

Original Article

Treatment with capecitabine + bevacizumab following induction treatment with FOLFIRI + bevacizumab in metastatic colorectal carcinoma

Ali Murat Tatlı¹, Hasan Şenol Coşkun², Mükremin Uysal³, Deniz Arslan⁴, Sema Sezgin Göksu⁵, Şeyda Güenay Gündüz², Selda Çakal², Hakan Şat Bozcuk², Burhan Savaş²

¹Department of Medical Oncology, Van Training and Research Hospital, Van, Turkey; ²Department of Medical Oncology, Akdeniz University, Antalya, Turkey; ³Department of Medical Oncology, Afyon Kocatepe University, Afyon, Turkey; ⁴Department of Medical Oncology, Erzurum Training and Research Hospital, Erzurum, Turkey; ⁵Department of Medical Oncology, Kayseri Training and Research Hospital, Kayseri, Turkey

Received June 25, 2014; Accepted July 11, 2014; Epub August 15, 2014; Published August 30, 2014

Abstract: Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor, and it has been found to increase both progression-free survival and overall survival when it is combined with chemotherapeutic agents in the first-line and subsequent treatment of metastatic colorectal carcinoma. The objective of this study was to show the efficacy of maintenance treatment with capecitabine plus bevacizumab in patients with metastatic colorectal cancer who responded to treatment with FOLFIRI plus bevacizumab. The study included patients with metastatic colorectal cancer who received FOLFIRI plus bevacizumab as a first-line treatment. Patients who had objective response with FOLFIRI plus bevacizumab treatment after an average period of 6 months received a maintenance treatment with capecitabine plus bevacizumab (capecitabine 2 x 1000 mg/m², 1 - 14 days, every 21 days, bevacizumab 7.5 mg/m², every 21 days) until disease progression or toxicity. The time to progression on bevacizumab treatment was evaluated. A total of 29 patients (15 male, 14 female) were included. The mean age was 62 years. The mean number of cycles for maintenance treatment with capecitabine plus bevacizumab was 12. The median PFS was 16 ± 3 months, and OS was 42 ± 11 months. PFS and OS were remarkably higher in patients with a complete or near complete response to induction treatment. Fourteen patients (48%) experienced hand-foot syndrome associated with capecitabine plus bevacizumab treatment, without any severe toxicity. Inselected patients with metastatic colorectal carcinoma who had a remarkable objective response to FOLFIRI plus bevacizumab treatment, a maintenance treatment with capecitabine plus bevacizumab following FOLFIRI plus bevacizumab until disease progression may be a suitable, effective and tolerable regimen, which requires further studies.

Keywords: Metastatic colorectal carcinoma, FOLFIRI, maintenance treatment, induction treatment

Introduction

Colorectal cancer is one of the most common cancers in Europe, and substantially accounts for cancer deaths all over the world [1, 2]. Colorectal carcinoma represents 9.7% of all cancer patients with 1.23 million cases. It is the most common type of cancer in the world following breast and lung cancers [3]. Approximately 20 - 35% of patients with colorectal cancer have shown metastasis at the time of diagnosis. And, approximately 20 - 25% of patients develop metastasis during follow-up, resulting in an overall mortality rate of 40 - 45% in colorectal cancer. In addition to that, during

the last two decades, development of new scanning techniques and early detection methods in colorectal carcinoma as well as widespread use of curative and adjuvant therapies have resulted in reduced mortality rate [4].

The optimal duration of chemotherapy remains unclear. Whether continued chemotherapy provides better outcomes than intermittent therapy to the best response followed by a chemotherapy "holiday" has been addressed in several trials. Although early data from the OPTIMOX2, MRC COIN, NO16966, and CAIRO-3 trials suggested that a complete stop of chemotherapy (with or without biologics) might be

Table 1. Demographic data

		Number of patients N (%)
Sex	Male	15 (51.7%)
	Female	14 (48.3%)
Age		62 ± 10
Initial treatment	Xeliri + B	3 (10.3%)
	Folfiri + B	26 (89.7%)
Response to initial treatment	Complete-near complete	16 (55.2%)
	Partial	13 (44.8%)
Metastatic focus	Hepatic	23 (79.3%)
	Non-hepatic	6 (20.7%)
Primary focus	Colon	19 (65.5%)
	Rectum	10 (35.5%)
Hand-foot syndrome	Grade 1-2	14 (48%)
Mortality		16 (55.2%)
PFS		16 ± 3 months
OS		42 ± 11 months

treatment with capecitabine plus bevacizumab after an average of 6-months treatment until disease progression or toxicity (Capecitabine 2 × 1000 mg/m², 1 - 14 days, every 21 days; bevacizumab 7.5 mg/m², every 21 days).

Progression-free survival, overall survival and treatment-induced toxicity were retrospectively evaluated. Time to progression on bevacizumab-containing regimen and overall survival were

calculated. We excluded one patient who had metastasis at the time of diagnosis and who underwent metastasectomy with a primary tumor before chemotherapy.

Statistical analysis

For statistical analysis, we used SPSS software, version 18. Progression-free survival was defined as time to radiological detection of progression on a first-line irinotecan-containing chemotherapy regimen, and overall survival was defined as the time from first diagnosis of metastatic disease until death. The survival rates were calculated using the Kaplan-Meier survival analysis. We also calculated the impact of response to first-line chemotherapy on survival using the log rank test. A type-1 error level below 5% was considered statistically significant.

Results

The study included a total of 29 patients (15 male and 14 female) with metastatic colorectal cancer. The mean age was 62 ± 10 years (range, 35 - 79 years). The demographic characteristics of patients are shown in **Table 1**. All patients received a maintenance treatment with capecitabine plus bevacizumab and a mean cycle of 12 ± 10 (range, 4 - 44 cycles). Of eligible patients, 14 patients had metastasis at the time of diagnosis, and 15 patients had undergone operation and received adjuvant treatment, and developed recurrence during

associated with an inferior outcome, these results have been called into question by a more recent meta-analysis that did not find adverse survival with an intermittent as compared to continuous treatment strategy [5]. Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor [6], and it increases both PFS and OS when it is combined with chemotherapy agents in first-line and second-line treatment of metastatic colorectal carcinoma [7, 8].

In the present study, we retrospectively evaluated survival and tolerability data of patients with metastatic colorectal carcinoma, who received an initial treatment with FOLFIRI plus Bevacizumab followed by treatment with Capecitabine plus Bevacizumab in our clinic.

Materials and methods

We conducted a retrospective review of records of patients with metastatic colorectal carcinoma who received FOLFIRI plus Bevacizumab as a first-line treatment between November 2006 and January 2013 at Akdeniz University.

The study included 30 patients diagnosed with radiologically and histopathologically confirmed metastatic colorectal cancer. Patients with metastatic colorectal cancer who received FOLFIRI plus bevacizumab as first-line treatment were eligible. Those patients with an objective response to treatment with FOLFIRI plus bevacizumab received a maintenance

Following induction treatment with FOLFIRI + bevacizumab

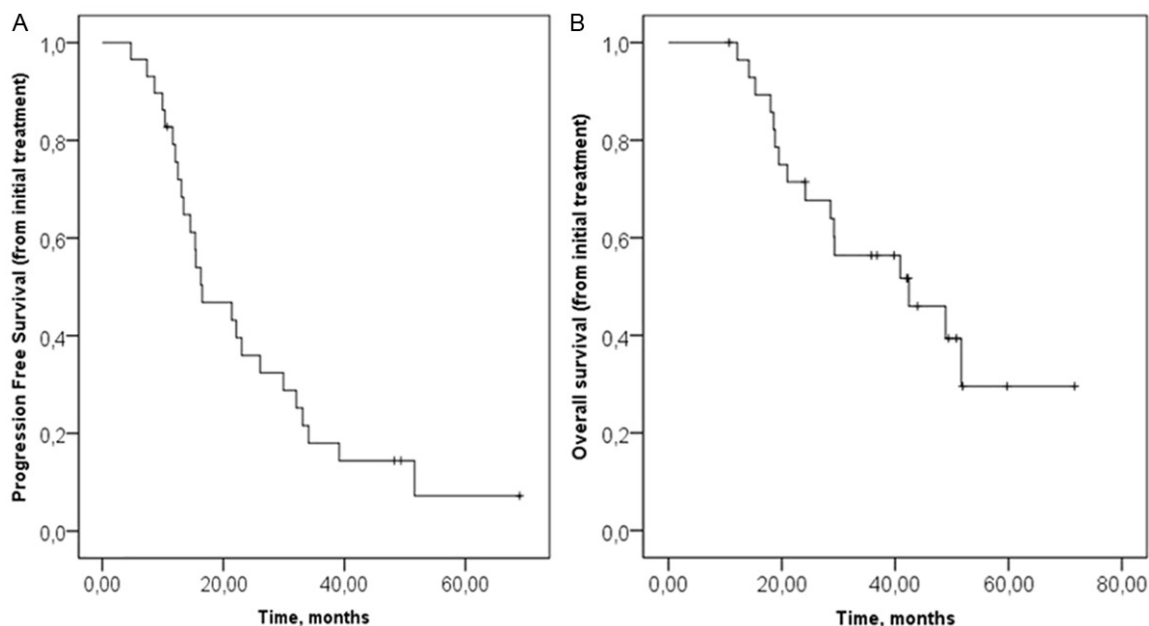


Figure 1. PFS (A) and OS (B) in patients who received maintenance treatment with capecitabine plus bevacizumab following initial irinotecan-based treatment (Median PFS 16 ± 3 months, median OS 42 ± 11 months).

Table 2. Grading of chemotherapy toxic effects according to common criteria

	Grade 1-2* Toxicity N (%)	Grade 3-4* Toxicity N (%)
Hand-foot syndrome	14 (48%)	0
Vascular thrombosis	1 (3%)	0
Hemorrhage	2 (6%)	0
Hypertension	2 (6%)	1 (3%)
Cerebrovascular event	0	1 (3%)
Diarrhea	2 (6%)	1 (3%)
Neutropenia	2 (6%)	0
Fatigue	3 (9%)	1 (3%)

*Common terminology criteria for adverse events (CTCAE), version 4.

Table 3. Comparison of overall survival in patients who had complete or near complete response to initial treatment

Survival from onset of initial treatment	Response to induction treatment with FOLFIRI-B		P
	Partial response N:13	Complete or near complete response N:17	
PFS (months)	15	22	0.016
OS (months)	28	NA	0.003

NA: not available.

follow-up. The primary tumor site was colon in 19 patients, and rectum in 10 patients. An overall evaluation of all patients showed a median PFS of 16 ± 3 months, and median overall survival of 42 ± 11 months (**Figure 1**).

Fourteen patients (48%) had acceptable hand-foot syndrome associated with capecitabine plus bevacizumab, with no life-threatening or severe toxicity (**Table 2** shows grades of toxicities according to common toxicity criteria). One patient

had nasal bleeding, and another had rectal bleeding while two patients had Grade 2 neutropenia. One patient on maintenance treatment developed deep vein thrombosis simultaneously with progression. Seven patients who showed progression while on maintenance treatment with capecitabine plus bevacizumab were reintroduced with FOLFIRI plus bevacizumab, which was used as initial treatment. Three patients were unresponsive, 1 patient was stable and 3 patients had partial response.

PFS and OS analysis of patients showed that PFS was 28 months in group of

Following induction treatment with FOLFIRI + bevacizumab

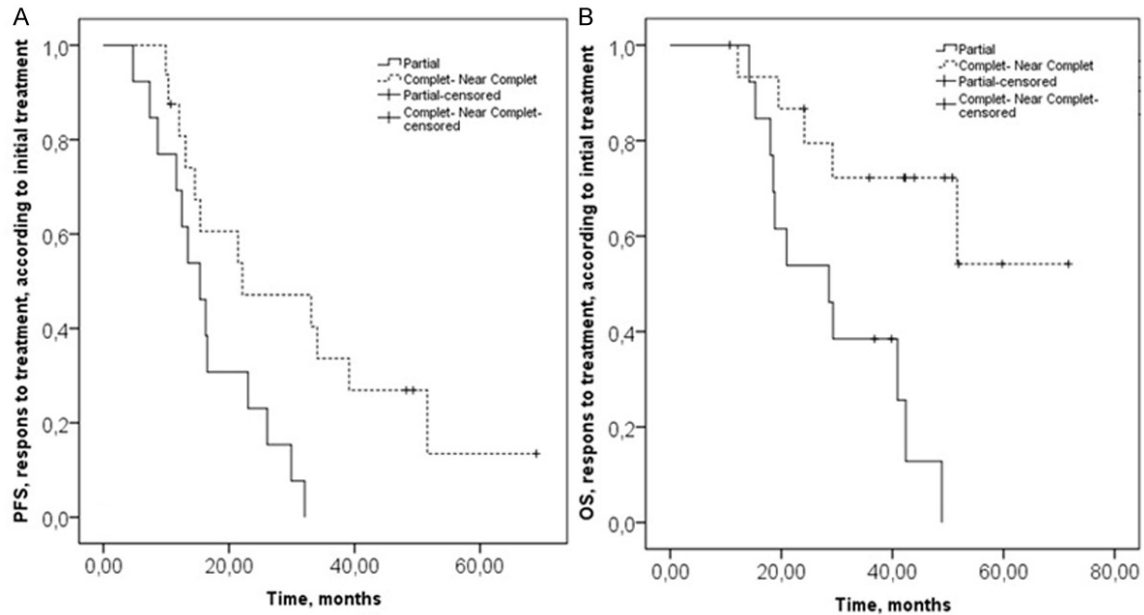


Figure 2. PFS (A) and OS (B) by response to initial treatment (Median PFS 16 ± 3 months, median OS 42 ± 11 months).

patients with complete or near complete response whereas it was 15 months in the group who had partial response to initial treatment ($p = 0.016$). Similarly, OS was 22 months in the group who had partial response to initial treatment. The median OS was not reached in the group with complete or near complete response ($p = 0.003$). PFS and OS were remarkably higher in patients with complete or near complete response to initial treatment (**Table 3, Figure 2**).

Discussion

Whether a maintenance treatment should be given for treatment of metastatic colorectal carcinoma does not pose a significant problem since current guidelines recommend continuation of chemotherapy until disease progression. However, median duration of treatment is up to 6 months in a majority of patients due to disease progression or toxicity. Dose reduction is required in treatments lasting more than six months due to impaired quality of life, mostly resulting from side effects of drugs [9]. Therefore, several options for continuing therapy with regimens such as intermittent treatment schemes [10], maintenance or discontinuation of the same protocol [11-13] or reduced combination treatment that was initially received [11, 15] have been studied in order to

develop more comfortable and beneficial regimens for maintenance treatment of metastatic colorectal carcinoma.

Whether continued chemotherapy provides better outcomes than intermittent therapy to best response followed by a chemotherapy “holiday” has been addressed in several trials. The OPTIMOX-1 study compared patient groups receiving FOLFOX-4 regimen until disease progression with those receiving 6 cycles of initial FOLFOX-7 regimen followed by maintenance regimen with 12 cycles of 5-FU leucovorin regimen, and then reinduction treatment with FOLFOX-7. The median PFS was similar in both groups, with 6.7 months in the FOLFOX-4 arm, and 6.5 months in FOLFOX-7 arm [12]. The COIN study compared continuous administration of oxaliplatin-fluoropyrimidine-based chemotherapy until disease progression with treatment-free intervals and intermittent treatment in a non-progressive group after a 12-week treatment period. Although there was no significant difference in overall survival between the intermittent- and continuous-treatment groups, a better quality of life and lower drug toxicity were observed in intermittent-treatment group [13]. The MACRO study, another recent study, made a comparison between maintenance treatment with single-agent bevacizumab fol-

Following induction treatment with FOLFIRI + bevacizumab

lowing induction chemotherapy with XELOX plus bevacizumab and continuation of initial treatment with XELOX plus bevacizumab, and found no statistically significant difference in median PFS and median OS between two groups. However, toxicity was remarkably lower in the group who received a maintenance treatment with bevacizumab as biological agent alone [16].

There are less data on the advantages of maintenance therapy for patients treated initially with the irinotecan-based regimen. In the GISCAD, trial was to evaluate whether an intermittent chemotherapy with levo-leucovorin + 5-fluorouracil (5-FU) + irinotecan (CPT-11) was at least as effective as the same regimen given continuously, both administered until progression, in patients affected with advanced colorectal cancer and not previously exposed to chemotherapy for metastatic disease [10].

Although early data from the OPTIMOX-2, MRC COIN, NO16966, and CAIRO3 trials suggested that a complete stop of chemotherapy (with or without biologics) might be associated with an inferior outcome, these results have been called into question by a more recent meta-analysis that did not find adverse survival with an intermittent as compared to continuous treatment strategy. In a preliminary report presented at the 2013 annual ASCO meeting, intermittent delivery of chemotherapy did not result in a significantly reduced overall survival compared to continuous delivery, whether or not maintenance treatment was included. Quality of life was the same or better with intermittent therapy [5].

The common point in these studies is that their objective was to maintain patients' quality of life and use a maintenance treatment with less toxicity in responders to initial induction therapy. Therefore, we should use a maintenance treatment regimen with an acceptable toxicity and tolerable side effect profile, which will both provide benefit to the patient and not require discontinuation of the assigned therapy.

In the present study, none of the patients who received initial treatment for a mean period of 6 months and responded to the treatment experienced severe toxicity, which may require discontinuation of treatment with capecitabine plus bevacizumab. Furthermore, median PFS was 16 months in this selected group of

patients. Maintenance treatment with capecitabine plus bevacizumab was an effective and tolerable regimen for treatment of these patients.

Conclusion

In patients with metastatic colorectal disease who had a remarkable objective response with initial treatment of FOLFIRI plus bevacizumab and an adequate duration of treatment, a maintenance treatment with capecitabine plus bevacizumab until disease progression may be a suitable regimen for administration to avoid side effects and toxicity associated with treatment and not to disrupt quality of life. In general, the decision to permit treatment breaks during therapy must be individualized and based upon several factors, including tolerance of and response to chemotherapy, disease bulk and location and symptomatology.

Further studies and new data on this subject may help establish an optimal maintenance treatment in patients who respond to initial treatment of metastatic colorectal carcinoma.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ali Murat Tatlı, Department of Medical Oncology, Van Training and Research Hospital, Van, Turkey. Fax: +9043221-21954; E-mail: alimurattat@hotmail.com

References

- [1] Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010; 46: 765-781.
- [2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69-90.
- [3] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127: 2893-2917.
- [4] Malvezzi M, Arfe A, Bertuccio P, Levi F, LaVecchia C, Negri E. European cancer mortality predictions for the year 2011. *Ann Oncol* 2011; 22: 947-956.
- [5] Berry SR, Cosby R, Asmis TR, Chan KK, Hammad N, Krzyzanowska MK. Randomized controlled trials (RCTs) examining continuous

Following induction treatment with FOLFIRI + bevacizumab

- (CS) versus intermittent strategies (IS) of delivering systemic treatment (Tx) for untreated metastatic colorectal cancer (mCRC): A meta-analysis from the Cancer Care Ontario program in evidence-based care (abstract). *J Clin Oncol* 2013; 31: Suppl; abstr 3534.
- [6] Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003; 9: 669-676.
- [7] Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzen F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* 2008; 26: 2013-2019.
- [8] Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB 3rd; Eastern Cooperative Oncology Group Study E3200. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; 25: 1539-1544.
- [9] Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, Smith DB, Shepherd S, Maraveyas A, Ferry DR, Meade AM, Thompson L, Griffiths GO, Parmar MK, Stephens RJ. For the FOCUS Trial Investigators and the National Cancer Research Institute Colorectal Clinical Studies Group. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007; 370: 143-152.
- [10] Labianca R, Sobrero A, Isa L, Cortesi E, Barni S, Niclèlla D, Aglietta M, Lonardi S, Corsi D, Turci D, Beretta GD, Fornarini G, Dapretto E, Floriani I, Zaniboni A; Italian Group for the Study of Gastrointestinal Cancer – GISCAD. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. *Ann Oncol* 2011; 22: 1236-1242.
- [11] Labianca R, Sobrero A, Isa L, Cortesi E, Barni S, Niclèlla D, Aglietta M, Lonardi S, Corsi D, Turci D, Beretta GD, Fornarini G, Dapretto E, Floriani I, Zaniboni A; Italian Group for the Study of Gastrointestinal Cancer – GISCAD. Intermittent versus continuous chemotherapy in advanced colorectal cancer: A randomised 'GISCAD' trial. *Ann Oncol* 2011; 22: 1236-1242.
- [12] Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, Andre T, Tabah-Fisch I, de Gramont A. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol* 2006; 24: 394-400.
- [13] Adams R, Wilson R, Seymour MT, Meade AM, Madi A, Cassidy J, Maughan TS. Intermittent versus continuous oxaliplatin-based combination chemotherapy in patients with advanced colorectal cancer: A randomized non-inferiority trial (MRC COIN) [abstract 15LBA]. *Eur J Cancer* 2009; Suppl 7: 259.
- [14] Tveit K, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, Kure E, Ikdahl T, Skovlund E, Christoffersen T. Randomized phase III study of 5-fluorouracil/folinic acid/oxaliplatin given continuously or intermittently with or without cetuximab, as first-line treatment of metastatic colorectal cancer: The NORDIC VII study (NCT00145314), by the Nordic Colorectal Cancer Biomodulation Group [abstract 365]. *J Clin Oncol* 2011; 29 Suppl 4: 10.
- [15] Grothey A, Hart LL, Rowland KM, Ansari RH, Alberts SR, Chowhan NM, Shpilsky A, Hochster HS. Intermittent oxaliplatin (oxali) administration and time-to-treatment failure (TTF) in metastatic colorectal cancer (mCRC): Final results of the phase III CONcept trial [abstract 4010]. *J Clin Oncol* 2008; 26: 180.
- [16] Díaz-Rubio E, Gómez-España A, Massutí B, Sastre J, Abad A, Valladares M, Rivera F, Safont MJ, Martínez de Prado P, Gallén M, González E, Marcuello E, Benavides M, Fernández-Martos C, Losa F, Escudero P, Arrivi A, Cervantes A, Dueñas R, López-Ladrón A, Lacasta A, Llanos M, Taberero JM, Antón A, Aranda E; Spanish Cooperative Group for the Treatment of Digestive Tumors. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. *Oncologist* 2012; 17: 15-25.