Adverse Effects of Bevacizumab During Treatment for Metastatic Colorectal Cancer

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Abstract: *Objective*: Bevacizumab has been increasingly used in combination chemotherapy for the treatment of metastatic or recurrent colorectal cancer. The aim of this report is to underline the possible risks associated with bevacizumab use.

Methods: Between July 2005 and March 2013, a total of 130 patients with metastatic colorectal cancer who received oxaliplatin as first-line chemotherapy were divided into 2 groups those treated with bevacizumab (group A) and those without (group B), and compared. The primary endpoint was to clarify the profile of bevacizumab - induced adverse effects. Secondary endpoints examined therapeutic effects, including overall survival (OS).

Results: The incidence of major side effects was almost equivalent, except for bleeding, between the 2 groups. With regard to the therapeutic effects, 1 patient in group A showed complete disappearance of multiple lung metastases without any evidence of recurrence. The median OS was 926 days (95% confidence interval [CI], 756 - 1257) in group A and 534 days (95% CI, 421 – 621) in group B ($p < 0.01$).

Conclusion: The results demonstrate that bevacizumab prolonged survival in these patients although there was an increased risk of clinically significant bleeding.

Keywords: Bevacizumab, colorectal cancer, bleeding, interstitial pneumonitis.

INTRODUCTION

Bevacizumab is a recombinant humanized monoclonal antibody that targets the vascular endothelial growth factor (VEGF) [1]. Endothelial growth factor is produced by a variety of tumors, and acts on endothelial cells to enhance angiogenesis which facilitates tumor growth [2]. Bevacizumab blocks the blood supply of a variety of tumors and therefore is being used as an adjunct to standard chemotherapy [3,4]. In randomized controlled trials, the addition of bevacizumab to cytotoxic chemotherapy resulted in clinical improvement of metastatic colorectal cancer (mCRC) [5-7]. Moreover, a recent study suggests that consistent use of a single biological agent like bevacizumab, maintains treatment benefit beyond disease progression without the potential for additional toxicities associated with the inclusion of a new agent [8]. Accordingly, bevacizumab should be used more frequently in mCRC treatment. However, one of the complications of bevacizumab is that it can increase the incidence of hemorrhage in patients with a variety of tumors secondary to altering vascular integrity or by inhibition of the coagulation cascade [9-11]. It is important for medical oncologists to be familiar with bevacizumab-related adverse effects that occur in the community setting, as these may differ from those seen in clinical trials that select well-conditioned patients [12,13]. In this study the safety and efficacy of bevacizumab was studied in patients with mCRC.

METHODS

Patients

We reviewed 130 mCRC patients who received oxaliplatin as first-line therapy at Nagoya Memorial Hospital, Nagoya from July 1, 2005 to March 31, 2013. The inclusion criteria for participation in this study were as follows: histologically proven colorectal adenocarcinoma; unresectable advanced or recurrent disease; Eastern Cooperative Oncology Group performance status of 0-3; adequate baseline marrow, hepatic, and renal functions. Our institutional review board approved all aspects of this retrospective study and written informed consent was obtained from all patients participating in the study, prior to the start of any treatment regimen.

Treatment

Bevacizumab was administered in combination with oxaliplatin, 5-fluorouracil, and leucovorin (modified FOLFOX6), capecitabine plus oxaliplatin [14,15], irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI), S-1 plus irinotecan (IRIS) [16,17], or a bolus injection of

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5-fluorouracil (400 mg/m^2) on day 1 and then continuous infusion of 5-fluorouracil (2400 mg/m^2) over 46 hours plus *l*-leucovorin (200 mg/m^2). The treatment was continued until one of the following events occurred: disease progression, unacceptable toxicity, or patient's refusal to continue treatment.

Study Assessments

Progression was defined when any of the following 3 events occurred: (1) disease progression according to the Response Evaluation Criteria in Solid Tumors version 1.0; (2) clinical progression judged by experienced medical oncologists; or (3) death from any cause without progression. OS was calculated from the date of commencing chemotherapy to the date of death from any cause. Surviving patients, including those lost to follow-up, were censored at the date of last confirmation of survival. The severities of all adverse events were evaluated on the basis of the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The original data graded according to CTCAE version 3.0 were reassessed according to CTCAE version 4.0.

Statistical Analysis

OS was estimated using the Kaplan – Meier method and the time-to-event distributions were compared using the log-rank test. The 95% confidence interval (CI) for median OS was calculated using the Brookmeyer and Crowley method. All *p*-values were 2-sided and statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

The clinical characteristics of 130 mCRC patients are shown in Table **1**. Group A comprises 67 patients who underwent bevacizumab therapy; of these, 19 were >70 years. Group B included 63 patients who did not receive this biological agent during chemotherapy. The OS of group A (median, 926 days; 95% CI, 756 - 1257) was significantly longer than that of group B (median, 534 days; 95% CI, 421-621; log-rank test, $p < 0.01$). Figure **1** shows the complete response against lung metastases induced by FOLFOX therapy combined with bevacizumab. This patient is still alive without any recurrence >5 years after the cessation of chemotherapy.

The severe adverse events reported are listed in Table **2**. Although hypertension and proteinuria were commonly observed with bevacizumab use, occurring in 23 and 14 patients, respectively, the incidence of thrombosis, gastrointestinal perforation, interstitial pneumonitis, and tuberculosis was not different between the 2 groups. Grade 3 hemorrhage occurred in 5 group A patients (macrohematuria, hemoptysis, melena, and gingival bleeding occurred in 1, 1, 2, and 1 case, respectively), and only 2 group B patients. Once bevacizumab administration ceased, the bleeding eventually stopped in all 5 patients. The macrohematuria case was due to bladder invasion of a recurrent lesion (Figure **2**), and up to her death, the patient did not experience any further bleeding episodes following discontinuation of this biological agent. Figure **3** shows the 2 patients with interstitial pneumonitis, probably due to bevacizumab use.

Table 1: Patient Characteristics

	Group A	Group B
Number	67	63
Gender (male/ female)	35/ 32	42/ 21
Age (years)	42 - 82	41 - 85
Performance status		
0	46	45
1	11	12
2	7	5
3	3	1
Primary lesion	8	6
Liver metastasis alone	21	19
Lung metastasis alone	4	9
Metastatic lesions >2	25	13

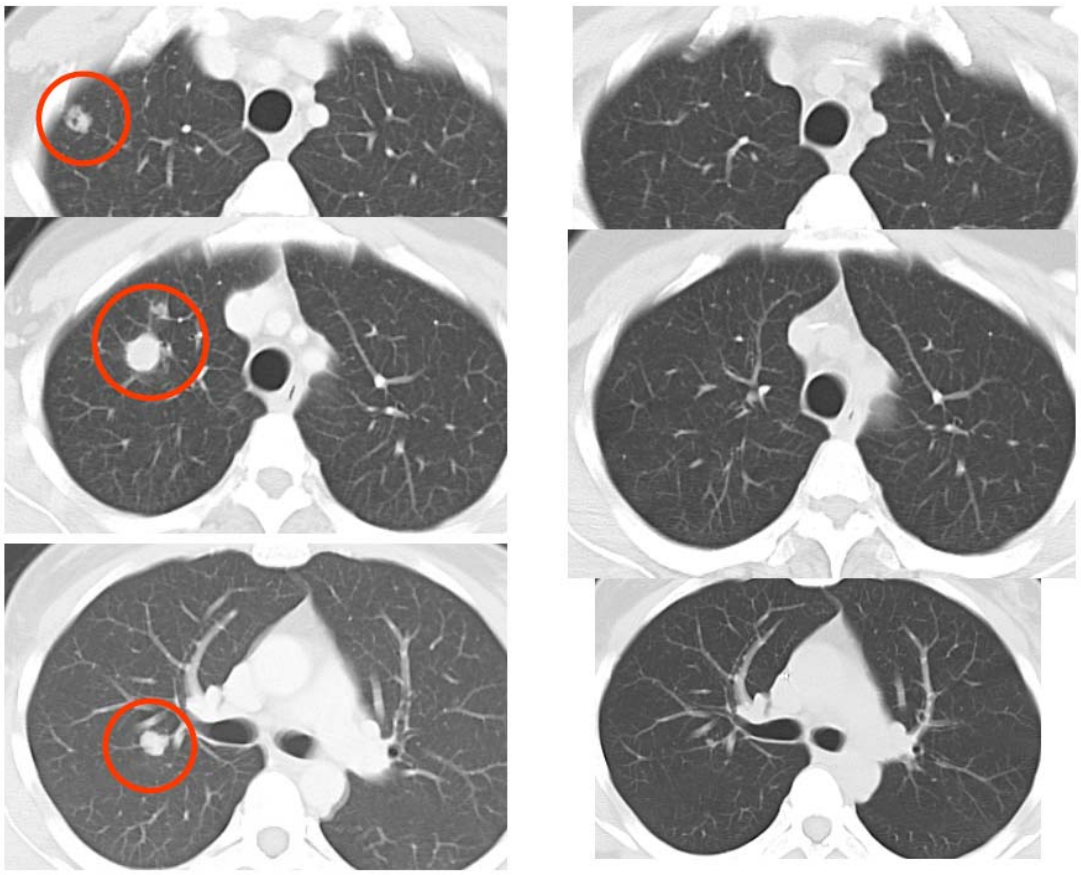

Figure 1: Left panel: Multiple lung metastases (red circle) were observed before chemotherapy.

Right panel: Lung metastatic lesions completely disappeared after 10 courses of chemotherapy of oxaliplatin, 5-fluorouracil, and leucovorin combined with bevacizumab.

Symptoms such as dyspnea and fever alleviated immediately after its cessation, and the ground glass appearance on the computed tomography scan gradually improved when it ceased to be administered. In group B, both cases of interstitial pneumonitis were induced by irinotecan use [18].

Table 2: Severe Adverse Effects Induced by Chemotherapy

	Group A	Group B
Bleeding	5	2
Thrombosis	1	2
GI perforation	0	0
Tuberculosis	1	1

GI, gastrointestinal.

DISCUSSION

This retrospective study demonstrated that the addition of bevacizumab to cytotoxic chemotherapy improved OS in mCRC patients. Recent evidence showed that anti-angiogenic treatment with bevacizumab plus chemotherapy beyond disease progression, correlated with prolonged survival, compared to chemotherapy alone (11.2 versus 9.8 months) [8]. Our data from representative mCRC patients in the community setting supports the beneficial effect of VEGF inhibition on tumor growth and metastasis [5-8, 19].

Comparison of mCRC patients who were treated with and without bevacizumab revealed that the incidence of major side effects was almost equivalent, except for bleeding, between the 2 groups. The importance of bevacizumab-associated hemorrhage is emphasized, because the incidence of fatal hemoptysis was 31% in squamous cell cancer patients receiving bevacizumab in combination with other chemotherapeutic agents [20]. A meta-analysis from 20 randomized controlled trials encompassing a total of 12,617 patients (bevacizumab-treated 6,711; controls 5,906) showed that bevacizumab significantly increased the risk of hemorrhage (relative risk, 2.48; 95% CI, 1.93 - 3.18), including fatal bleeding (relative

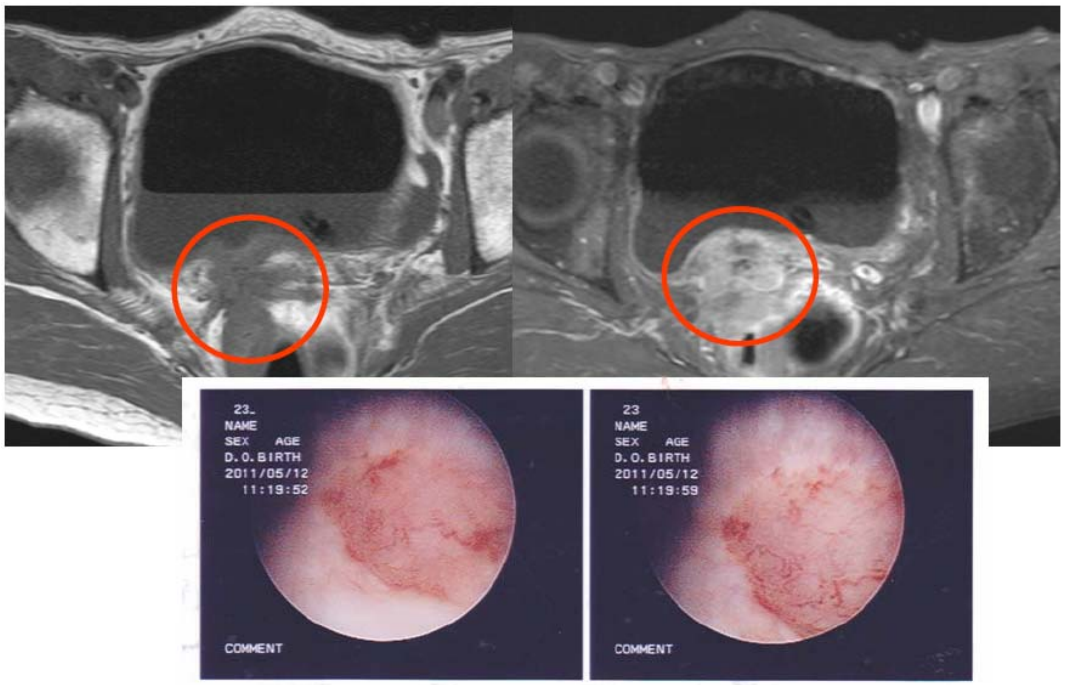

Figure 2: Magnetic resonance imaging showed bladder invasion of the recurrent lesion (left, plain; right, enhanced). Cystoscopic findings revealed the depressed lesion with dilated vessels.

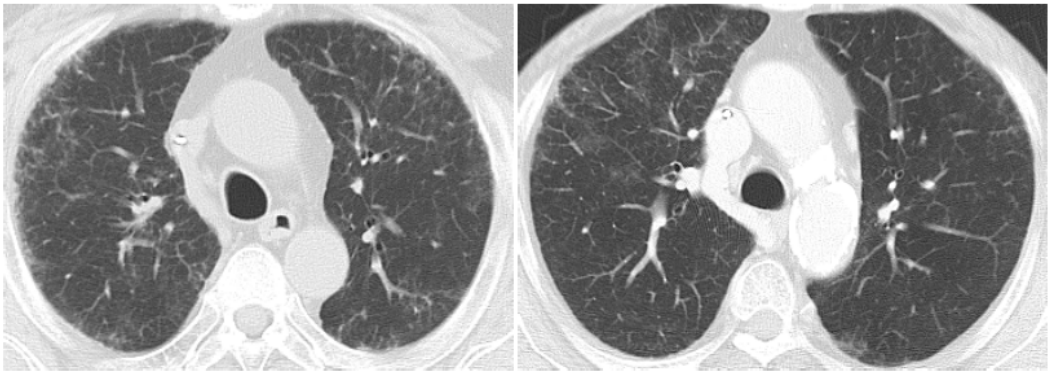

Figure 3: Patients who developed interstitial pneumonitis induced by bevacizumab use.

Left panel: A 77-year-old woman.

Right panel: A 62-year-old man.

risk, 3.56; 95% CI, 1.71 - 7.41) [21]. Our review revealed that the incidence of grade 3 hemorrhage was 7.5% and 3.2% in patients treated with bevacizumab and in the controls, respectively, although this was not statistically significant. The anti-VEGF effect of bevacizumab on the vascular endothelium may cause bleeding to develop. One possible mechanism is that bevacizumab may alter vascular integrity by inhibiting endothelial survival and proliferation [22], particularly in tissues where VEGF expression is augmented, such as peptic ulcers and injured mucosal membranes. Bevacizumab may inhibit the coagulation cascade regulated by tissue factor [23], increasing the risk of bleeding. In addition to these 2 mechanisms, bevacizumab indirectly causes substantial damage to the vascular wall infiltrated with cancer cells by having an enhanced cytotoxic effect on tumors [24].

We also reported 2 cases of interstitial pneumonitis, which probably occurred as an adverse effect of bevacizumab treatment. The causative role of bevacizumab has not been definitely proven as this agent was administered in combination with cytotoxic chemotherapy. However, we reinitiated irinotecan without bevacizumab after a 1-month treatment holiday and no pulmonary side effects were noted, suggesting that bevacizumab was the cause of interstitial pneumonitis. The Food and Drug Administration's

Table 3: Characteristics of Patients who Developed Interstitial Pneumonitis Induced by Bevacizumab Use

	Case 1	Case 2
Age/ gender	77/ female	62/ male
Performance status	1	0
Smoking	No	20 /day
Serum albumin	3.4	3.6
C-reactive protein	4.62	11.61
Bevacizumab (cycle)	5	7
Chemotherapy	FOLFIRI	IRIS
Primary lesion	No	Rectum cancer
Metastases	Liver and lung	Liver and lung

FOLFIRI: irinotecan, 5-fluorouracil, and leucovorin, IRIS: S-1 combined with irinotecan.

Adverse Event Reporting System database showed that interstitial pneumonitis occurred in 96 of 12,010 patients receiving bevacizumab and its frequency was not statistically significant on sensitivity analysis [25]. Usui *et al*. reported 4 cases of interstitial pneumonitis among 104 CRC patients treated with bevacizumab (3.85%) [26]. Risk factors for interstitial pneumonitis during chemotherapy include older age, poor performance status, and reduced normal lung area on computed tomography scans. Kang *et al*. demonstrated that a low serum albumin level was associated with the development of pulmonary complications in a multivariate analysis [27]. Our patients did not have such clear risk factors (Table **3**), and recovered without steroid treatment, eventually receiving chemotherapy without bevacizumab.

In conclusion, bevacizumab-containing chemotherapy significantly prolonged longevity and was well tolerated by the majority of mCRC patients, but may be associated with an increased risk of clinically significant bleeding. Although the incidence of bevacizumab-induced pneumonitis was not obviously raised, interstitial pneumonitis should be suspected in cases of fever and dyspnea when accompanied by elevated C-reactive protein levels during this treatment.

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