Clinical Oncology xxx (2016) 1–10

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

# Analysis of Clinical End Points of Randomised Trials Including Bevacizumab and Chemotherapy versus Chemotherapy as First-line Treatment of Metastatic Colorectal Cancer

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Received 26 September 2015; received in revised form 14 March 2016; accepted 15 March 2016

## Abstract

*Aims:* Progression-free survival is recognised as an appropriate end point for randomised clinical trials of chemotherapy of patients with metastatic colorectal cancer, although it is not clear if it is reliable after chemotherapy plus bevacizumab.

*Materials and methods:* A literature search of randomised trials of systemic treatment including chemotherapy plus bevacizumab versus chemotherapy in patients with metastatic colorectal cancer was undertaken. For each trial the differences in overall survival and in either time-to-event or response-related end points were calculated. A Spearman test was carried out between the difference in each end point and the difference in survival. For the end points with the higher relationships with overall survival a regression analysis was carried out and $R^2$ (proportion of variability explained) was reported.

*Results:* Progression-free survival is closely related to overall survival ($r = 0.817$; $R^2 = 0.706$) and this relationship does not seem to be changed by the discontinuation of bevacizumab. The response-related end points have a better overall performance than the other time-to-event end points, even when only phase III trials are considered. In phase III trials, the disease control rate seems to be strongly related to overall survival ($r = 0.975$; $R^2 = 0.889$) and the overall response rate reports a good performance ($r = 0.866$; $R^2 = 0.484$). An open-label design and the timing of disease radiological evaluation do not seem to interfere with the correlation of differences of progression-free survival and overall survival.

*Conclusions:* A validation of the disease control rate and the overall response rate as a surrogate end point of survival at a patient level and a standardised definition of the timing for their measurement are strongly recommended in trials of chemotherapy plus bevacizumab.



*Key words:* Bevacizumab; chemotherapy; colorectal cancer; progression-free survival

## Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality among men and the third among women in the European Union, with a predicted number of deaths for the year 2014 of 92 900 and 75 500, respectively [1].

The overall survival of patients with metastatic colorectal cancer (mCRC) is progressively increased with the approval of new drugs and a more aggressive surgical approach for liver, lung and peritoneal metastases. After the introduction of irinotecan and oxaliplatin in clinical practice in the early 2000s, a review of seven randomised clinical trials (RCTs) reported that the strategy of making all effective drugs available to all patients along the course of their disease maximised overall survival. That study raised the question whether or not overall survival should be regarded as the most appropriate end point by which to assess the efficacy of the first-line medical treatment of patients with mCRC [2].

The objective response rate (ORR) is another good measure of efficacy of treatments and is often associated with subjective improvement in symptoms. It is assessed during the course of treatment using standardised criteria [3–5]. Some analyses of data from RCTs of patients with mCRC showed that the ORR is a potent independent predictive factor of overall survival [6,7], whereas other authors reported that an improved ORR has minimal or no impact on overall survival [8]. Even though the ORR and progression-

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http://dx.doi.org/10.1016/j.clon.2016.05.001

0936-6555/

free survival (PFS) were correlated significantly with each other, the results of studies of the fluorouracil era concluded that PFS was the most appropriate end point for phase III trials [9,10]. An analysis of 29 RCTs documented a good relationship between ORR and overall survival and between PFS and overall survival after chemotherapy [9], whereas a more recent similar study, including 39 trials of first-line chemotherapy, reported a strong association between PFS and overall survival and a weaker relationship between ORR and overall survival [11]. In particular, after first-line chemotherapy improvements in PFS were strongly associated with improvements in overall survival; consequently PFS has been accepted as an appropriate surrogate end point of overall survival [11]. However, with the increase in median overall survival and the introduction of effective second-line therapies, the correlation of PFS with overall survival is now weaker than in the past, and the treatment effect on PFS no longer predicts the treatment effect on overall survival [12,13]. The fact that PFS is an acceptable surrogate end point of overall survival in patients with mCRC receiving fluorouracil does not imply that the same will be true for all the other drugs, and with the current available second- and third-line effective regimens [14].

A preliminary analysis of four RCTs questioned the reliability of PFS as the end point of studies including bevacizumab plus chemotherapy [15]. Another analysis of 11 bevacizumab-based RCTs, enrolling 3310 mCRC patients, exhibited a high correlation between treatment effects on PFS and overall survival, but a low correlation between PFS and overall survival within this treatment group. Even though analyses of bevacizumab plus chemotherapy suggest that PFS might serve as a suitable surrogate end point for these regimens, heterogeneous data yielded weak correlation among the end points themselves, requiring confirmation in a larger set of trials and at the patient level [16]. A recent study evaluated 28 RCTs and also confirmed the predictive role of PFS on overall survival after targeted therapy in mCRC; the paper did not report in detail the results of the few studies including bevacizumab [17]. It has been suggested that the weakness of PFS as a surrogate end point of overall survival could be related to several factors, such as the open-label design, different duration of chemotherapy, high rates of cross-over and further active therapies, timing and schedule of disease assessment [18–20]. Finally, preclinical and preliminary clinical data suggest that the discontinuation of bevacizumab is associated with an acceleration of tumour growth [21,22]. This loss of angiostatic response has been recently studied in a phase II trial of patients with renal cell carcinoma: this study documented that after the discontinuation of sunitinib, but not of bevacizumab, an accelerated proliferation of endothelial cells in the primary tumour occurred [23].

The purpose of the present study was to carry out a systematic review of trials including a first-line treatment of bevacizumab plus chemotherapy versus chemotherapy alone in patients with mCRC, with the aim to assess the trial level surrogacy of time-to-event and response-related end points, and to evaluate differences among studies in both the types of end point.

## Materials and Methods

A literature search of randomised trials of systemic treatment including chemotherapy plus bevacizumab versus chemotherapy in patients with mCRC was undertaken in July 2015. This search was carried out on the electronic database Pubmed. The criteria used for the search were as follows: ('colon cancer' or 'colorectal cancer') and ('advanced' or 'metastatic') and 'bevacizumab' and ('chemotherapy' or 'oxaliplatin' or 'irinotecan' or 'capecitabine' or 'fluorouracil'). The search was restricted to randomised prospective studies published from 2000 to 2014. Editorials, commentaries and letters were excluded; reviews were considered for references, but were not included in the final analysis, as well as other non-randomised studies. A manual search was carried out for abstracts presented at the annual meetings of the American Society of Clinical Oncology and of the European Society for Medical Oncology. A first selection of eligible studies was carried out by GC and DG, who selected by title and abstract, randomised studies that enrolled patients with mCRC and report the analysis of one or more end points. Candidate articles were then selected for inclusion in the review. This was followed by a further evaluation of the selected articles (AV, GC) and only those that examined overall survival and at least one end point in relation to overall survival were included in the study analysis; furthermore, only reports of trials with a sample size of at least 50 patients were included. Trials involving unapproved drugs for mCRC and trials containing anti-epidermal growth factor receptor antibodies (anti-EGFR), at present only registered for patients with KRAS wild-type tumours, were excluded. KRAS-independent results were used for the analyses of the present study. The authors labelled an end point as PFS or time to progression (TTP) according to RECIST definitions, regardless of the terminology used in the original study. The ORR and disease control rate (DCR) were analysed for response-related end points, PFS, TTP, time to treatment failure (TTF) and duration of response for time-to-event end points.

Two arms per trial were selected for the analysis, one arm containing bevacizumab and one without it (control arm). The differences in the results of these two arms for every end point (Δ, delta) were calculated. For each trial the differences in overall survival (ΔOS), and in the other end points, either time-to-event end point or response-related end point as listed in Figure 1, were calculated as the estimate in the bevacizumab arm minus the estimate in the control arm. The non-parametric Spearman ρ correlation coefficient ($r$) was used as a measure of correlation between the difference in each end point and the difference in overall survival.

A subsequent analysis of the data evaluated the treatment effects on ΔPFS, ΔORR or ΔDCR and ΔOS. The analysis was carried out by separate linear regressions for every end point. Three linear regression analyses evaluating ΔOS as a function of ΔPFS, ΔORR and of ΔDCR were used to determine the proportion of variability explained ($R^2_{trial}$) on overall survival for the three end points, PFS, ORR and DCR.

Please cite this article in press as: Colloca G, et al., Analysis of Clinical End Points of Randomised Trials Including Bevacizumab and Chemotherapy versus Chemotherapy as First-line Treatment of Metastatic Colorectal Cancer, Clinical Oncology (2016), http://dx.doi.org/10.1016/j.clon.2016.05.001