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Patient-Reported Outcomes and Health-Related Quality of Life for cetuximab versus bevacizumab in metastatic colorectal cancer: a prospective cohort study

Rui Pedro Marques (rui.p.marques@chln.min-saude.pt) [a,b], Peter Heudtlass [c], Helena Luna Pais [b], António Quintela [b], Ana Paula Martins [a]

[a] Research Institute of Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal; [b] Centro Hospitalar Universitário de Lisboa Norte (CHULN) – Hospital de Santa Maria, Lisbon, Portugal; [c] Centre for Health Evaluation & Research (CEFAR), Portuguese Pharmacy Association (ANF), Lisbon, Portugal

Background and Objectives

The current standard for treating newly-diagnosed metastatic colorectal cancer (mCRC) consists of a doublet backbone chemotherapy plus cetuximab or bevacizumab. However, uncertainty exists concerning the comparative risk-benefit assessment of these interventions in mCRC, particularly due to the absence of clinical data studying their impact in patients' Health-Related Quality of Life (HRQoL). Patient-Reported Outcomes (PROs), which provide direct measurements of cancer patients' experiences through validated scales, offer a unique angle on treatment toxicity assessments, often showing clinically meaningful differences when compared to standardised clinician assessed tools, as the universally used Common Terminology Criteria for Adverse Events (CTCAE). Moreover, as the cornerstone of a Value-Based Health Care (VBHC) concept, a patient-centred approach requires that patient-driven health information completes the objective clinical data traditionally demanded by regulatory agencies upon drug approval. Patients with mCRC commonly present a considerable burden of symptoms that can, adding to treatment toxicities, have a substantial negative effect on HRQoL and functioning. Therefore, the repercussion of existing treatments on symptom control and HRQoL needs to be considered alongside survival, when comparing the clinical effectiveness of competing therapies. Nevertheless, although two head-to-head clinical trials tested the efficacy and safety of cetuximab versus bevacizumab, none of the studies included PROs as endpoints, and only "equivalent" CTCAE assessed toxicities were reported. We aimed to bridge this gap by conducting a prospective cohort study in mCRC, in order to measure and compare HRQoL outcomes reported by patients treated with cetuximab or bevacizumab.

Methods and Results

PROs were measured through two disease-specific instruments, widely used and thoroughly validated: EORTC QLQ-C30 and QLQ-CR29 questionnaires, which were answered at three sequential time points during treatment, including baseline. Global Health Status (GHS), functional and symptom scales, and Overall Treatment Utility (OTU, a survival endpoint derived from clinical and patient-reported outcomes) were compared for the two treatments. Methods and reporting followed STROBE guidelines for observational studies and SISAQOL / SPIRIT-PRO recommendations for HRQoL data.

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 clinically meaningful (≥10%) deterioration in GHS in cetuximab arm – 53.8% (95%CI: 25.1% to 80.8%) at 6 weeks and 66.7% (95%CI: 29.9% to 92.5%) at 12 weeks – comparing to bevacizumab cohort: 18.2% (95%CI: 5.2% to 40.3%) at 6 weeks and 12.5% (95%CI: 1.6% to 38.3%) at 12 weeks (Table 1, Figure 1).

	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

Table 1 – Median scores during follow-up and deterioration from baseline for GHS, functional and symptom scales

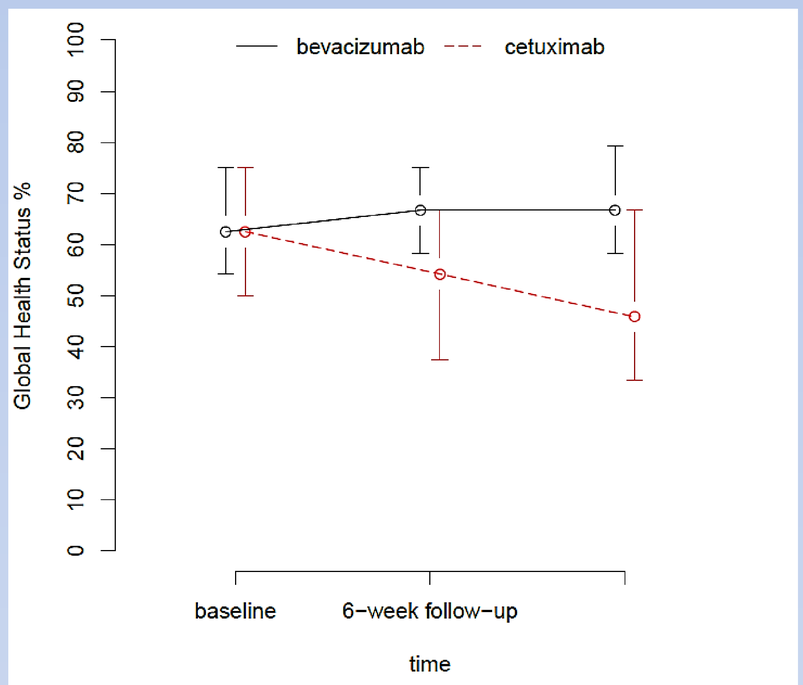

Figure 1 – GHS median scores from both cohorts at baseline, 6-week and 12-week follow-up

Functional scales seemed less affected by treatment allocation (Table 1, Figure 2), but we observed an increased scoring on symptom scales in cetuximab cohort comparing to the bevacizumab arm (Table 1, Figure 3). Treatment utility rates at 6 and 12 weeks, with utility defined by absence of a clinical event or a ≥10% degradation in GHS (Figure 4), were, respectively, 88.6% and 69.8% for bevacizumab, compared to 49.0% and 19.1% for cetuximab (p=0.004), a difference confirmed in subset analyses.

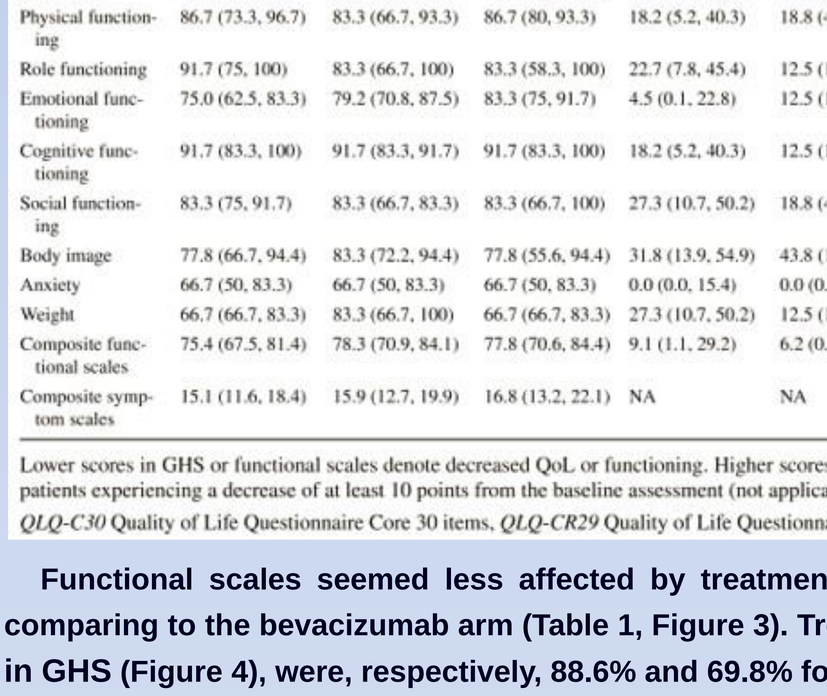

Figure 2 – Functional scales median scores from both cohorts at baseline, 6-week and 12-week follow-up

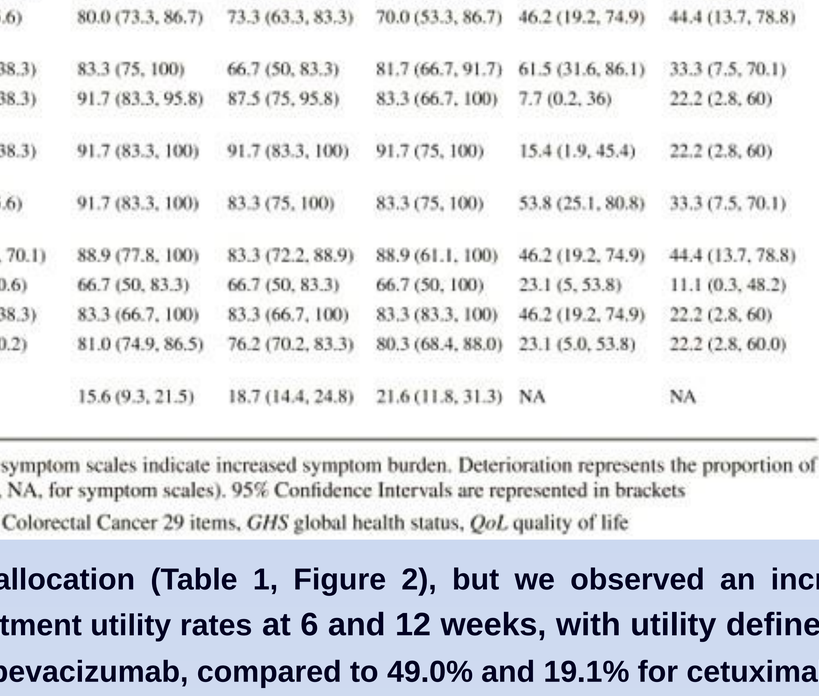

Figure 3 – Symptom scales median scores from both cohorts at baseline, 6-week and 12-week follow-up

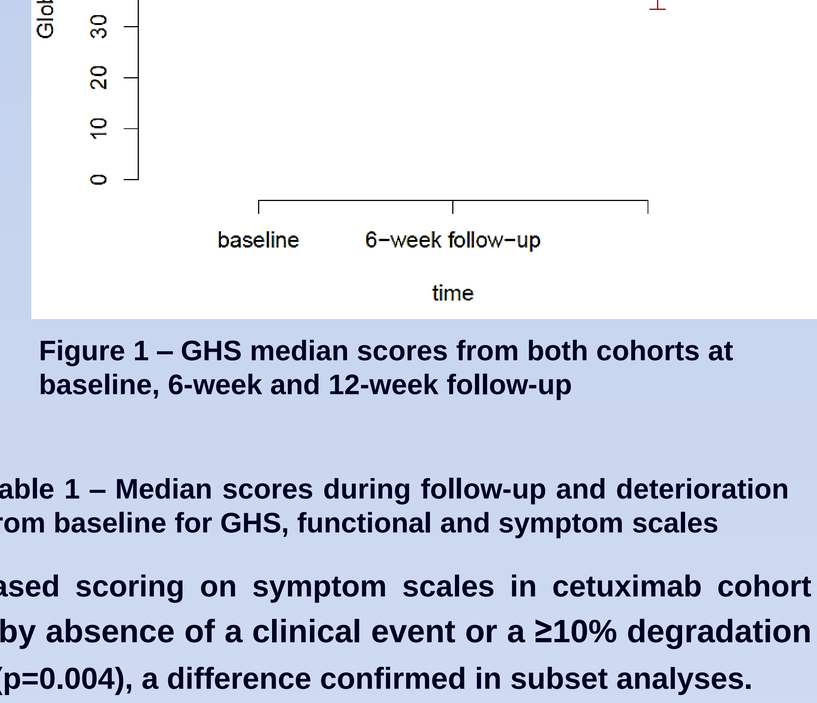

Figure 4 – OTU survival curves from both cohorts

Conclusions and Relevance

This head-to-head prospective cohort study provides evidence suggesting that, in mCRC patients, cetuximab-containing regimens lead to a progressive negative impact on PROs and 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.