SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 3: 415-419, 2015

Response to bevacizumab combination chemotherapy of malignant pleural effusions associated with non-squamous non-small-cell lung cancer

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Received September 18, 2014; Accepted October 29, 2014

DOI: 10.3892/mco.2014.457

Abstract. Malignant pleural effusion (MPE) is a common complication of lung cancer with devastating consequences. Since vascular endothelial growth factor (VEGF) has been implicated in MPE, we hypothesized that bevacizumab, an anti-VEGF antibody, may be effective against MPE in patients with non-small-cell lung cancer (NSCLC). We analysed the records of 21 patients treated for NSCLC-associated MPE between February, 2010 and August, 2013 who consequently underwent bevacizumab combination chemotherapy at the Institute of Biomedical Research and Innovation Hospital. The results were retrospectively analysed using case records and radiographic imaging records. Three patients exhibited complete response of the pleural effusion to bevacizumab treatment, 8 patients achieved a partial response (PR) and 6 patients showed no response. When efficacy was assessed by the response of the measurable primary or metastatic lesions to the treatment, 5 patients achieved a PR, 13 patients had stable disease and 3 patients exhibited progressive disease. The response rate (RR) of the pleural effusion to the antibody treatment was 71.4% and the overall RR of measurable lesions was 23.8%. The median time-to-response for pleural effusion was 132 days. In conclusion, this study demonstrated a high RR to bevacizumab combination therapy for the MPE associated with non-squamous NSCLC. Therefore, bevacizumab therapy may be considered a therapeutic option for patients with non-squamous NSCLC who develop MPE.

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Key words: bevacizumab, malignant pleural effusion, non-small-cell lung cancer, vascular endothelial growth factor

Introduction

Malignant pleural effusion (MPE) is a common and devastating complication of lung cancer, with 15% of lung cancer patients presenting with pleural effusion at the time of initial diagnosis, whereas half of the patients develop pleural effusion at a later stage of the disease (1,2). MPE may cause significant dyspnea, cough and chest pain. There are currently several management options for MPE, including chemical pleurodesis with chest tubes or medical thoracoscopy, video-assisted thoracic surgery, pleuroperitoneal shunts and chronic indwelling pleural catheter. However, all these management options have certain disadvantages (3).

Vascular endothelial growth factor (VEGF) is the founding member of an expanding family of endothelial cell growth factors. VEGF, also known as vascular permeability factor, has been implicated in MPE (4). VEGF is a powerful inducer of vascular permeability; it is 50,000 times more potent than histamine (5). In addition, VEGF expression may be induced by nearly all cell types and is often overexpressed in lung cancer cells (6,7).

Bevacizumab is a humanized monoclonal antibody against VEGF with demonstrated antitumour effects in lung cancer cell lines and animal models (8). Results from *in vitro* studies have demonstrated that this monoclonal antibody is able to effectively neutralize almost all VEGF-mediated activities (9). It was previously shown that the administration of an anti-VEGF antibody lead to a significant reduction in the amount of pleural fluid within the first week following intrapleural injection of talc or nitrate (10). This antibody was also successfully used for the treatment of recurrent pleural effusions in a patient with amyloidosis (11). Bevacizumab in combination with carboplatin/paclitaxel improved overall survival (OS) and is currently approved in the United States and Japan for use in patients with recurrent or metastatic non-squamous, non-small cell lung cancer (NSCLC) chemotherapy (12).

Therefore, we hypothesized that the administration of the anti-VEGF antibody bevacizumab may be beneficial as a treatment option for MPE in NSCLC patients. In this

study, we retrospectively analysed the efficacy of combination chemotherapies that included bevacizumab against NSCLC-associated MPE.

Materials and methods

Patient selection. We analysed records from 21 patients with advanced NSCLC and MPE who consequently underwent bevacizumab combination chemotherapy between February, 2010 and August, 2013 at the Institute of Biomedical Research and Innovation Hospital, Kobe, Hyogo, Japan. Data were retrospectively collected from case records and radiographic imaging records. Written informed consent regarding bevacizumab therapy was acquired from all patients. This study was approved by the Institutional Review Board of our institute.

Evaluation of efficacy. Measurable lesions and the size of the MPE were determined by computed tomography (CT) scan prior to bevacizumab combination chemotherapy. Tumour response was evaluated by CT every 4-8 weeks according to the Response Evaluation Criteria in Solid Tumours Committee (13). If a patient was documented to exhibit a complete response (CR) or a partial response (PR), a confirmation with a second scan was required after an additional 4 weeks. The response of each tumour was recorded as the best tumour response observed over the entire course of treatment. Response rate (RR) was defined as CR+PR.

The size of the pleural effusion was defined as follows: Massive, effusion volume >75% of the hemithorax; large, effusion volume 50-75% of the hemithorax; moderate, effusion volume 25-50% of the hemithorax; and small, effusion volume <25% of the hemithorax. The objective response of the MPE was evaluated using chest X-rays and CT scans and a method similar to a previous report (14). CR was defined as the complete disappearance of pleural fluid for 4 weeks. PR was defined as a distinguishable decrease for 4 weeks. No response was defined as failure to meet the abovementioned criteria. CR was evaluated only by CT scans. The time-to-response was defined as the period between the initiation of bevacizumab therapy and the first detectable reduction of the pleural effusion volume by CT or chest X-ray. Time-to-response was calculated using only patients with either a CR or a PR; patients that showed no response were not included in this calculation.

Results

Patient characteristics. First, we reviewed the demographics of the patients included in the study. The patient characteristics are summarized in Table I. All the patients were Japanese and included 11 men (52%) and 10 women (48%), with a median age of 46 years (range, 30-86 years). Eleven patients (52%) were never-smokers and 10 patients (48%) were current or former smokers. All the patients had stage IV adenocarcinoma according to the 7th edition of the TNM classification (15). The majority of the patients (12/21, 57.1%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2. EGFR mutations were detected in 13 of the 21 patients (61.9%) and anaplastic lymphoma kinase (ALK) rearrangement was detected in 3 cases (14.7%).

The patients were grouped based on the size of the pleural effusion; 7 patients (33.3%) had a moderate effusion size, 6 patients (28.5%) had large effusions, whereas 4 patients (19.1%) each had massive and small effusions. A total of 15 patients (71.4%) had received prior chemotherapy. The standard dose of bevacizumab (15 mg/kg) was administered to all the patients. In combination with bevacizumab, the patients received one of the following regimens: carboplatin plus paclitaxel (n=6), erlotinib (n=5), vinorelbine (n=4), carboplatin plus pemetrexed (n=2), docetaxel (n=2), or paclitaxel (n=2).

Response to treatment. We assessed the response of the patients to the combination therapy including bevacizumab by reviewing the change in the effusion volume over the course of the treatment. Of the 21 patients, 7 achieved a CR, 8 had a PR and 6 patients did not show a response. We next investigated the patient assessments of the primary or metastatic lesion response to the combination therapy. A total of 5 patients exhibited a PR, 13 patients had stable disease and 3 patients showed progressive disease (Table II). The RR of the pleural effusion to therapy was 71.4% and the overall RR of measurable lesions to therapy was 23.8%. Of the 6 patients who exhibited no response, 5 had no increase in the effusion volume compared to the original measurement. Of the 15 patients who achieved a CR or PR regarding the pleural effusion, 3 patients (25%) did not exhibit a re-accumulation of pleural effusion following completion of the treatment.

Discussion

The goal of our study was to review the RR of MPE to a combination therapy that included bevacizumab. Overall, we observed that 23.8% of measurable lesions showed a response. This tumour RR is similar to those of previous reports examining a high dose bevacizumab combination therapy, which reported RRs of ~30% (12,16). However, this study also demonstrated a high RR of NSCLC-associated MPE to the high-dose bevacizumab combination therapy; 71.4% of MPE has some measurable decrease in volume.

In a number of patients with NSCLC-associated MPE, standard systemic chemotherapy was proven to be ineffective (3,18). Kitamura *et al* reported that bevacizumab in combination with chemotherapy was highly effective for the management of MPE in patients with non-squamous NSCLC (18). Combined intrapleural therapy with bevacizumab and cisplatin was found to be effective and safe in managing NSCLC-associated MPE, with a curative efficacy of 83.33% (19). According to another study, intense combination chemotherapy including cisplatin, ifosfamide, irinotecan and recombinant human granulocyte colony-stimulating factor support achieved high RRs of the pleural effusions and measurable lesions (58.8 and 73.5%, respectively) (14). Notably, our study demonstrated a higher RR of pleural effusion to a combinatorial therapy that included a high dose of bevacizumab.

Several studies demonstrated that VEGF is associated with the formation of pleural effusion, the effusion size and poor patient survival (20-24). It was also reported that VEGF receptor phosphorylation inhibited the formation of malignant effusion in mice with lung adenocarcinomas. This result was attributed to reduced vascular permeability (25).

Table I. Patient characteristics (n=21).

Characteristics	Patient no.	%
Age (years)		
Range	30-86	
Median	46	
Gender		
Male	11	52.0
Female	10	48.0
Smoking status		
Never-smoker	11	52.0
Current or former-smoker	10	48.0
ECOG PS[a]		
1	9	42.9
2	12	57.1
Histology		
Adenocarcinoma	19	90.4
Large-cell neuroendocrine cell carcinoma	1	4.8
Non-small-cell lung cancer NOS	1	4.8
Stage		
IV	21	100.0
EGFR status		
Mutation[b]	13	61.9
Wild-type	7	33.3
Unknown	1	4.8
ALK rearrangement		
Positive	3	14.7
Negative	7	33.3
Unknown (number of EGFR mutants)	11 (5)	52.0
Size of pleural effusion		
Small	4	19.1
Moderate	7	33.3
Large	6	28.5
Massive	4	19.1
Prior chemotherapy		
Yes	15	71.4
No	6	28.6
Chemotherapy schema		
Carboplatin + paclitaxel + bevacizumab	6	28.5
Erlotinib + bevacizumab	5	23.8
Vinorelbine + bevacizumab	4	18.9
Carboplatin + pemetrexed + bevacizumab	2	9.6
Docetaxel + bevacizumab	2	9.6
Paclitaxel + bevacizumab	2	9.6

[a]Performance status evaluated prior to the administration of bevacizumab. [b]EGFR mutation-positive; exon 19 del, exon 21 L858R, L861Q. SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma kinase gene.

Mesiano *et al* reported that the production of ascitic fluid induced by intraperitoneal inoculation of ovarian cancer cells was almost completely inhibited by neutralizing antibodies that block the action of VEGF (26). Considering the results from those *in vitro* studies, anti-VEGF therapy may be more effective for malignant effusion rather than for primary tumours. Recombinant human endostatin (Endostar) reduced the expression of VEGF-A and MPE in mice with Lewis lung

Table II. Response to bevacizumab-containing treatment.

Response of pleural effusion (no.)[b]	Tumour response (no.)[a]		
	Partial response	Stable disease	Progressive disease
Complete response (n=7)	3	3	1
Partial response (n=8)	0	7	1
No response (n=6)	2	3	1
Total (n=21)	5	13	3

[a]Tumour response rate, 23.8%. [b]Response rate of pleural effusion, 71.4%.

carcinoma (27). This result may explain the differences we observed between the response of pleural effusions and that of measurable lesions to bevacizumab.

In this study, all the patients received the standard dose of bevacizumab (15 mg/kg). Pichelmayer *et al* reported data on 4 patients with malignant effusions who received bevacizumab therapy (11). In that study, 2 patients who received low-dose bevacizumab (5 or 10 mg/kg) achieved no significant reduction of the malignant effusions. By contrast, 2 patients who received the standard dose (15 mg/kg) achieved a reduction of the malignant effusion. The results of those studies suggest that treatment of malignant effusion with bevacizumab may require administration of the standard dose.

There are currently several management options for MPE, such as chemical pleurodesis with chest tubes, medical thoracoscopy, video-assisted thoracic surgery, pleuroperitoneal shunts and chronic indwelling pleural catheter (3,17). Chemical pleurodesis is the most commonly used modality for managing MPE. However, patients with a multi-loculated effusion, trapped lung, or bronchial obstruction are unlikely to benefit from intrapleural therapy. Typically, such patients may be treated with systemic chemotherapy. Therefore, intrapleural therapy is not ideal and should be reserved for patients who are refractory to or meet the exclusion criteria for systemic chemotherapy. Based upon our results, bevacizumab therapy alone may be a treatment option for non-squamous NSCLC patients with MPE and poor performance status.

This study had certain limitations. First, there are no standard criteria to evaluate response in patients with MPE. Therefore, we used the response criteria reported by a previous study (14). Second, we were unable to confirm negative cytological findings in the pleural effusions following bevacizumab therapy, as a thoracentesis was difficult in cases where a CR or PR was observed. However, a confirmation of the response, which requires over 4 weeks and a RR of 67.0% were considered satisfactory. Finally, this study was conducted entirely by retrospectively reviewing electronic medical charts. A prospective study may improve our understanding of the potential and efficacy of anti-VEFG therapy.

In conclusion, this study demonstrated a high RR to bevacizumab combination therapy of the MPE associated with non-squamous NSCLC. Therefore, bevacizumab therapy may be a management option for patients with MPE associated with non-squamous NSCLC.

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