and tumor characteristics in overall population: cohort A and cohort B.

| Grade<sup>c</sup> | Low grade | High grade | Unknown |
|------------------|-----------|------------|---------|
|                  | 57 (46.0%) | 43 (46.2%) | 14 (45.2%) |
| Microsatellite instability | | | |
| No               | 73 (58.9%) | 57 (61.3%) | 16 (51.6%) |
| Yes              | 9 (7.3%)   | 5 (5.4%)   | 4 (12.9%)   |
| Unknown          | 42 (33.9%) | 31 (33.3%) | 11 (35.5%)  |
| BRAF status      | | | |
| Wild-type        | 53 (42.7%) | 44 (47.3%) | 9 (29.0%)   |
| Mutated          | 13 (10.5%) | 7 (7.5%)   | 6 (19.4%)   |
| Unknown          | 58 (46.8%) | 42 (45.2%) | 16 (51.6%)  |
| Timing of metastasis | | | |
| Metachronous     | 55 (44.4%) | 36 (38.7%) | 19 (61.3%)  |
| Synchronous      | 69 (55.6%) | 57 (61.3%) | 12 (38.7%)  |
| Number of metastatic sites<sup>d</sup> | | | |
| 1                | 80 (64.5%) | 63 (67.7%) | 17 (54.8%)  |
| >1               | 44 (35.5%) | 30 (32.3%) | 14 (45.2%)  |
| Metastatic sites | | | |
| Liver only       | 50 (40.3%) | 45 (48.4%) | 5 (16.1%)   |
| Lung only        | 11 (8.9%)  | 7 (7.5%)   | 4 (12.9%)   |
| Liver and other sites | 28 (22.6%) | 22 (23.7%) | 6 (19.4%)   |
| Peritoneal only  | 6 (4.8%)   | 2 (2.2%)   | 4 (12.9%)   |
| Non-regional lymph nodes only | 11 (8.9%) | 7 (7.5%) | 4 (12.9%) |
| Others<sup>e</sup> | 18 (14.5%) | 10 (10.8%) | 8 (25.8%)  |
| CEA, median (range), ng/mL | 14.8 (1.2-17572.0) | 25.9 (1.2-17572.0) | 9.8 (1.4-1558.0) |

<sup>a</sup>Right-sided colon: cecum, ascending colon, hepatic flexure, or transverse colon.<br>
<sup>b</sup>Left-sided colon: splenic flexure, descending colon, sigmoid colon or rectum.<br>
<sup>c</sup>Grade of histologic differentiation according to the WHO classification.<br>
<sup>d</sup>Number of organs involved by metastasis.<br>
<sup>e</sup>Other sites: metastasis located at other sites than lung, liver, peritoneum, or non-regional lymph nodes.

EGFR, epithelial growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; CEA, carcinoembryonic antigen

Treatment exposure is described in Table 2. Patients in cohort B were more likely to be previously treated with adjuvant chemotherapy (29.0% vs 67.7%; p<0.001) and pelvic irradiation (17.2% vs 41.9%; p=0.010). A higher proportion of patients in cohort A had irinotecan-based regimens (FOLFIRI or irinotecan) as first-line chemotherapy (93.5% vs 51.6%; p <0.001). Patients in cohort A were more likely to receive oxaliplatin-based regimens (FOLFOX or CAPOX) as second-line chemotherapy (90.3% vs 19.4%; p<0.001). Multimodal therapies (metastasis resection and/or ablative therapies) were performed in 38.7% in cohort A and 35.5% in cohort B (p=0.748). Metastasectomy was conducted in 31.2% patients in cohort A and 19.4% in cohort B (p=0.205). In the subset of patients with synchronous metastasis, primary tumor resection was conducted in 38 (40.9%) patients of cohort A and 9 (29.0%) of cohort B (p=0.739).
| Treatment exposure                      | Overall (n=124) | Cohort A (anti-EGFR/bevacizumab) (n=93) | Cohort B (bevacizumab/anti-EGFR) (n=31) | p-Value |
|----------------------------------------|-----------------|---------------------------------------|----------------------------------------|---------|
| **First-line chemotherapy backbone**   |                 |                                       |                                        |         |
| Oxaliplatin-based                      | 21 (16.9%)      | 6 (6.5%)                              | 15 (48.4%)                             | <0.001  |
| Irinotecan-based                       | 103 (83.1%)     | 87 (93.5%)                            | 16 (51.6%)                             |         |
| **Second-line chemotherapy backbone**  |                 |                                       |                                        |         |
| Oxaliplatin-based                      | 90 (72.6%)      | 84 (90.3%)                            | 6 (19.4%)                              | <0.001  |
| Irinotecan-based                       | 29 (23.4%)      | 6 (6.5%)                              | 23 (74.2%)                             |         |
| Others                                 | 5 (4.0%)        | 3 (3.2%)                              | 2 (6.5%)                               |         |
| **Multimodal therapy**                |                 |                                       |                                        |         |
| No                                     | 77 (62.1%)      | 57 (61.3%)                            | 20 (64.5%)                             | 0.748   |
| Yes                                    | 47 (37.9%)      | 36 (38.7%)                            | 11 (35.5%)                             |         |
| **Metastasis resection**               |                 |                                       |                                        | 0.205   |
| No                                     | 35 (28.2%)      | 29 (31.2%)                            | 6 (19.4%)                              |         |
| Yes                                    | 97 (71.8%)      | 64 (68.8%)                            | 25 (80.6%)                             |         |
| **Primary tumor resection**            |                 |                                       |                                        | 0.278   |
| No                                     | 22 (17.7%)      | 19 (20.4%)                            | 3 (9.7%)                               |         |
| Yes                                    | 102 (82.3%)     | 74 (79.6%)                            | 28 (90.3%)                             |         |
| **In patients with synchronous**       |                 |                                       |                                        | 0.739   |
| metastasis                             |                 |                                       |                                        |         |
| No                                     | 47 (37.9%)      | 38 (40.9%)                            | 9 (29.0%)                              |         |
| Yes                                    | 97 (62.1%)      | 74 (59.1%)                            | 26 (71.0%)                             |         |
| **Prior adjuvant chemotherapy**        |                 |                                       |                                        | <0.001  |
| No                                     | 76 (61.3%)      | 66 (71.0%)                            | 10 (32.3%)                             |         |
| Yes                                    | 48 (38.7%)      | 27 (29.0%)                            | 21 (67.7%)                             |         |
| **Prior pelvic irradiation**           |                 |                                       |                                        | 0.010   |
| No                                     | 95 (76.6%)      | 77 (82.8%)                            | 18 (58.1%)                             |         |
| Yes                                    | 29 (23.4%)      | 16 (17.2%)                            | 13 (41.9%)                             |         |

**TABLE 2: Treatment exposure in overall population: cohort A and cohort B.**

*Resection of metastasis or ablative therapies (hepatic thermoablation, chemoembolization, radioembolization, hepatic/pulmonary SBRT)

EGFR, epithelial growth factor receptor; SBRT, stereotactic body radiation therapy

**Survival outcomes**

Median follow-up was 29.4 months for cohort A (95% CI: 6.1-87.3) and 30.0 months for cohort B (95% CI: 6.1-80.6). OS was similar between treatment groups, with an mOS of 34.9 months in cohort A (95% CI: 28.3-44.0) and 29.2 months (95% CI: 22.4-42.5) in cohort B (p=0.590) (Figure 2). No significant differences were observed for median PFS1, with 13.1 months (95% CI: 11.9-16.3) in cohort A and 8.2 months (95% CI: 5.3-22.8) in cohort B (p=0.600) (Figure 3). Median PFS2 was also similar, with 7.4 months (95% CI: 6.7-88) in cohort A and 5.5 months (95% CI: 3.4-8.5) in cohort B (p= 0.110) (Figure 4).
FIGURE 2: Kaplan-Meier curves for overall survival of the two treatment sequences.

FIGURE 3: Kaplan-Meier curves for PFS1 of the two treatment sequences.

PFS1, progression-free survival with first-line treatment
FIGURE 4: Kaplan-Meier curves for PFS2 of the two treatment sequences.

PFS2, progression-free survival with second-line treatment

No significant survival differences were observed between treatment sequences in subgroup analyses conducted according to age, gender, primary tumor location, sidedness, timing of metastasis, number of metastatic sites, multimodal therapy, primary tumor resection, and first-line chemotherapy backbone (Table 3).

| Variables          | OS        | PFS1              | PFS2              |
|--------------------|-----------|-------------------|-------------------|
|                    | HR 95% CI | p-Value           | HR 95% CI p-Value | HR 95% CI p-Value |
| Age                |           |                   |                   |
| <58 years          |           |                   |                   |
| Anti-EGFR/Bevacizumab | 1.00     | 1.00              | 1.00              |
| Bevacizumab/anti-EGFR | 0.90   | 0.47-1.74         | 0.87              | 0.45-1.69         | 0.63  | 0.32-1.26 | 0.192 |
| ≥58 years          |           |                   |                   |
| Anti-EGFR/Bevacizumab | 1.00     | 1.00              | 1.00              |
| Bevacizumab/anti-EGFR | 1.39   | 0.73-2.64         | 1.50              | 0.82-2.74         | 1.49  | 0.63-2.65 | 0.178 |
| Gender             |           |                   |                   |
| Male               |           |                   |                   |
| Anti-EGFR/bevacizumab | 1.00     | 1.00              | 1.00              |
| Bevacizumab/anti-EGFR | 1.38   | 0.73-2.59         | 1.69              | 0.91-3.16         | 1.16  | 0.64-2.13 | 0.623 |
| Female             |           |                   |                   |
| Anti-EGFR/bevacizumab | 1.00     | 1.00              | 1.00              |
| Bevacizumab/anti-EGFR | 1.10   | 0.55-2.20         | 0.777             | 1.03              | 0.54-1.95 | 0.936  | 0.41-1.46 | 0.418 |
| Primary tumor location |         |                   |                   |
| Colon              |           |                   |                   |
| Anti-EGFR/bevacizumab | 1.00     | 1.00              | 1.00              |
| Bevacizumab/anti-EGFR | 1.01   | 0.56-1.83         | 0.968             | 1.55              | 0.89-2.69 | 0.121  | 0.94     | 0.55-1.61 | 0.811 |
| Rectum             |           |                   |                   |
| Anti-EGFR/bevacizumab | 1.00     | 1.00              | 1.00              |
### TABLE 3: Univariable Cox-proportional hazards model for OS, PFS1, and PFS2

OS, overall survival; EGFR, epithelial growth factor receptor

|                          | Bevacizumab/anti-EGFR | Tumor sidedness | Anti-EGFR/bevacizumab | Bevacizumab/anti-EGFR | Right-sided | Tumor sidedness | Anti-EGFR/bevacizumab | Bevacizumab/anti-EGFR | Right-sided | Tumor sidedness | Anti-EGFR/bevacizumab | Bevacizumab/anti-EGFR | Right-sided | Tumor sidedness | Anti-EGFR/bevacizumab | Bevacizumab/anti-EGFR | Right-sided |
|--------------------------|------------------------|-----------------|------------------------|------------------------|-------------|-----------------|------------------------|------------------------|-------------|-----------------|------------------------|------------------------|-------------|-----------------|------------------------|------------------------|-------------|-----------------|------------------------|------------------------|-------------|
|                          | 1.36                   | 0.64-2.92       | 0.445                  | 0.67                   | 0.32-1.40   | 0.284           | 0.89                   | 0.44-1.83               | 0.759       |                 |
| Timing of metastasis     |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
| Synchronous              |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
| Metachronous             |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
| Number of metastatic sites |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
| 1                        |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
|                         | 1.00                    | 1.00            | 1.00                   | 1.00                   | 1.00        | 1.00            | 1.00                   | 1.00                   | 1.00        |                 |
|                         | 1.13                    | 0.63-2.03       | 0.682                  | 0.99                   | 0.57-1.72   | 0.976           | 0.95                   | 0.55-1.66               | 0.867       |                 |
| >1                       |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
|                         | 1.00                    | 1.00            | 1.00                   | 1.00                   | 1.00        | 1.00            | 1.00                   | 1.00                   | 1.00        |                 |
|                         | 1.27                    | 0.60-2.68       | 0.530                  | 1.30                   | 0.62-2.71   | 0.488           | 0.96                   | 0.47-1.95               | 0.901       |                 |
| Multimodal therapies     |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
|                         |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
| Primary tumor resection  |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
|                         |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
|                         |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
| First-line chemotherapy  |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
| Oxaliplatin              |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
|                         | 1.00                    | 1.00            | 1.00                   | 1.00                   | 1.00        | 1.00            | 1.00                   | 1.00                   | 1.00        |                 |
|                         | 0.68                    | 0.18-2.58       | 0.571                  | 0.52                   | 0.18-1.56   | 0.244           | 0.73                   | 0.26-2.05               | 0.549       |                 |
| Irinotecan               |                        |                 |                        |                        |             |                 |                        |                        |             |                 |
|                         | 1.00                    | 1.00            | 1.00                   | 1.00                   | 1.00        | 1.00            | 1.00                   | 1.00                   | 1.00        |                 |
|                         | 1.41                    | 0.80-2.50       | 0.233                  | 1.62                   | 0.92-2.84   | 0.094           | 0.90                   | 0.50-1.60               | 0.717       |                 |
Response rates

Response rates are summarized in Table 4. Patients treated with a first-line EGFRi in cohort A had a significantly higher ORR with first-line treatment (55.9%) than patients treated with first-line bevacizumab in cohort B (22.6%) (p=0.001). In cohort A, 53.7% of patients had partial responses (vs 19.4% in cohort B) and 3.2% patients had complete responses (vs 3.2% in cohort B).

| Best response, n (%)     | Cohort A (n=93) | Cohort B (n=31) | p-Value |
|--------------------------|-----------------|-----------------|---------|
| Complete response        | 3 (3.2)         | 1 (3.2)         |         |
| Partial response         | 49 (52.7)       | 6 (19.4)        |         |
| Stable disease           | 32 (34.4)       | 16 (51.6)       |         |
| Progressive disease      | 9 (9.7)         | 8 (25.8)        |         |
| ORR, %                   | 55.9            | 22.6            | 0.001   |

TABLE 4: Response rates to first-line treatment in cohort A (EGFRi) and cohort B (bevacizumab)

ORR, overall response rate; EGFRi, epithelial growth factor receptor inhibitors

Safety

At the final follow-up, there were no significant differences in the rate of SAEs (grade ≥ 3) between treatment groups (Table 5). The rate of suspension of monoclonal antibody due to toxicity was low for both groups (8.6% vs 6.5%) with no statistically significant differences.
|                      | Cohort A (anti-EGFR/bevacizumab), n=93 | Cohort B (bevacizumab/anti-EGFR), n=31 | p Value |
|----------------------|----------------------------------------|----------------------------------------|---------|
| Grade ≥ 3 AEs<sup>a</sup> | No. (%)                               | No. (%)                               | 0.827   |
| VEGF inhibitor-specific |                                       |                                       |         |
| Hypertension         | 6 (6.5)                                | 1 (3.2)                                | 0.679   |
| Proteinuria          | 1 (1.1)                                | 2 (6.5)                                | 0.154   |
| Hemorrhage           | 3 (3.2)                                | 0 (0)                                  | 0.572   |
| Thrombosis           | 1 (1.1)                                | 0 (0)                                  | 1.000   |
| GI perforation       | 0 (0)                                  | 0 (0)                                  | -       |
| EGFR inhibitors class-specific |                                       |                                       |         |
| Cutaneous            | 19 (20.4)                              | 3 (9.7)                                | 0.175   |
| Infusional reaction  | 2 (2.2)                                | 0 (0)                                  | 1.000   |
| Hematologic          | 42 (45.2)                              | 15 (48.4)                              | 0.755   |
| Non-hematologic      |                                       |                                       |         |
| GI                   | 4 (4.3)                                | 2 (6.5)                                | 0.639   |
| Neurological         | 3 (3.2)                                | 1 (3.2)                                | 1.000   |
| Hepatic              | 1 (1.1)                                | 0 (0)                                  | 1.000   |
| Pulmonary            | 0 (0)                                  | 0 (0)                                  | -       |
| Others               | 2 (2.2)                                | 2 (6.5)                                | 0.280   |
| Antibody suspension due to toxicity | 8 (8.6)                                | 2 (6.5)                                | 1.000   |
| EGFR inhibitor       | 2 (2.2)                                | 0 (0)                                  | 1.000   |
| Bevacizumab          | 6 (6.5)                                | 2 (6.5)                                | 1.000   |

**TABLE 5: Serious AEs (≥ grade 3) in cohort A and cohort B**

<sup>a</sup>Number of patients with at least one grade ≥ 3 AE

AE, adverse event; VEGF, vascular endothelial growth factor; GI, gastrointestinal; EGFR, epithelial growth factor receptor

**Discussion**

We conducted a real-world retrospective study that included RAS wt mCRC patients sequentially treated with EGFRi and bevacizumab in the largest comprehensive cancer in Portugal with a long follow-up period. This study is of particular interest since data regarding the best treatment sequence with these therapies is lacking and, also because, most studies that compared bevacizumab and EGFRi in first-line setting did not account for the impact of subsequent therapies [3,8].

In our study, we found no significant survival differences between mCRC patients treated with a first-line anti-EGFR followed by second-line bevacizumab versus the reverse treatment sequence. Additionally, there were no significant differences regarding the time to treatment failure in either first or second lines. In contrast, we observed a significantly higher ORR in patients treated with an EGFRi during first-line treatment.

The findings in our study are consistent with the published data from the CALGB 80405 trial [3]. While this trial did not show significant differences in OS and PFS, response rates were significantly higher with first-line cetuximab [12]. Our study reinforces the data that EGFRi may be a more suitable option when cytoreduction is the main goal of treatment, especially in patients with symptomatic tumors and borderline resectable metastasis needing tumor response [15].
Our study, however, contrasts with the data from the FIRE-3 trial [8]. A retrospective analysis of this study showed that patients treated with bevacizumab in second-line after previous first-line cetuximab had a longer second-line survival. This study suggested that first-line treatment with an EGFRi followed by second-line bevacizumab may be a more suitable option than reverse sequence [9]. Additionally, a recent meta-analysis of 13 randomized trials and four observational studies evaluating the efficacy of different target therapy sequences showed an OS benefit for cetuximab followed by bevacizumab, in comparison with the reverse order, regardless of the chemotherapy backbone [16]. In vitro studies have supported this data as they have shown that EGFRi resistance was associated with a higher sensitivity to anti-VEGF therapy, while previous treatment with bevacizumab impaired the sensitivity to EGFRi through an EGFR-independent RAS activation [17-19].

It should be noted, nevertheless, that some prospective clinical trials found no detrimental impact of prior VEGF inhibition on the efficacy of subsequent therapies. The SPIRITT randomized phase II trial assessed the efficacy of second-line treatment with FOLFIRI plus panitumumab or bevacizumab, after progression on FOLFOX plus bevacizumab, and reported no significant differences in survival between both target therapies [20]. Similarly, the randomized ASPECTCT trial that compared cetuximab and panitumumab in chemotherapy-refractory patients reported similar survival for those who had been previously treated with bevacizumab versus those who had no prior bevacizumab treatment [21]. These data suggest that for patients willing to avoid the cutaneous toxicity of EGFRi the choice of bevacizumab may also be an adequate option with no detriment in long-term outcomes.

Recently, it has been proposed that tumor sidedness may help in the selection of the optimal first-line target agent [22]. A retrospective analysis of FIRE-3 trial has shown that patients with left-sided tumors had a longer second-line survival with a sequence of first-line cetuximab and second-line anti-VEGF, as compared with the reverse sequence. This benefit was, however, not observed in patients with right-sided tumors [23]. In our study, tumor sidedness was not associated with a differential benefit according to treatment sequence. However, these data must be interpreted with caution as there may have been a potential bias 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 EGFRi and bevacizumab in mCRC and, due to the fact that all patients have been exposed to both types of treatment, we were able to evaluate the potential interaction between them. However, our study had several limitations. These were inherent to its retrospective nature, the limited small sample size in subgroups, and the bias regarding treatment selection, which depended on the physician’s choice. Further validation with prospective multicenter studies is required. Ongoing clinical phase III trials (CR-SEQUENCE and STRATEGIC-1) are evaluating the sequential approach of these targeted therapies in mCRC and may in the future elucidate on the optimal sequencing of these agents [24,25]. Until they yield their results, treatment selection should be determined by patients’ clinical features and preferences, tumor characteristics, toxicities, and goal of treatment.

Conclusions

In conclusion, while there remains considerable ongoing debate regarding the optimal use and sequence of biologic therapy in mCRC, our data support the evidence that EGFRi may be a more suitable first-line option as it provides higher tumor-response rates. Our data do not support, however, the hypothesis that first-line bevacizumab use negatively impacts the subsequent efficacy of anti-EGFR therapy. Further prospective research is needed to clarify the present results.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Portuguese Institute of Oncology Ethics Committee issued approval 242/021. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J
Cancer. 2015, 15:496.

GERCOR phase III study in patients with unresectable wild-type RAS metastatic colorectal cancer

metastatic, primary left (L)-sided, unresectable colorectal cancer (CRC): The CR-SEQUENCE
bevacizumab followed by FOLFIRI + panitumumab (Sequence 2) in untreated patients with wild-type RAS

efficacy of FOLFOX + panitumumab followed by FOLFIRI + bevacizumab (Sequence 1) versus FOLFOX+
(AIOKRK0306)

therapeutic efficacy across treatment lines in patients with metastatic colorectal cancer: analysis of FIRE-3

patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials

Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V:

68:51-9. 10.1159/000452551

Hypoxia activates the K-ras proto-oncogene to stimulate

angiogenesis and inhibit apoptosis in colon cancer cells

Venook AP, Niedzwiecki D, Lenz HI, et al.: Cetuximab and chemotherapy as initial treatment for metastatic
colorectal cancer

Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer: results from a large international registry. Clin Cancer Res 2008, 14:5069-80. 10.1159/000452551

Van Cutsem E, Moiseeva V, et al.: Bevacizumab treatment for patients with wild-type KRAS metastatic colorectal cancer: a randomized, controlled trial. J Clin Oncol. 2015, 33:5718-26. 10.1200/JCO.2015.61.2887

Bianco R, Rosa R, Damiano V, et al.: Vascular endothelial growth factor receptor-1 contributes to resistance to anti-epidermal growth factor receptor drugs in human cancer cells. Clin Cancer Res. 2008, 14:5069-80. 10.1159/000452551

Zeng M, Ikizki H, Pino MS, Chung DC: Hypoxia activates the K-ras proto-oncogene to stimulate angiogenesis and inhibit apoptosis in colon cancer cells. PLoS One. 2010, 5:e10966. 10.1371/journal.pone.0010966

Zaniboni A, Formica V: The Best. First. Anti-EGFR before anti-VEGF, in the first-line treatment of RAS
wild-type metastatic colorectal cancer: from bench to bedside. Cancer Chemother Pharmacol. 2016, 78:233-44. 10.1007/s00280-016-3032-8

Hecht JR, Cohn A, Dhakil S, et al.: SPIRITT: a randomized, multicenter, phase II study of panitumumab with FOLFIRI and bevacizumab with FOLFIRI as second-line treatment in patients with RAS wild-type metastatic colorectal cancer. Clin Colorectal Cancer. 2015, 14:72-80. 10.1016/j.ccc.2015.05.009

Price T, Kim TW, Li J, et al.: Final results and outcomes by prior bevacizumab exposure, skin toxicity, and hypomagnesaemia from ASPECCT: randomized phase 3 non-inferiority study of panitumumab versus cetuximab in chemorefractory wild-type KRAS exon 2 metastatic colorectal cancer. Eur J Cancer. 2016, 68:51-9. 10.1016/j.ejca.2016.08.010

Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V: The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. Eur J Cancer. 2017, 70:87-98. 10.1016/j.ejca.2016.10.007

Modest DP, Stintzing S, von Weikersthal LF, et al.: Exploring the effect of primary tumor sidedness on therapeutic efficacy across treatment lines in patients with metastatic colorectal cancer: analysis of FIRE-3 (AIORKR0306). Oncotarget. 2017, 8:105749-60. 10.18632/oncotarget.22596

Salazar R, Carrato A, Garcia TG, et al.: Phase III randomized sequential open-label study to evaluate the efficacy of FOLFIRI + panitumumab followed by FOLFIRI + bevacizumab (Sequence 1) versus FOLFIRI + bevacizumab followed by FOLFIRI + panitumumab (Sequence 2) in untreated patients with wild-type RAS metastatic, primary left (L)-sided, unresectable colorectal cancer (CRC): The CR-SEQUENCE. J Clin Oncol. 2019, 37:5618-5618. 10.1200/JCO.2019.37.15_suppl.TPS5618

Chibaudel B, Bonnetain F, Tournigand C, et al.: STRATEGIC-1: a multiple-lines, randomized, open-label GERCOR phase III study in patients with unresectable wild-type RAS metastatic colorectal cancer. BMC Cancer. 2015, 15:496. 10.1186/s12885-015-1507-3