Journal of Cancer Research and Clinical Oncology (2019) 145:1719–1728
https://doi.org/10.1007/s00432-019-02924-0

ORIGINAL ARTICLE – CANCER RESEARCH

Patient-reported outcomes and health-related quality of life for cetuximab versus bevacizumab in metastatic colorectal cancer: a prospective cohort study

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Received: 9 March 2019 / Accepted: 20 April 2019 / Published online: 29 April 2019

Abstract

Purpose Uncertainty exists regarding Patient-Reported Outcomes (PROs) and Health-Related Quality of Life (HRQoL) of patients with metastatic colorectal cancer (mCRC) treated with cetuximab or bevacizumab. We conducted a prospective cohort study comparing PROs and HRQoL from both therapies.

Methods We assessed PROs and HRQoL from patients treated with cetuximab or bevacizumab using QLQ-C30 and QLQ-CR29 questionnaires at three sequential time points, including baseline. Global Health Status (GHS), functional and symptom scales, and Overall Treatment Utility (derived from clinical and patient-reported outcomes) were compared for the two treatment strategies.

Results Between January 2017 and April 2018, 44 patients were allocated to cetuximab ($n=19$) or bevacizumab ($n=25$). Except for RAS mutation status, patient baseline characteristics were generally well balanced across treatment groups. A higher proportion of patients experienced a deterioration in GHS ($\geq 10\%$) in cetuximab arm − 53.8% (95% CI 25.1–80.8%) at 6 weeks and 66.7% (95% CI 29.9–92.5%) at 12 weeks—comparing to bevacizumab cohort: 18.2% (95% CI 5.2–40.3%) at 6 weeks and 12.5% (95% CI:1.6–38.3%) at 12 weeks. Treatment utility rates at 6 and 12 weeks were, respectively, 88.6% and 69.8% for bevacizumab, compared to 49% and 19.1% for cetuximab ($p=0.004$), a difference confirmed in subset analyses.

Conclusions In patients with mCRC, cetuximab-containing regimens led to a progressive negative impact on PROs and global HRQoL, when compared to baseline and bevacizumab. Future research is needed to confirm these results. Our findings demonstrate the value of PROs when assessing comparative effectiveness of different treatment regimens.

Keywords Patient-reported outcome measures · Quality of life · Targeted therapy · Cetuximab · Bevacizumab · Metastatic colorectal cancer

Introduction

Worldwide, around 1.7 million individuals are diagnosed with colon or rectal cancer, every year (Fitzmaurice et al. 2018). About 20% of this population presents with metastatic colorectal cancer (mCRC) at time of diagnosis, while another 20% eventually develops advanced disease after recurrence (Siegel et al. 2017; Wille-Jørgensen et al. 2018). Targeted therapy, using monoclonal antibodies binding to either the Epidermal Growth Factor Receptor (EGFR) like cetuximab or panitumumab, or the Vascular Endothelial Growth Factor (VEGF) such as bevacizumab, currently constitutes the standard of care for first-line treatment of mCRC. Combined with a fluoropyrimidine-based chemotherapy backbone, it leads to a median overall survival (OS) of around 30 months, but at the expense of significant

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-019-02924-0) contains supplementary material, which is available to authorized users.

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toxicity (Van Cutsem et al. 2016; Elez et al. 2015; Marques et al. 2017).

Knowledge of the potential toxicity burden underlying a therapeutic option is key to decision-making in clinical oncology (Cherny et al. 2015; Schnipper et al. 2016), particularly when palliation is the therapy goal (Kaasa et al. 2018), as it happens for a large proportion of mCRC patients (Van Cutsem et al. 2016). Reporting of adverse events by investigators in Randomised Clinical Trials (RCTs), according to the Common Terminology Criteria for Adverse Events (CTCAE), has been the most widely used method for quantifying harm from treatment experienced by patients, mostly due to its high objectivity and reproducibility. However, in light of recent research, Patient-Reported Outcomes (PROs), which provide direct measurements of cancer patients' experiences through validated scales, can offer a different angle on treatment toxicity assessments, often showing clinically meaningful differences when compared to clinician-assessed tools (Di Maio et al. 2016; LeBlanc and Abernethy 2017; Basch 2010; Di Maio et al. 2015). Moreover, as the cornerstone of a value-based health care concept, a patient-centred approach requires that patient-driven health information completes the objective clinical data traditionally demanded by regulatory agencies upon drug approval (Porter 2010; Kluetz et al. 2018). PROs' recognised regulatory importance has led to their growing interest as RCT endpoints and, thus, to several methodological refinements to bolster their utility for stakeholders (Bottomley et al. 2016; Calvert et al. 2018).

Patients with mCRC often present a considerable burden of symptoms that can, adding to common treatment toxicities, have a substantial negative effect on health-related quality of life (HRQoL) and functioning. Therefore, the repercussion of existing treatments on symptom control and HRQoL needs to be considered alongside survival. Nevertheless, although three head-to-head trials tested the efficacy and safety of anti-EGFR versus anti-VEGF treatment modalities, none has reported PROs as endpoints, and other informative studies about the subject are scarce (Heinemann et al. 2014; Schwartzberg et al. 2014; Venook et al. 2017; Rees et al. 2015). Hence, our objective was to bridge this gap by conducting a cohort study in mCRC, to measure and compare HRQoL outcomes reported by patients treated with cetuximab or bevacizumab.

Patients and methods

This study assessed and compared PROs from two prospective treatment cohorts set in a Portuguese comprehensive hospital centre. Methods and reporting followed STROBE (von Elm et al. 2007) guidelines for observational studies and SISAQOL (Bottomley et al. 2016)/SPIRIT-PRO (Calvert et al. 2018) recommendations for HRQoL data.

Patient selection

Patients initiating treatment with cetuximab or bevacizumab during enrolment period were recruited from a local database comprising every new clinical request for the study drugs. To be eligible for inclusion, patients needed to be at least 18 years old, and to present clinically confirmed stage IV colon or rectal adenocarcinoma. We excluded patients with history of systemic treatment with anti-EGFR or anti-VEGF therapy within five years of the inclusion date.

Patient-reported outcomes measurement and collection process

HRQoL and PROs were measured through two cancer-specific instruments: a core questionnaire, QLQ-C30 Version 3.0 (European Organisation for Research and Treatment of Cancer Quality of Life Department, n.d.), and a complementary colorectal cancer module, QLQ-CR29 Version 2.1. (European Organisation for Research and Treatment of Cancer Quality of Life Department, n.d.) Both questionnaires were designed by EORTC (European Organization for Research and Treatment of Cancer) for the self-reporting of quality of life from cancer patients within clinical studies, and are widely used and thoroughly validated (Groenvold et al. 1997; Whistance et al. 2009; Velikova et al. 2012). Previous research has shown that QLQ-C30 and QLQ-CR29 are preferential instruments for measuring HRQoL from colorectal cancer patients, particularly when evaluating patients receiving chemotherapy (Wilson et al. 2012; Uwer et al. 2011; Wong et al. 2015; Snyder et al. 2014).

Both QLQ-C30 and QLQ-CR29 combined measure a global health and QoL scale, denominated Global Health Status (GHS), nine functional dimensions or scales (physical, role, emotional, cognitive, and social functioning, body image, anxiety, weight perception, and sexual interest), and twenty-five symptom scales or items (fatigue, nausea or vomiting, pain, dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, financial difficulties, urinary frequency, incontinence, dysuria, blood or mucus in stool, stool frequency, abdominal pain, buttock pain, bloating, dry mouth, hair loss, altered taste, flatulence, faecal incontinence, sore skin, embarrassment, and impotence or dyspareunia) (European Organisation for Research and Treatment of Cancer Quality of Life Department, n.d.).

Selected patients completed both questionnaires at three sequential time points: baseline, 6 weeks, and 12 weeks from inception date, and the assessments were synchronised with treatment schedule. Completion assisted by

proxy was allowed when justified (e.g. due to illiteracy or frailty), whenever exact same conditions could be adequately maintained through all the assessments of a specific patient.

Patients were withdrawn from the study (i.e. any further assessments were cancelled) if their treatment (entire chemotherapy protocol or solely the targeted therapy) was suspended for at least four weeks from due date, and all clinical or non-clinical motives behind the suspension were subsequently analysed. HRQoL data from patients that did not complete the baseline assessment, or that declined to participate in the study, were not analysed.

Ethical approval for the study was obtained before its initiation from the institutional ethics committee. All patients provided written informed consent to participate.

Statistical methods

Descriptive statistics of patients' baseline characteristics were estimated by cohort: means and standard deviations for continuous variables, medians, minima and maxima for discrete variables, and frequencies and proportions for binary and categorical data. Two composite scales were constructed as averages of sets of individual scales: the composite of functional scales and the composite of symptom scales. Trends in the GHS and the composite scales were assessed estimating median scores and 95% confidence intervals for the two cohorts at the three points of assessment, using all patients for whom QoL data were available. Furthermore, we estimated the percentage of patients with a deterioration in GHS by at least 10% (compared to baseline) at 6 and 12 weeks.

Finally, we compared Overall Treatment Utility (OTU) (Secord et al. 2015) in the two cohorts. For this, we estimated "progression"-free survival, with progression defined here by one or more of the clinical and patient-reported outcomes: deterioration in GHS by at least 10% (from baseline), treatment discontinuation due to toxicity, clinically assessed disease progression, or death. We estimated the survival functions in both cohorts with the Turnbull estimator for interval censored data (as we only observe the interval in which the event occurs, not the point in time) and compared them using the log-rank test. We repeated this analysis with the subgroup of patients on FOLFIRI backbone chemotherapy, with the subset of patients who presented wild-type BRAF status (by excluding patients with a confirmed BRAF mutation) and with the proportion of individuals presenting a left-sided primary tumour, to assess the sensitivity of our results to the type of supporting chemotherapy, to the tumour mutation status, and to the sidedness of the primary tumour.

Statistical analyses were performed using R x64 3.3.2.

Results

Patient characteristics

Between January 2017 and April 2018, 44 patients complied with all the inclusion and exclusion criteria and were recruited. Of these, 25 (57%) were clinically selected for bevacizumab therapy, while 19 (43%) patients were prescribed a cetuximab-containing regimen. The study flow diagram is illustrated in Fig. 1.

Except for RAS mutation status—all patients from bevacizumab cohort harboured RAS activating mutations, whereas every cetuximab patient presented wild-type RAS status—and choice of backbone chemotherapy, baseline characteristics were generally well balanced across treatment groups, with no significant differences found (Table 1).

Patient-reported outcomes

Six patients in cetuximab arm and three patients in bevacizumab arm were allocated to treatment but did not complete the PRO instruments at the first two time points (Fig. 1). Thus, the full analysis set for the QoL outcomes comprised 35 patients (cetuximab, $n = 13$; bevacizumab, $n = 22$). QLQ-C30/QLQ-CR29 completion consistently decreased from baseline to 6-week and 12-week assessments, as an increasing number of patients discontinued the study drugs due to disease progression, intolerable toxicity, physician decision, or non-medical reasons (Fig. 1). At the end of the follow-up, only 9 cetuximab (47.4%) and 16 bevacizumab (64.0%) patients were available for the PRO measurements. Questionnaire compliance—defined as the proportion of patients who completed both questionnaires among those who were expected to complete them at each time point, i.e. excluding those patients who discontinued the study follow-up due to reasons defined in the protocol—was 100% at all preplanned assessments.

Median baseline scores from the GHS and the composites of functional and symptom scales were similar between both treatment groups (Figs. 2, 3 and 4). Throughout the study period, we observed a progressive deterioration in median QoL as measured by the GHS, but only in the cetuximab arm, whereas no such decline was detected in the same outcome measure for patients treated with bevacizumab (Fig. 2). In the cetuximab cohort, we observed a deterioration of at least 10% in GHS in 53.8% (95% CI 25.1–80.8%) of the patients between baseline and 6-week assessment, and in 66.7% (95% CI 29.9–92.5%) of the patients between baseline and 12-week assessment. In the bevacizumab cohort, only 18.2% (95% CI 5.2–40.3%)

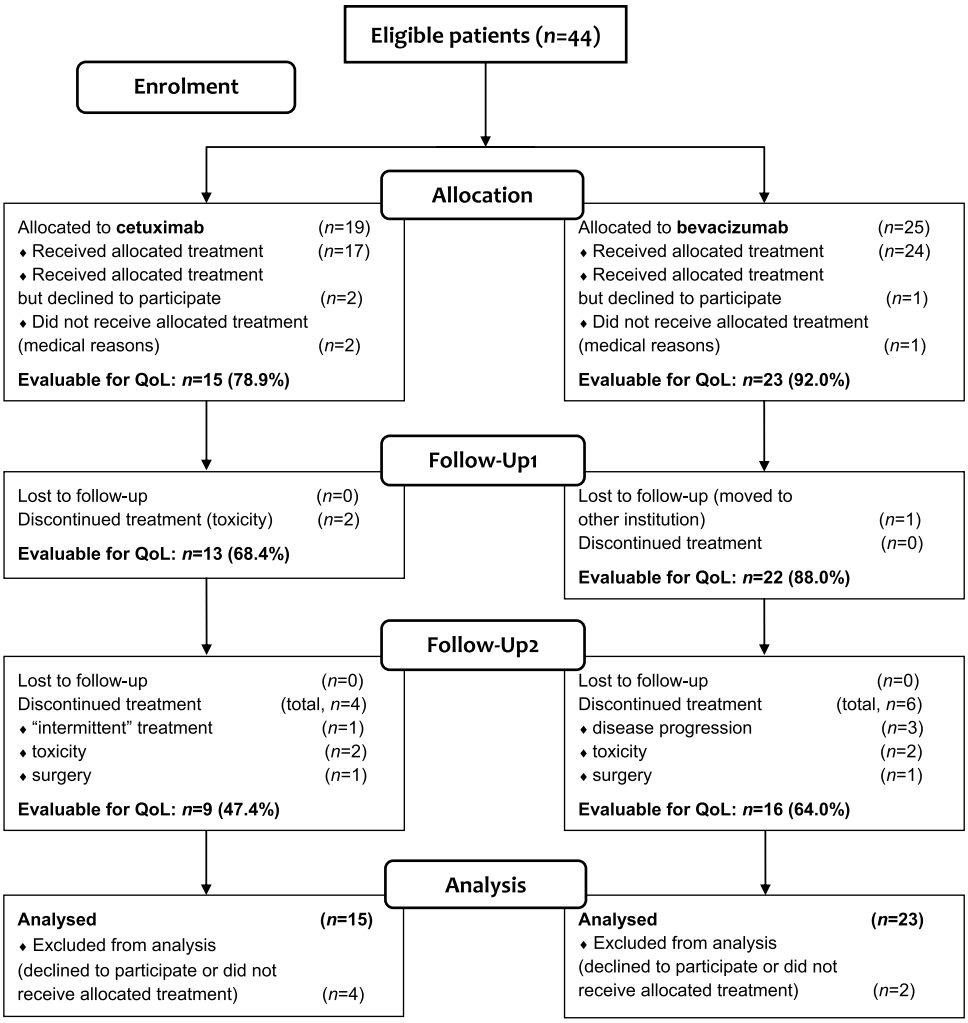

Fig. 1 Study flow diagram. Diagram illustrating the progress through the phases of the parallel cohort study. *QoL* quality of life

of the patients deteriorated in GHS between baseline and 6-week assessment, and 12.5% (95% CI 1.6–38.3%) between baseline and 12-week assessment (Table 2). There was no apparent difference between arms in the composite measure of functional scales through time (Fig. 2). However, the proportion of patients experiencing a decline in functional scales was higher for cetuximab (Table 2). Additionally, we observed an increased scoring on the aggregated symptom scales in cetuximab arm comparing to the bevacizumab cohort (Fig. 3, Table 2).

Overall treatment utility (OTU)

All patients who completed the baseline questionnaires ($n=38$, Fig. 1) were included in the OTU survival analysis. Treatment utility rates were 88.6% at 6 weeks and 69.8% at 12 weeks for bevacizumab, compared to 49.0% at 6 weeks and 19.1% at 12 weeks for cetuximab (Fig. 5). The difference in the estimated survival probabilities between the two cohorts was statistically significant ($p=0.004$) and proved robust to three sensitivity analyses, where we restricted the analysis to the subset of patients who did not present BRAF mutations, to the subgroup of patients receiving FOLFIRI chemotherapy as backbone, and to the proportion of individuals with left-sided primary tumours (Supplementary material).

Discussion

Evidence assessment

Our findings suggest that treating mCRC patients with cetuximab plus chemotherapy results in considerable deterioration of HRQoL and progressively poorer PRO scoring throughout the first three months of treatment. As a point of reference, the GHS degradation here reported for an important proportion of cetuximab patients corresponds to a clinically meaningful change in QoL as pointed by others (Snyder et al. 2015; Osoba et al. 1998). Interestingly, no

Table 1 Patient baseline characteristics and distribution of backbone chemotherapy

Baseline characteristics	Bevacizumab ($N=25$)	Cetuximab ($N=19$)
Female [% (*n*)]	44.0 (11)	42.1 (8)
Ostomised patients [% (*n*)]	28.0 (7)	26.3 (5)
RAS mutation [% (*n*)]	100 (25)	0 (0)
BRAF mutation [% (*n*)]	0 (0)	5.3 (1)
Age [mean (SD)]	62.6 (11.6)	66.5 (9)
BMI [mean (SD)]	25.3 (4.6)	27.6 (5.7)
Therapy line [median (min; max)]	1 (1; 3)	1 (1; 3)
Previous CT cycles [median (min; max)]	1 (0; 6)	1 (0; 8)
ECOG PS [median (min; max)]	0 (0; 2)	0 (0; 2)
Primary tumour location		
Left sided [% (*n*)]	64.0 (16)	68.4 (13)
Right sided [% (*n*)]	36.0 (9)	26.3 (5)
Left and right sided (synchronous tumours) [% (*n*)]	0 (0)	5.3 (1)
Metastatic location(s)		
Liver only [% (*n*)]	20.0 (5)	15.8 (3)
Lung only [% (*n*)]	20.0 (5)	10.5 (2)
Peritoneal only [% (*n*)]	4.0 (1)	10.5 (2)
Multiple locations [% (*n*)]	56.0 (14)	63.2 (12)
Backbone chemotherapy		
FOLFIRI [% (*n*)]	48.0 (12)	84.2 (16)
FOLFOX [% (*n*)]	36.0 (9)	10.5 (2)
CAPOX [% (*n*)]	8.0 (2)	0 (0)
Irinotecan [% (*n*)]	8.0 (2)	5.3 (1)

SD standard deviation, *BMI* body mass index (kg/m^2), *CT* (backbone) chemotherapy, *ECOG PS* Performance Status per Eastern Cooperative Oncology Group criteria, *FOLFIRI* 5-fluorouracil + irinotecan, *FOLFOX* 5-fluorouracil + oxaliplatin, *CAPOX* capecitabine + oxaliplatin

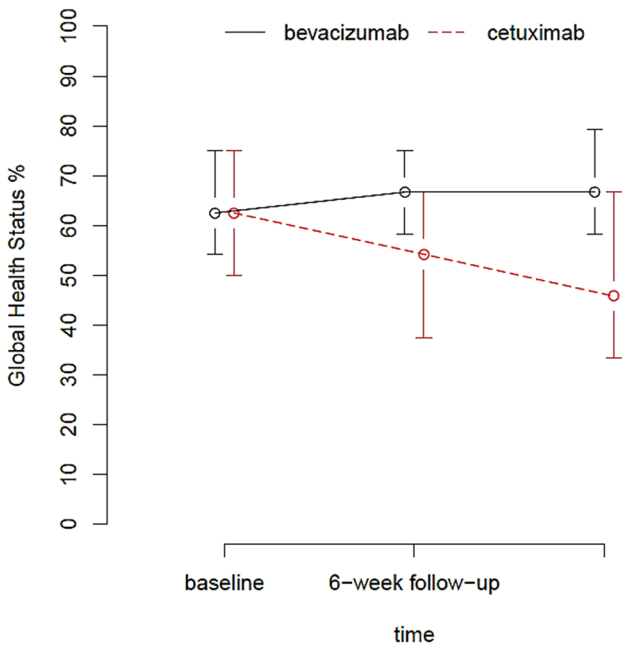

Fig. 2 Global Health Status. Global Health Status median scores from both cohorts at baseline, 6-week follow-up, and 12-week follow-up. Vertical lines represent 95% Confidence intervals

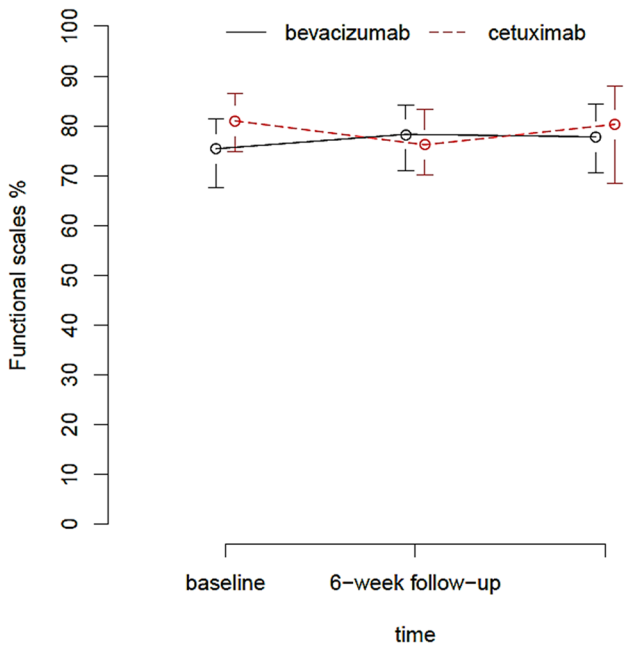

Fig. 3 Functional scales. Composite of functional scales median scores from both cohorts at baseline, 6-week follow-up, and 12-week follow-up. Vertical lines represent 95% Confidence intervals

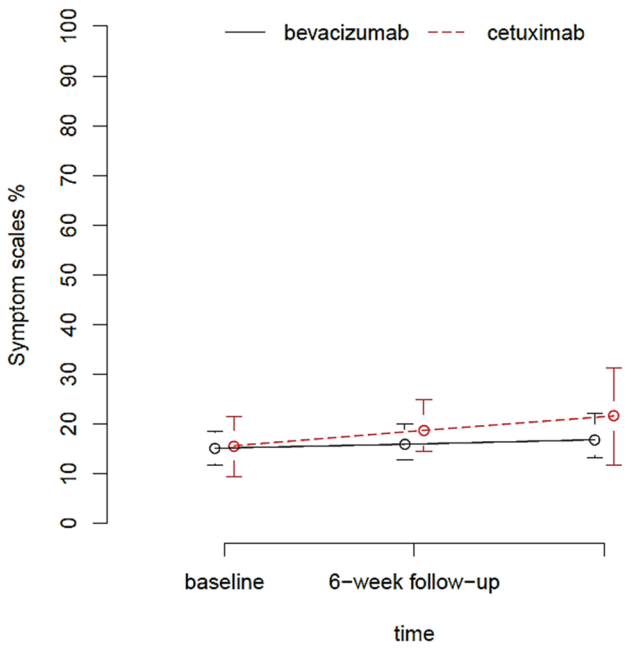

Fig. 4 Symptom scales. Composite of symptom scales median scores from both cohorts at baseline, 6-week follow-up, and 12-week follow-up. Vertical lines represent 95% Confidence intervals

significant variations from baseline were observed in these patients for the composite of functional scales, although we can distinguish a trend towards degradation in some isolated functional domains, mainly in physical, role, emotional, and social functioning, but not in body image (Table 2). Conversely, we would expect a change in the body image scale, driven by the incidence of skin-related toxicities that frequently occur in cetuximab-treated patients (Heinemann et al. 2014; Venook et al. 2017). This implies that the downgrading of GHS could be mostly attributed to patients' individual experiences derived from an increasing symptom burden, and its perceived impact in daily routine in terms of magnitude or frequency, rather than the result from a major change in self-image.

A similar deterioration in self-reported QoL was not observed, however, in bevacizumab-treated patients, whose scoring on GHS, and aggregate of functional and symptom scales maintained steady throughout both follow-up time points. Such difference between cohorts suggests that patients without a RAS mutation, the main observed driver for patient allocation, could potentially have benefited in terms of QoL by having received bevacizumab instead of cetuximab.

The difference in PRO scoring between arms was also reflected in the results of the Overall Treatment Utility outcome. This time-to-event analysis, a composite of Progression-Free Survival (PFS) and HRQoL, favoured the use of bevacizumab-containing regimens, implying that, in the short term, there is an improvement in the trade-off between QoL and clinical effectiveness for bevacizumab when compared to cetuximab, driven by the higher risk of deterioration of cetuximab patients' QoL. Our results sustained their consistency when we restrained the analysis to FOLFIRI chemotherapy backbone, BRAF wild-type, and left-sided primary tumour subgroups.

We observed a high dropout rate (36.0% in bevacizumab arm vs 52.6% in cetuximab arm), which is coherent with the safety profile of the treatment strategies used and with the natural history of this aggressive disease, since treatment discontinuations were mostly in consequence of toxicity or disease progression. Considering the dropout rates, and the relatively small initial size of both cohorts, our results should be interpreted carefully. For this reason, we have chosen to mainly substantiate our interpretation of functional and symptom scales in the more robust composite outcomes, rather than in the singular domains that result of fewer observations.

Limitations

This study presents with some intrinsic limitations that should be discussed in light of our findings. PRO studies support their assessments in patient perspectives, which can be influenced by the response shift phenomenon, defined as a change over time in "internal standards, values, or conceptualizations" leading to patient-level variations on how they would have responded retrospectively (Snyder et al. 2015). Degradation in QoL through time, as we encountered in this study, is considered to be sensitive to response shifts, leading to potential bias through the underestimation of self-perceived negative effects (Snyder et al. 2015). On the other hand, PRO measurements derived from real-world data are less likely to be influenced by patient expectations than they would be, for instance, in an open-label RCT evaluating a new drug.

Nonetheless, the observational nature of the study leads to an underlying selection bias, which can convey to an unbalanced distribution of unknown confounding. However, our findings suggest that RAS mutation status (the presence of a mutation in exons 2, 3 or 4 of KRAS or NRAS genes) was probably the only variable directly influencing treatment selection, and could have functioned, therefore, as an instrumental variable. Such variable has the potential for indirectly adjusting the sample for other known or unknown covariates throughout a quasi-randomization process, minimizing selection bias from other sources (Burgess et al. 2017). This hypothesis is supported by the balance found in the distribution of all baseline characteristics other than RAS status, including the primary tumour location, which apparently did not influence the choice of targeted therapy strategy.

Table 2 Median scores at the three time points and deterioration from baseline for QLQ-C30/QLQ-CR29 global health status (GHS), isolated and composite functional scales, and composite symptom scales

	Bevacizumab cohort					Cetuximab cohort				
	Baseline (t0)	6-week follow-up (t1)	12-week follow-up (t2)	Deterioration (%): t0 vs t1	Deterioration (%): t0 vs t2	Baseline (t0)	6-week follow-up (t1)	12-week follow-up (t2)	Deterioration (%): t0 vs t1	Deterioration (%): t0 vs t2
GHS/QoL	62.5 (54.2, 75)	66.7 (58.3, 75)	66.7 (58.3, 79.2)	18.2 (5.2, 40.3)	12.5 (1.6, 38.3)	62.5 (50, 75)	54.2 (37.5, 66.7)	45.8 (33.3, 66.7)	53.8 (25.1, 80.8)	66.7 (29.9, 92.5)
Physical functioning	86.7 (73.3, 96.7)	83.3 (66.7, 93.3)	86.7 (80, 93.3)	18.2 (5.2, 40.3)	18.8 (4, 45.6)	80.0 (73.3, 86.7)	73.3 (63.3, 83.3)	70.0 (53.3, 86.7)	46.2 (19.2, 74.9)	44.4 (13.7, 78.8)
Role functioning	91.7 (75, 100)	83.3 (66.7, 100)	83.3 (58.3, 100)	22.7 (7.8, 45.4)	12.5 (1.6, 38.3)	83.3 (75, 100)	66.7 (50, 83.3)	81.7 (66.7, 91.7)	61.5 (31.6, 86.1)	33.3 (7.5, 70.1)
Emotional functioning	75.0 (62.5, 83.3)	79.2 (70.8, 87.5)	83.3 (75, 91.7)	4.5 (0.1, 22.8)	12.5 (1.6, 38.3)	91.7 (83.3, 95.8)	87.5 (75, 95.8)	83.3 (66.7, 100)	7.7 (0.2, 36)	22.2 (2.8, 60)
Cognitive functioning	91.7 (83.3, 100)	91.7 (83.3, 91.7)	91.7 (83.3, 100)	18.2 (5.2, 40.3)	12.5 (1.6, 38.3)	91.7 (83.3, 100)	91.7 (83.3, 100)	91.7 (75, 100)	15.4 (1.9, 45.4)	22.2 (2.8, 60)
Social functioning	83.3 (75, 91.7)	83.3 (66.7, 83.3)	83.3 (66.7, 100)	27.3 (10.7, 50.2)	18.8 (4, 45.6)	91.7 (83.3, 100)	83.3 (75, 100)	83.3 (75, 100)	53.8 (25.1, 80.8)	33.3 (7.5, 70.1)
Body image	77.8 (66.7, 94.4)	83.3 (72.2, 94.4)	77.8 (55.6, 94.4)	31.8 (13.9, 54.9)	43.8 (19.8, 70.1)	88.9 (77.8, 100)	83.3 (72.2, 88.9)	88.9 (61.1, 100)	46.2 (19.2, 74.9)	44.4 (13.7, 78.8)
Anxiety	66.7 (50, 83.3)	66.7 (50, 83.3)	66.7 (50, 83.3)	0.0 (0.0, 15.4)	0.0 (0.0, 20.6)	66.7 (50, 83.3)	66.7 (50, 83.3)	66.7 (50, 100)	23.1 (5, 53.8)	11.1 (0.3, 48.2)
Weight	66.7 (66.7, 83.3)	83.3 (66.7, 100)	66.7 (66.7, 83.3)	27.3 (10.7, 50.2)	12.5 (1.6, 38.3)	83.3 (66.7, 100)	83.3 (66.7, 100)	83.3 (83.3, 100)	46.2 (19.2, 74.9)	22.2 (2.8, 60)
Composite functional scales	75.4 (67.5, 81.4)	78.3 (70.9, 84.1)	77.8 (70.6, 84.4)	9.1 (1.1, 29.2)	6.2 (0.2, 30.2)	81.0 (74.9, 86.5)	76.2 (70.2, 83.3)	80.3 (68.4, 88.0)	23.1 (5.0, 53.8)	22.2 (2.8, 60.0)
Composite symptom scales	15.1 (11.6, 18.4)	15.9 (12.7, 19.9)	16.8 (13.2, 22.1)	NA	NA	15.6 (9.3, 21.5)	18.7 (14.4, 24.8)	21.6 (11.8, 31.3)	NA	NA

Lower scores in GHS or functional scales denote decreased QoL or functioning. Higher scores in symptom scales indicate increased symptom burden. Deterioration represents the proportion of patients experiencing a decrease of at least 10 points from the baseline assessment (not applicable, NA, for symptom scales). 95% Confidence Intervals are represented in brackets

QLQ-C30 Quality of Life Questionnaire Core 30 items, *QLQ-CR29* Quality of Life Questionnaire Colorectal Cancer 29 items, *GHS* global health status, *QoL* quality of life

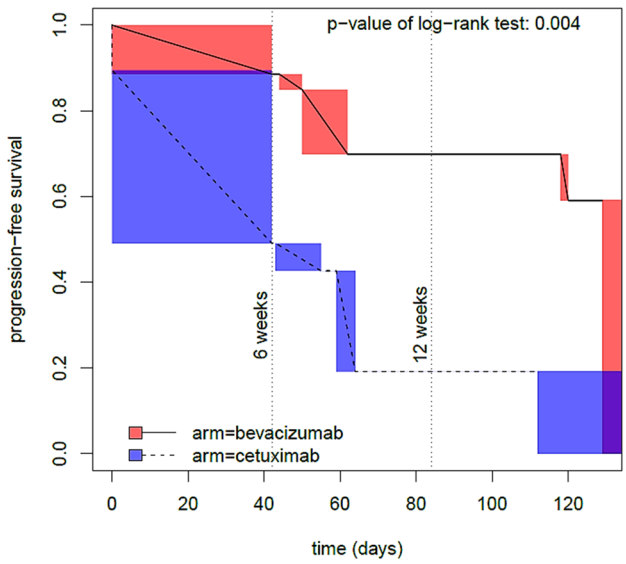

Fig. 5 Overall treatment utility. "Progression"-free survival curves from both cohorts, with progression defined by a clinical event or a meaningful degradation in patient-reported outcomes. Turnbull's estimator was used to calculate the survival function

Additionally, our real-world data are exposed to information bias, as they were collected from records generated in daily practice and the assessments (e.g. disease progression) were performed as per clinician discretion, with the single exception of PRO measurements.

As expected, since mutated patients are unresponsive to cetuximab, RAS status was unbalanced between both cohorts, leading to different molecular patient profiles. Considering that all bevacizumab patients carried a RAS mutation, any attempt to conduct a sensitivity analysis based on this variable was impaired. Nevertheless, RAS mutation status is not considered to be a predictor of PFS in bevacizumab-treated patients (Cremolini et al. 2015; Hegewisch-Becker et al. 2018) and, thus, it is unlikely that a more aggressive disease in these patients could have influenced our findings.

To minimise a potential survival bias, the study was designed to capture PROs solely for the first six cycles of fortnightly chemotherapy (or for the four initial cycles of every 3-week schedule, considered equivalent), which implied only a short-term follow-up of approximately three months per patient. Consequently, we were unable to assess medium- or long-term outcomes of both treatment strategies.

Lastly, our study was conducted in a single institution throughout a relatively short period of 19 months. Although this is not a limitation per se, it led, as we anticipated, to a reduced sample size, which does not provide enough statistical power to detect modest differences in outcomes, particularly when it comes to analyse variations in individual domains from PRO instruments.

Implications for research

Further research is needed to validate our findings, by conducting larger and randomised studies, which should compare both PRO measurements and standardised clinical outcomes from cetuximab and bevacizumab. Two previous RCTs assessed comparative safety of both drugs in first-line setting, and no noteworthy toxicity signals were found that could distinguish between them in what concerns to tolerability (Heinemann et al. 2014; Venook et al. 2017). Our results suggest that the patient-perceived impact of toxicities from both treatments differs from the physician-assessed CTCAE measurements used in those studies. This is in line with previous research (Basch 2010; Di Maio et al. 2015; Atkinson et al. 2016), and should be further explored in mCRC therapy, particularly due to the underlying palliation intent that is assumed for most patients.

Additionally, and given the low tolerability found for cetuximab regimens in a considerable proportion of patients, future research should focus on testing innovative risk-reduction strategies, such as the identification of new patient-level (bio)markers that could help to predict individuals more likely to benefit from cetuximab therapy or at a higher risk of developing serious toxicity. This would allow a more accurate patient selection to this treatment, tailoring therapy to maximise its risk–benefit profile.

Implications for clinical practice

The results of our study are of particular importance to inform clinical practice, since they apply directly to most mCRC patients. On the one hand, we found no significant deterioration in quality of life of RAS-mutated patients treated with bevacizumab, which firmly supports current treatment guidelines for this population (Van Cutsem et al. 2016). On the other hand, our results also make an interesting case for recommending first-line bevacizumab in RAS wild-type disease, particularly for situations where palliation is considered as the major goal, as cetuximab appears to be less tolerable, when valuing patients' experiences.

In the choice of all chemotherapeutic regimens, it is crucial to discuss patient values and preferences. We believe that the comparative benefit of cetuximab, when considering long-term Overall Survival in extended-RAS wild-type patients (Heinemann et al. 2014; Venook et al. 2017; Elez et al. 2015), can still outweigh its undesirable consequences, at least for individuals who are more fit and have a higher life expectancy at baseline. However, not all patients would be best served with this treatment, owing to its perceived impact on quality of life, particularly when analysed in the context of its associated PFS (Fallowfield and Fleissig 2012). The trade-off between the expected clinical effectiveness, overall or specific toxicities, and tolerability, should be

paramount for the shared decision-making process underpinning the choice of a treatment strategy. This must be based on full available evidence of the balance between benefits and harms, resource implications, and, crucially, on patient expectations and preferences, implying that therapy should be tightly tailored to the individual patient's circumstances.

Conclusions

This prospective head-to-head cohort study provides evidence suggesting that, in patients with mCRC, cetuximab-containing regimens lead to a progressive negative impact on PROs and global HRQoL, when compared to baseline and bevacizumab. Future research is needed to confirm these results. Our findings demonstrate the value of PROs when assessing comparative effectiveness of different treatment regimens.

Author contributions RPM and APM conceived, designed, and planned the study. RPM led the study assessments and data acquisition process. HLP and AQ provided expertise on metastatic colorectal cancer and contributed to data acquisition. RPM interpreted and discussed the results. PH performed the statistical analysis, interpreted, and discussed the results. RPM and PH contributed to drafting of the manuscript. All authors read, provided feedback, and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Approved by local committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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