JBUON 2013; 18(3): 647-652
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Survival analysis of metastatic colorectal cancer patients who were treated with the five major therapeutic agents over the course of disease

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Summary

Purpose: *Exposure to all active agents may be more important than specific sequence of drug administration in the treatment of patients with metastatic colorectal cancer (mCRC). The purpose of this study was to evaluate the overall survival (OS) of mCRC patients who were treated with all 5 major therapeutic agents used in this malignancy.*

Methods: *We retrospectively reviewed the medical records of 395 mCRC patients referred to our clinic. The study included patients who received 5-fluorouracil (5-FU)-, irinotecan- or oxaliplatin-based chemotherapy and at least 3 cycles of bevacizumab and 4 weeks of cetuximab sequentially in various combinations.*

Results: *Forty mCRC patients received the 5 major therapeutic agents effectively and sequentially, and their mean OS was 26.43±2.04 months. The 3- and 4- year OS survival rates were 26.7% and 16.7%, respectively. When survival analysis was limited to the metastatic patients with at least 6 cycles of bevacizumab therapy in addition to standard duration of other chemotherapeutic agents (N=33), the mean OS was 26.7±2.38 months. With a further survival analysis limited to metastatic patients who were treated with at least both 6 cycles of bevacizumab and 8 weeks of cetuximab in addition to other therapies (N=17), the mean OS was 44.8±11.03 months.*

Conclusion: *This study demonstrated that in mCRC patients there may be a significant survival advantage if an adequate tumor response was achieved with all major therapeutic agents. Therefore, we believe that we should treat our patients with the 5 major therapeutic drugs as effectively as possible.*

Key words: *bevacizumab, cetuximab, colorectal cancer, 5-fluorouracil, irinotecan, oxaliplatin*

Introduction

Colorectal cancer (CRC) is a common and lethal disease [1]. The majority of patients with metastatic colon or rectal cancer cannot be cured. However, the mortality of CRC has declined over the last 25 years through well-established screening, surgical techniques, as well as the development of new targeted therapies [1].

For several decades, 5-FU was the sole active agent for mCRC, despite having no major impact on survival. Recently, this has changed markedly with the approval of multiagent chemotherapy, consisting of either irinotecan or oxaliplatin combined with 5-FU ± leucovorin (LV) as first-line treatment for mCRC. Patients exposed to all 3 conventional chemotherapy agents during the course of their therapy have shown improved OS in all large published phase III trials [2-4]. Furthermore, resection of metastatic disease after a highly active first-line chemotherapy regimen is possible in a small but important subset of patients with mCRC, with encouraging OS rate and time to disease progression (TTP) [5]. Tournigand et al. randomized previously untreated patients to receive the simplified 5-FU+LV (de Gramont regimen) combined either with irinotecan (FOLFIRI) or with oxaliplatin (FOLFOX6) until progression, and eventually found no significant difference [6].

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Received: 19/12/2012; Accepted: 09/01/2013

The addition of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab and epidermal growth factor inhibitor (EGFR) cetuximab to standard chemotherapy may improve response rates, which may, in turn, favorably influence patient survival [7,8].

The initial and subsequent single-agent or doublet or triplet combination therapies may differ concerning their effectiveness on response rate and possibly on patient survival. However, exposure to all active agents may be more important than the sequence of administration. Therefore, the question is if survival is positively affected by subsequent therapy of all active agents with or without combinations in mCRC. The objective of this study was to evaluate the OS of mCRC patients who were treated with all 5 major therapeutic drugs during their treatment period.

Methods

We retrospectively reviewed the medical records of 397 mCRC patients referred to the Medical Oncology Department of Ege University Faculty of Medicine, between January 2005 and March 2010. This period was chosen for analysis, because in our country bevacizumab and cetuximab were approved after the year 2005. None of the patients received panitumumab, an EGFR inhibitor like cetuximab, since it was not available in our country. Appropriate institutional review board approval was obtained. Age, sex, date of diagnosis and metastasis, initial stage, localization of the tumor, histological data, site of metastasis and all subsequent treatments (chemotherapy, radiation therapy, surgery) were registered from medical records.

Inclusion/exclusion criteria

The study included mCRC patients who were treated with 5-FU-, irinotecan-, and oxaliplatin-based chemotherapy and at least 3 cycles of bevacizumab and 4 weeks of cetuximab sequentially in various combinations. Prior adjuvant chemotherapy including oxaliplatin was allowed if completed at least 6 months before starting the study treatment. Patients who were treated with less than 5 major active agents or any protocol not including these regimens during their treatment period were excluded. Patients who had any hepatic or pulmonary metastasectomy either initially or after neoadjuvant chemotherapy were also excluded because, as the possibility of metastasectomy at any time during therapy substantially improved the outcome of mCRC patients, it might have led to overestimation of chemotherapy benefits.

Evaluation of therapeutic efficacy

Baseline tumor assessments were performed by computed tomography (CT)/magnetic resonance imaging (MRI) of the abdomen/pelvis and chest X-ray or CT/MRI of the chest. Assessments were repeated every 6-8 weeks until disease progression or discontinuation of therapy. If a patient responded to treatment or remained stable at the time of treatment withdrawal, the patient was observed every 6-8 weeks until disease progression. Tumor response was based on the RECIST guidelines [9].

Treatment

Nearly all of the patients were treated with modified-FOLFOX-6, XELOX or FOLFIRI. Actual dosing of the drugs administered to the patients in this study were as follows: oxaliplatin 100mg/m^2; irinotecan 180mg/m^2; leucovorin 400mg/m^2; capecitabine 1250-2000 mg/m^2; 5-FU 400 mg/m^2 iv bolus; 5-FU 2400mg/m^2 24-h infusion with a chemotherapy infusion pump; bevacizumab 5-7.5 mg/kg in 2 or 3 week intervals; and cetuximab 250 mg/m^2 weekly or 500 mg/m^2 biweekly. In each arm, the 5-FU, irinotecan or oxaliplatin dose intensity with vs without bevacizumab was comparable. In the bevacizumab arms, bevacizumab was not continued after discontinuation of treatment with other agents.

Statistics

We used the SPSS package programme v. 11.0 for statistical analysis. Our objective was to show the impact of chemotherapeutic and modecular agents in 3 different treatment groups.

So, the primary efficacy endpoint was OS among the patients treated with the 5 active therapeutic regimens. The OS values for the different therapies were estimated using the Kaplan-Meier method. We did not compare statistically the 3 groups because the first group included the second and third ones, while the second group included the third one. Demographic properties were studied with descriptive analysis. Description of all available variables were given as numbers, percentages, and results were expressed as mean ± standard deviation (SD).

Results

Patient characteristics

Among patients with mCRC presented to our medical oncology department, there were 40 (10%) who were treated with 5-FU-, irinotecan-, and oxaliplatin-based chemotherapy and at least 3 cycles of bevacizumab and 4 weeks of cetuximab, and therefore they were included in the analysis. Among these 40 patients, 33 (82%) had at least 6 cycles of bevacizumab and 17 (42%) had at least both 6 cycles of bevacizumab and 8 weeks of ce-

tuximab. The number of the treatment cycles represented the actual response duration with molecular agents. KRAS mutation status was available only for a few patients receiving cetuximab-containing therapies. Eleven patients had previously received adjuvant chemotherapy while 6 of them had oxaliplatin-containing treatment and only 3 had adjuvant radiotherapy. They became metastatic during their follow-up.

Males prevailed (67.5%). The mean age in all groups was 55.57 ± 11.07 years. Tumor was localized in the rectum in 12 (30%) patients and in the colon in 28 (70%). Demographic and treatment characteristics are shown in Table 1. Sites of metastasis in our mCRC patients were as follows: liver in 12 patients, lung in 4, peritoneum in 3, lymph nodes in 3, local recurrence in 3, rare sites in 3 and several combinations of them in 12 patients.

Twenty-two (55%) patients had been treated with irinotecan, 17 (42%) with oxaliplatin and 20 (50%) with bevacizumab and combination chemotherapies as first-line treatment. All patients had received 5-FU-based treatment while none of them had received cetuximab-based treatment as first-line therapy. The number of patients who received combination therapy with irinotecan, oxaliplatin bevacizumab, and cetuximab as second-line therapy was 22, 17, 19 and 5, respectively. Only 3 patients had not received 5-FU-based chemotherapy as second-line therapy. For third-line therapy, 29 patients had received cetuximab, nearly all in combination with irinotecan.

Survival

Mean OS of 40 mCRC patients who were treated with the 5 major therapeutic agents effectively and sequentially was 26.43±2.04 months. Three- and 4-year survival rates were 26.7 and 16.7%, respectively. When survival analysis was limited to the metastatic patients with at least 6 cycles of bevacizumab therapy in addition to standard duration of other chemotherapeutic agents (N=33), mean OS was 26.7±2.38 months. Three- and 4-year survival rates were 32.1 and 20.1%, respectively. With a further survival analysis limited to metastatic patients who were treated with at least both 6 cycles of bevacizumab and 8 weeks of cetuximab administration in addition to minimum 4 cycles of conventional chemotherapies (N=17), mean OS was 44.8±11.03 months. Three- and 4-year survival rates were 46.9 and 31.3%, respectively. Outcome data are shown in Table 2 and survival in Figure 1.

Table 1. Demographic data and kinds of therapies

Characteristics	*≥3 cycles bevacizumab + 4 weeks cetuximab Patients, N (%)*	*≥6 cycles bevacizumab + 4 weeks cetuximab Patients, N (%)*	*≥6 cycles bevacizumab + 8 weeks cetuximab Patients, N (%)*
Patients, N	40 (100)	33 (82)	17 (42)
Age,years, mean±SD	55.57 ± 11.07	55.47 ± 14.87	55.76 ± 07.58
Gender			
Male	27 (67)	22 (55)	12 (30)
Female	13 (33)	11 (27)	5 (12)
Tumor localization			
Colon	28 (70)	25 (62)	15 (37)
Rectum	12 (30)	8 (20)	2 (5)
Kind of therapies			
Adjuvant CT	11 (27)	8 (20)	3 (5)
Adjuvant RT	3 (7)	1 (5)	0 (0)
Primary tumor resection	29 (76)	23 (57)	12 (30)

SD: standard deviation, CT: chemotherapy, RT: radiotherapy

Table 2. Overall survival in relation to different kinds of treatment

Survival	*≥3 cycles bevacizumab + 4 weeks cetuximab*	*≥6 cycles bevacizumab + 4 weeks cetuximab*	*≥6 cycles bevacizumab + 8 weeks cetuximab*
OS (mean±SD; months)	31.03±2.45	32.4±2.81	38.9±4.04
3-year OS (%)	26.7	32.1	46.9
4-year OS (%)	16.7	20.1	31.3

OS: overall survival, SD: standard deviation

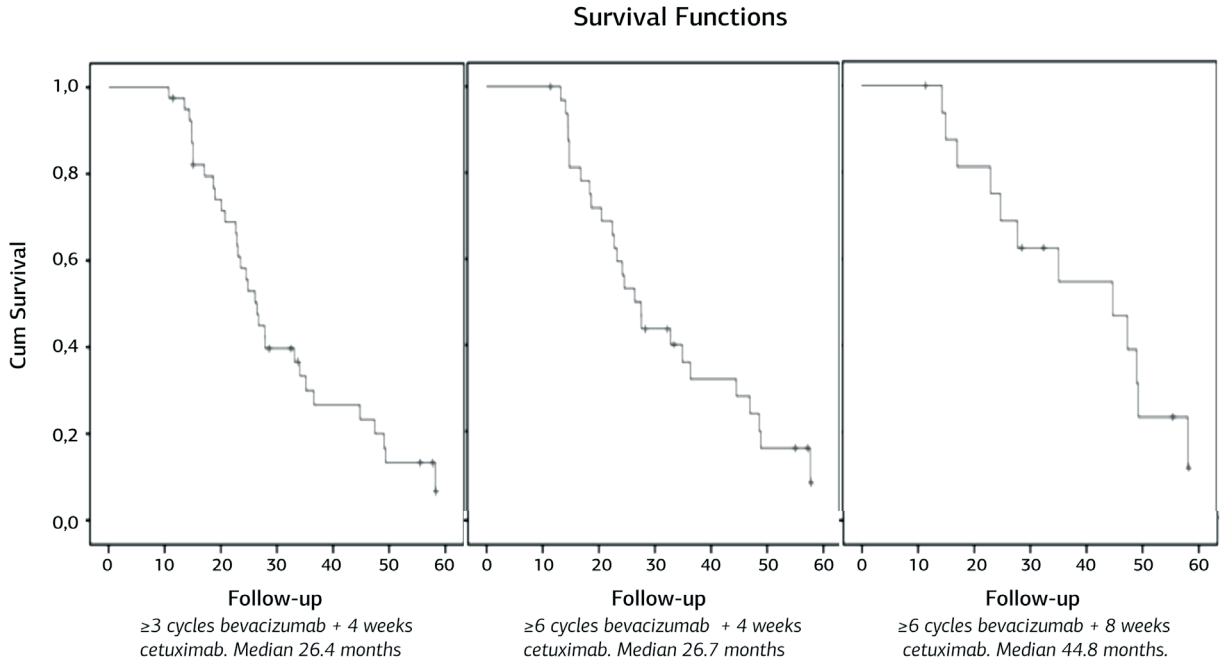

Figure 1. Patient survival of the 3 different groups

Discussion

The results from randomized clinical trials conducted across the world have led to important advances in the management of mCRC. These studies fostered the evolution from a standard single-agent approach using 5-FU to new combination regimens including irinotecan and oxaliplatin. The integration of oxaliplatin and irinotecan in the treatment of patients with advanced disease has improved median survival in a meaningful way [2,3]. The recent administration of molecular agents such as bevacizumab and cetuximab in addition to chemotherapeutic agents provided better response rates and further significant improvements in survival. Approximately 25% of CRC patients, even with resectable hepatic metastases, survived 5 years after surgery metastasectomy. In addition, many patients present with unresectable metastases and few can manage to survive 5 years. Recent results show that the resection of previously unresectable metastases became possible in up to 15% of patients after neoadjuvant chemotherapy [5,7].

Response to chemotherapy also seems to be important in predicting long-term outcome. In a retrospective study with 131 patients and metastases on presentation receiving neoadjuvant systemic chemotherapy, there were 58 (44%) patients who underwent hepatectomy after an objective tumor response (group 1), 39 (30%) after tumor stabilization (group 2), and 34 (26%) after (8% vs 37% and 30% , respectively at 5 years; p<0.0001). This result indicates that control of tumor growth with chemotherapy is crucial for achieving a prolonged remission [10].

There are numerous studies concerning the impact of combination chemotherapy on patient survival. The results from these clinical studies suggest that combination chemotherapy increases the likelihood of achieving objective response and improving survival of mCRC patients. Phase III randomized trials which compared sequential vs combination chemotherapy with 5-FU, irinotecan and oxaliplatin in advanced CRC found that combination treatment does not significantly improve OS [11,12]. In a very recent study, Ducreux et al. also demonstrated that upfront combination chemotherapy is more toxic and is not more effective than the sequential use of the same cytotoxic drugs in patients with advanced, non-resectable CRC [13]. However, no trial used bevacizumab or cetuximab either as first-line or salvage therapy, and the median survival for all groups was lower than expected for modern chemotherapy. More important was the low number of patients who eventually received all active 3 drugs in all trials. Thus, available evidence continues to support initial combination chemotherapy for most patients, particularly for those whose metastases might be

potentially resectable after an initial chemotherapy response [14].

According to previous studies, a combination of irinotecan with an infusional schedule of 5-FU+LV does not offer superior efficacy when compared with oxaliplatin+5-FU+LV-based regimens either in the first-line or second-line treatments of mCRC patients [15,16]. In the Tournigand study, both sequences provided a prolonged survival and similar efficacy except a difference in their toxicity profiles [6]. Median survival was 21.5 months in patients allocated to FOLFIRI, and then FOLFOX6 vs 20.6 months in patients allocated to FOLFOX6, and then FOLFIRI. It was one of the studies which demonstrated survival over 20 months even in the absence of targeted therapies during that period.

Bevacizumab is a humanized IgG1 monoclonal antibody that selectively binds to and neutralizes the biologic activity of human VEGF. Neutralization of the biologic activity of VEGF can result to reduction of tumor vascularization and subsequent reduction in tumor growth. For mCRC patients, bevacizumab is very active and improves outcomes when used with a variety of first-line regimens [17]. It prolonged survival up to 25 months in patients with mCRC when oxaliplatin was added to first-line irinotecan+5-FU+LV (IFL)+bevacizumab regimen. A subset analysis of this trial suggested that a treatment strategy incorporating all active agents over the course of the disease optimizes overall survival [18]. In the ECOG 3200 trial, addition of bevacizumab to oxaliplatin-containing second-line chemotherapy provided enhancement of activity in second-line regimens [19]. In this trial, bevacizumab was not a component of the first-line regimen and its activity in the second-line treatments was established. In patients who progress while receiving first-line bevacizumab therapy, even if there are oncologic reasons supporting continuation of bevacizumab with another regimen, there is insufficient data to consider it as a standard approach. In addition to the lack of evidence from randomized trials, potential toxicity and cost are also main problems [20,21].

Cetuximab is a chimeric IgG1 monoclonal antibody that targets the ligand-binding domain of the EGFR and may exert its antitumor efficacy through both EGFR antagonism and antibody-dependent cell-mediated cytotoxicity. Cetuximab is both active in combination with irinotecan, especially for patients with wild type K-ras tumors who are refractory to irinotecan, and as a single agent for those who are intolerant to irinotecan-based chemotherapy [8,22]. In the CRYSTAL trial, in previously untreated mCRC patients, first-line cetuximab was investigated and the patients were randomly assigned to FOLFIRI with or without cetuximab [23]. The median PFS was modestly but significantly better with cetuximab , as was the overall response rate. Among patients with wild type K-ras, response rates were significantly higher in those who received cetuximab in conjunction with chemotherapy. Patients receiving cetuximab had significantly higher rates of surgery for metastases and a higher rate of complete resection with curative intent before disease progression.

A number of authors reported that all of their metastatic patients were treated according to their risk factors, performance status, tumor burden, organ insufficiency and disease stage. So, for all patients different strategies of treatment were required during their therapy period [12,13]. In our study, we established a subgroup of CRC patients without metastasectomy who lived as long as the patients with metastasectomy with the help of active chemotherapeutic agents. Unfortunately, we could not still define these subgroups that had the maximum benefit from chemotherapeutics with the available methods. Maybe, with the help of translational studies, it will be possible to predict these subgroups and hereby to reduce the total therapeutic costs.

In the literature, there are only few survival analyses in mCRC patients who were exposed to all active treatments, particularly the molecular agents. The present study demonstrated that in mCRC patients if an adequate tumor response was achieved with all major therapeutic agents, there may be a significant survival advantage. No matter how therapies are combined or ordered, an early and rapid response is necessary in symptomatic or marginally resectable patients. Our priority should be to treat patients with the 5 five major chemotherapeutic agents as effectively as possible. Therefore, in order to prolong the patients' survival in advanced disease, sequential treatment of all chemotherapy regimens in various combinations may be critically important. The major limitation of our study was the limited number of patients included in this retrospective analysis, therefore, more comprehensive trials are essential so as to conclude it as a statement.

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