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Assessment of exposure-response relationship for bevacizumab in patients with metastatic colorectal cancer

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ABSTRACT

Limited literature is available for bevacizumab exposure-response relationship and there is not a concentration threshold associated with an optimal disease control. This prospective observational study in patients with metastatic colorectal cancer (mCRC) aims to evaluate, in a real-life setting, the relationship between bevacizumab through concentrations at steady state ($C_{trough,\ SS}$) and disease control. $C_{trough,\ SS}$ were drawn, coinciding with the radiological evaluation of the response (progression or clinical benefit). Generalized estimating equations (GEE) analysis was performed. To test the association between $C_{trough,\ SS}$ in each patient with overall survival (OS) or progression-free survival (PFS), Cox proportional hazard models were developed. Data included 50 bevacizumab $C_{trough,\ SS}$ from 27 patients. The GEE model did not suggest any positive association between bevacizumab $C_{trough,\ SS}$ and clinical benefit (OR 0.99, 95% CI: 0.98–1.02, p = 0.863). The Cox regression showed association between higher median $C_{trough,\ SS}$ with better OS (HR 0.86, 95% CI: 0.73–1.01, p = 0.060), but not with PFS. We cannot confirm a relationship between bevacizumab $C_{trough,\ SS}$ and clinical benefit but this is the first real-world study trying to show a relationship between bevacizumab $C_{trough,\ SS}$ and disease control in mCRC. It was conducted in a small sample size which reduces the level of evidence. Further controlled randomized studies with a sufficient number of patients are required.

1. Introduction

Colorectal cancer is the second most diagnosed cancer in women and the third most diagnosed cancer in men worldwide [1]. It has a high mortality rate [1], because 25% of patients are metastatic on diagnosis and 50% develop metastatic disease [2].

One of the treatments used in the metastatic setting is the monoclonal antibody (mAb) bevacizumab, an anti-vascular endothelial growth factor (VEGF) humanized mAb [3]. VEGF is essential for physiologic vascular homeostasis but also in the pathogenesis of tumor growth and metastasis [4].

Dosing of mAbs is often based on body surface area or weight, because of the general perception that dosing based on patients' body size reduces inter-subject variability in distribution and elimination. However, this has recently been challenged [5,6].

Furthermore, it is suggested that the current dosing of cancer mAbs may not be optimal from an efficacy-cost perspective [7]. This is explained, considering no impact in efficacy, when dose reductions would substantially decrease the cost of treatment or in patients with very high drug concentrations [8]. Moreover, in oncology dose

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modifications are usually reductions due to toxicity, but rarely is the dose increased in the absence of efficacy or toxicity [9,10].

Therapeutic drug monitoring (TDM) has the potential in oncology to optimize drug use in clinical practice. However, TDM in oncology is less developed than in other areas, like infectious diseases, psychiatry, neurology, etc. [9]. Despite the fact that mAbs have many of the requisites for TDM [8,11,12] – exposure-response relationship, no direct clinical measurement of drug effect, interindividual pharmacokinetic (PK) variability, flexibility in dosing and the availability of quantitative and reliable clinical testing – there is a limited number of studies in oncology supporting TDM of mAbs [5,12]. One of the reasons is the lack of a target concentration to be effective in each disease, information which is necessary for PK-Pharmacodynamic studies [13].

Important bevacizumab population PK research in oncology show its linearity, the PK parameters, the interindividual variability and the covariates [14–16]. Nevertheless, a limited number of studies making an association between clinical response and exposition for bevacizumab have been conducted so far [14,17–19]. A study performed on 13 glioma patients observed a treatment efficacy/side effects ratio with concentration between 200 and 250 mg/L [17]. In colorectal cancer, there are three studies: Caulet et al. [14] found a relationship between trough concentration (C_{trough}) on 14 day > 15.5 mg/L with higher overall survival (OS) ($p = 0.006$) and higher progression-free survival (PFS) ($p = 0.0039$). Also, on 14 day, Akbulut et al. [18] observed that patients with $C_{trough} > 25$ mg/L had higher OS ($p = 0.0198$). And it was Papachristos et al. [19] who found an association between trough concentrations at steady state ($C_{trough, SS}$) ≥ 87.9 mg/L with higher OS ($p = 0.0003$).

The aim of the present study was to assess the relationship between bevacizumab $C_{trough, SS}$ and clinical benefit in a real-world setting.

2. Material and methods

2.1. Design

A prospective observational study in a real-life setting was conducted in a tertiary referral hospital to assess the relationship between bevacizumab $C_{trough, SS}$ and response in patients with metastatic colorectal cancer (mCRC). This study was carried out in accordance with the Declaration of Helsinki and approved by the research ethics committee of Severo Ochoa University Hospital of Madrid (Spain). Prior to participating in this study, all patients provided signed informed consent. We complied with the law regarding patient confidentiality and data protection.

2.2. Participants

Patients were eligible, if they were over 18 years old with mCRC, measurable disease, receiving bevacizumab as part of their treatment and with a minimal life expectancy of three months after inclusion. Patients were enrolled between February 2018 and January 2020. The end of follow-up was 31 January 2020.

2.3. Treatment

Patients were treated according to standard guidelines and routine care of the institution. Bevacizumab was therefore administered following standard recommendations in patients with colorectal cancer, i.e., 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg every 3 weeks in combination with chemotherapy or not (maintenance).

2.4. Bevacizumab concentration measurements

Blood samples (3 mL) to determine bevacizumab concentrations were collected after at least three months of treatment to ensure that steady state has been reached [3] and immediately before administration of the next dose of bevacizumab ($C_{trough, SS}$). Furthermore, blood samples were drawn, coinciding with the radiological evaluation of the response. Bevacizumab $C_{trough, SS}$ were available across time (from one to six times according to tumor assessments and treatment discontinuation). Samples were collected in EDTA tubes and centrifuged at 1000 g for 10 min to obtain blood plasma. The samples were stored at −20 °C and transported at −80 °C for their analysis. Plasma concentrations were determined in University Hospital Complex of Canary (Tenerife, Spain) using an ELISA kit (SHIKARI Q-BEVA) with automated TRITURUS analysis system (Grifols). To minimize the internal variability of the procedure, each sample was analyzed in duplicate and the mean was used.

2.5. Clinical endpoints

Tumor assessments by radiological examination were performed every 12 weeks or when clinically indicated. The response was measured in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [20]. Patients responses were classified into 2 categories: progression or clinical benefit (complete response, partial response and stable disease).

At each time point alkaline phosphatase and serum albumin concentrations were measured.

PFS was defined as the time from first bevacizumab infusion to progressive disease or death from any cause or time of the last follow-up. OS was defined as the time from the first infusion of bevacizumab to death from any cause.

2.6. Statistical analysis

Numerical variables are shown as medians (percentiles 25 and 75) and categorical variables are presented as frequencies (percentages).

To assess the association between the bevacizumab $C_{trough, SS}$ and clinical benefit, a generalized estimating equations (GEE) regression analysis was performed [21]. This analysis takes into account the correlation of the different measures of $C_{trough, SS}$ throughout the study for each patient. A dependent variable was clinical benefit (proven or not) at each time point of tumor assessment. The link function was logit and the covariance structure was exchangeable. As an independent variable, bevacizumab $C_{trough, SS}$ was introduced at each time point. The odds ratio (OR) shows the association for each additional mg/L of bevacizumab $C_{trough, SS}$ with clinical benefit. The corresponding 95% confidence intervals (95% CI) were also obtained.

Median follow-up was estimated through the reverse Kaplan-Meier method [22]. OS and PFS were assessed. Four univariable Cox proportional hazard models were developed to test the association between the median bevacizumab $C_{trough, SS}$ (mg/L) in each patient or the last measure with each one of the outcomes (OS and PFS, respectively). Survival curves were estimated by means of the Kaplan-Meier method.

In addition, univariable Cox proportional hazard models were developed to test the association between the patients' variables with each one of the outcomes.

Significance level was established at 0.05. Software used has been Stata/IC v.16. (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

3. Results

3.1. Patients

A total of 31 patients provided signed informed consent. Two patients were excluded because they were not metastatic and one because the only concentration that had been determined for him was not in a steady state. Finally, 28 patients with mCRC were evaluated. Patients' baseline characteristics are shown in Table 1. Only 9 patients (32%) received bevacizumab in first-line treatment for metastatic disease.

Table 1
Patients' baseline characteristics. CAPECITABINE: bevacizumab 7.5 mg/kg d1, capecitabine 1000 mg/m^2 per 12 h d1–14 every 3 weeks; ECOG PS: Eastern Cooperative Oncology Group Scale of Performance Status; FOLFIRI: bevacizumab 5 mg/kg, irinotecan 180 mg/m^2, calcium folinate 400 mg/m^2, fluorouracil 400 mg/m^2 bolus, fluorouracil 2400 mg/m^2 over 46 h every 2 weeks; mFOLFOX 6: bevacizumab 5 mg/kg, oxaliplatin 85 mg/m^2, calcium folinate 400 mg/m^2, fluorouracil 400 mg/m^2 bolus, fluorouracil 2400 mg/m^2 over 46 h every 2 weeks; XELOX: bevacizumab 7.5 mg/kg d1, oxaliplatin 130 mg/m^2 d1, capecitabine 1000 mg/m^2 per 12 h d 1–14 every 3 weeks.

Characteristic	Median	Interquartile range
Age at inclusion, years	75	69–78
Body weight, Kg	70	58–79
Height, cm	162	155–168
	n	**%**
Sex		
Male	17	60.71
Female	11	39.29
Primary tumor site		
Colon	17	60.71
Rectum	11	39.29
ECOG PS at diagnosis		
0	14	50
1	11	39.29
2	3	10.71
Disease extent at inclusion		
Pulmonary metastasis	15	53.57
Peritoneal metastasis	7	25
Hepatic metastasis	20	71.43
Other location metastasis	7	25
Number of metastases		
1–5	13	46.43
6–10	9	32.14
>10	6	21.43
Comorbidities		
0	16	57.14
≥1	12	42.86
Concomitant chemotherapy at inclusion		
XELOX	4	14.29
mFOLFOX 6	5	17.85
FOLFIRI	7	25.00
CAPECITABINA	12	42.86
Bevacizumab posology		
5 mg/kg/2sem	11	39.29
7.5 mg/kg/3sem	17	60.71

3.2. Concentrations and responses

For identifying outliers we applied the rule based on 1.5 x interquartile range (IQR): only one value (198.68 mg/L) was above >1.5×IQR. Subsequently, this patient's unique concentration was excluded from posterior analysis.

Finally, data included 50 bevacizumab $C_{trough,\ ss}$ from 27 adult patients with mCRC (minimum 1 concentration measured per patient and maximum 6, average 1.9). Mean $C_{trough,\ ss}$ was 42.42 ± 36.37 mg/L. The dosing regimen that reached higher median concentrations (41 mg/L) was 7.5 mg/kg every 3 weeks, the most frequent dosing regimens in the study population (Table 2).

It was found that the mean $C_{trough,\ ss}$ in accordance with tumor response or progression was not homogeneous from first to sixth extraction.

Table 2
Trough concentrations at steady state according to bevacizumab dosage (n = 50). Max: maximum; Min: minimum; SD: standard deviation.

Bevacizumab dosage	Mean (mg/L)	SD (mg/L)	Median (mg/L)	Min (mg/L)	Max (mg/L)
5 mg/kg every 2 weeks	27.56	19.40	26.30	1.76	72.03
7.5 mg/kg every 3 weeks	53.19	41.96	41.3	2.03	171.4

3.3. Exposure-response relationship

We assessed if the drug exposure over time was associated with a clinical response. $C_{trough,\ ss}$ was measured more than once for each patient and was entered into the model as time 1, 2 and so on respectively for each patient. No relationship between drug exposure and clinical response was detected. The GEE model did not suggest any positive association between bevacizumab $C_{trough,\ ss}$ and clinical benefit (OR 0.99, 95%CI: 0.98–1.02, p = 0.863).

Therefore, a clinical benefit predicted probability plot (with 95% CI) versus $C_{trough,\ ss}$ at increments of 20 mg/mL was drawn (Fig. 1). As can be appreciated from this Figure, the predicted probability remained relatively constant around 70%, irrespective of the concentrations.

The median follow-up was 14 months (95% CI: 9–16 months). OS was 25 months (95% CI: 17.47- not estimable) (Fig. 2). The Cox regression showed that higher median $C_{trough,\ ss}$ was associated with better OS (HR 0.86, 95% CI: 0.73–1.01, p = 0.060) and this relationship was also found with last $C_{trough,\ ss}$ (HR 0.87, 95% CI: 0.74–1.01, p = 0.064).

The median PFS was 11 months (95% CI: 6.33–17.47 months). Conversely, no association was observed between median $C_{trough,\ ss}$ (HR 0.98, 95% CI: 0.96–1.01, p = 0.213) nor last $C_{trough,\ ss}$ (HR 0.99, 95% CI: 0.98–1.01, p = 0.312) with PFS.

We assessed whether there was an association between the ECOG PS at each point in time (0–1 vs ≥2) and the $C_{trough,\ ss}$. No association was found (OR 0.99, 95%CI: 0.97–1.02, p = 0.837).

The univariate analysis identified the age (HR 1.09, 95% CI: 1.01–1.18, p = 0.029), the median alkaline phosphatase concentration (HR 1.03, 95% CI: 1.00–1.06, p = 0.049) and the median serum albumin concentration (HR 0.27, 95% CI: 0.07–1.05, p = 0.059) as risk factors of progression.

4. Discussion

Unfortunately, the main outcome to assess the relationship between $C_{trough,\ ss}$ and clinical benefit was not found. Instead, exposure was associated with better OS with a slightly statistically significant value, probably due to the limited sample size. This association was not observed with PFS, a fact that may be explained by 3 of 16 patient progressions continuing treatment with bevacizumab. Previous studies, such as Bennouna et al. [23], have shown that the use of bevacizumab after disease progression could increase survival, a situation already observed by Caulet et al. [14] after two months of treatment.

Other studies found statistical relationship between exposure and response to bevacizumab treatment in mCRC [14,18,19]. This discrepancy with previous studies might be explained by the limitations in recruitment as unique center, differences in patient population (as study in clinical practice the patients were treated with different dosing

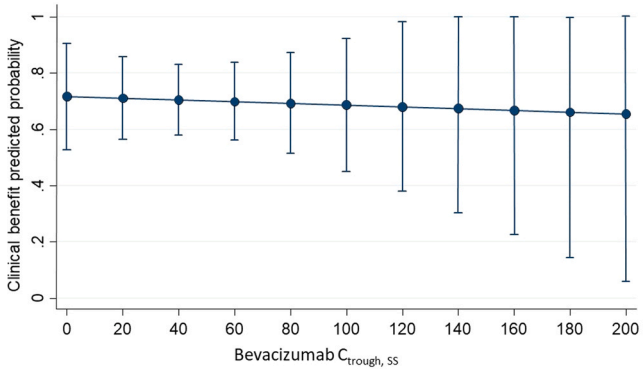

Fig. 1. Clinical benefit predicted probability plot (with 95% confidence intervals) versus bevacizumab trough concentrations at steady state ($C_{trough,\ ss}$) at increments of 20 mg/mL.

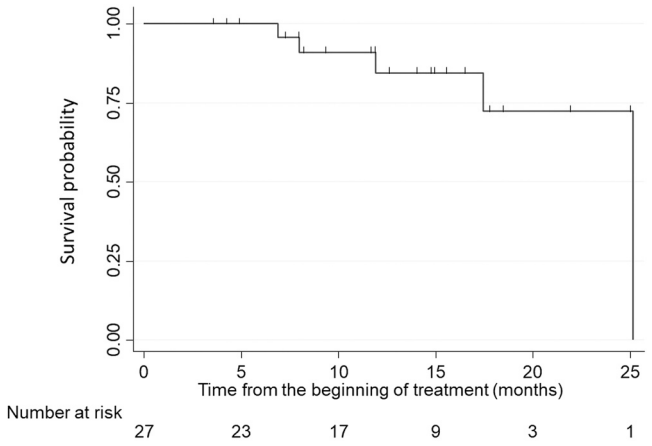

Fig. 2. Kaplan-Meier curve of overall survival.

regimens, chemotherapies and line treatment in metastatic disease), the high inter-individual variability in concentrations or poor correlation between response rate and survival. On the other hand, to validate target concentration of antitumor mAbs, comparing exposure with disease control, might be reasonable, but may not be the preferable outcome [11]. The effect cannot, therefore, be evaluated properly.

Previous studies differed about the threshold trough concentration which could predict efficacy. In a similar patient population, bevacizumab 5 mg/kg was administered intravenously every 2 weeks in combination with chemotherapy in mCRC, Akbulut et al. [18] proposed 25 mg/L and Caulet et al. [14] 15 mg/L as cut-off value at day 14 after the first infusion. Nevertheless, measuring only the initial plasma concentrations could be a disadvantage, because the tumor size may change after multiple dosing [24]. Only Papachristos et al. [19] investigated a threshold at steady state, however, despite having a good receiver operating characteristic curve, did not use it and patients were separated into three exposure groups depending on median bevacizumab $C_{trough,\ ss}$. They reported that median $C_{trough,\ ss} \geq 87.9$ mg/L was associated with longer OS in first line treatment of mCRC. In our study, we could not use this threshold, because only 3 patients had concentrations above this level.

As previously published by Lu et al. [16], we did not find an association between higher bevacizumab concentration with better performance status as was suggested [25].

The results of the Cox regression showed an association between PFS and alkaline phosphatase ($p = 0.049$) and negative with albumin ($p = 0.059$), i.e., we found that per 10 unit increase in alkaline phosphatase was associated with a higher risk of progression of 3%. It may be explained by previous population PK investigations with bevacizumab [15,16], where an increased clearance with increasing baseline alkaline phosphatase and decreasing baseline albumin was observed. These covariates might be related to disease severity. In our case, they must also be significant in a multivariable Cox analysis to associate them with PFS. Even though age was also related with PFS ($p = 0.029$), it does not seem to alter the pharmacokinetics of mAbs [26].

As previously described [15,16], there are several possible causes of variability in the PK of bevacizumab, including, sex, body weight, albumin, alkaline phosphatase or chemotherapy. We found that bevacizumab exposure levels were highly variable among patients (coefficient of variation of 79% for 7.5 mg/kg each 3 weeks and 70% for 5 mg/kg every 2 weeks) compared to Zhi et al. [27] (24% and 32%, respectively). Also exposure levels were lower compared to other investigations [18,27]. Other factors related to analytical determination [28], such as alteration of the binding equilibrium between the mAb and its target, biological and chemical transformation during blood collection, sample storage, transport or freeze/thaw cycles, and analytical interference from anti-drug antibodies, could also explain the variability.

The inter-individual variability in plasma concentrations of bevacizumab with weight-based dosing, the availability of commercial tests to measure plasma levels and the absence of clinical biomarkers predicting treatment response demand further progress in assessing the exposure-response relationship of this mAb. This relationship might be stronger with others mAbs [8], such as cetuximab, as we found a greater number of studies published, even with a similar number of patients and different patient groups [29,30] to our research.

The era of precision medicine must be accompanied by adequate drug exposure to obtain the greatest possible benefit. A tool to guide individual patient dosing of antitumor mAbs is TDM. It is important to generate knowledge around it, especially through studies that assess effectiveness and safety of oncology mAbs, their impact on patients' outcomes and on economic sustainability. These studies, together with diagnostic tests, should help to ensure the efficiency of the different treatments.

Prior to the implementation of TDM of bevacizumab, it is necessary for each group of patients and indication to establish both the exposure-response relationship and a limit of trough concentrations above which efficacy is demonstrated. Demonstrating the benefit of dose escalation in patients with low concentrations should be accompanied by the development of TDM-based treatment algorithms to help guide clinical decisions, advances that must come from prospective large multicenter trials.

5. Conclusions

We cannot confirm a relationship between bevacizumab exposure and efficacy. It was found that $C_{trough,\ ss}$ was stable regardless of response. To the best of our knowledge, this is the first real-world study trying to show a relationship between bevacizumab $C_{trough,\ ss}$ and disease control in mCRC. It was conducted in a limited number of patients who are recruited from a single institution, which reduces the level of evidence.

Further controlled randomized studies with a sufficient number of patients with mCRC are required.

Conflict of interest statement

None.

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