Bevacizumab in Combination with Paclitaxel and Platinum for Previously Treated Advanced Thymic Epithelial Tumor

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Abstract

Background

There are no optimal regimens for advanced thymic epithelial tumors (TETs) when front-line chemotherapy fails. In this study, we aimed to assess the activity of Bevacizumab in combination with routine chemotherapeutic regimen.

Methods

Patients with advanced TETs who had failed after previous chemotherapy were enrolled in this study. Paclitaxel (160mg/m²) or cisplatin (70mg/m²) and carboplatin (area under the curve, 6) plus Bevacizumab (7.5mg/kg) were intravenously injected on day 1. The treatment was repeated every 3 weeks until the disease progressed or intolerable toxicities occurred.

Results

Between March 2018 and August 2020, a total of 49 patients (21 thymoma and 28 thymic carcinoma) received the new treatment. There were 28 men and 21 women with a median age of 50 years (range: 21-73 years). The median number of cycles was 3 (range: 1-6) per patient. The objective response rate (ORR) for all patients was 43% (21/49). The ORRs for thymoma and thymic carcinoma were 24% and 57%, respectively. The median progression free survival for thymoma and thymic carcinoma were 6 and 8 months, respectively. Hematological toxicities were the main side effects.

Conclusions

Paclitaxel and platinum plus Bevacizumab showed promising effect in refractory or relapsed advanced TETs without severe toxicity. Even applied as salvage therapy, this regimen resulted in better ORR than the front-line chemotherapy.

1. Introduction

Thymic epithelial tumours (TETs) are the most common tumors arising in the anterior mediastinum [1]. TETs are basically classified as thymoma or thymic carcinoma based on atypia of thymic epithelial cells and their relative proportion to lymphocytes [2]. Although different subtype shows different biological behavior (aggressiveness, growing speed and tendency to metastases), surgical resection remains the mainstay of treatment for localized disease. However, each subtype has the potential to develop into an extensive condition in which systemic therapy such as chemotherapy has been used to reduce the tumor burden or to achieve longer disease control.

As recommended by the International Thymic Malignancies Interest Group (ITMIG), conventional regimens such as CAP (cisplatin + doxorubicin + cyclophosphamide), ADOC (cisplatin + doxorubicin + vincristine + cyclophosphamide) or EP (etoposide + cisplatin) have been mostly utilized by clinicians to

suppress late-staged TETs [3]. However, anthracyclines are associated with specific toxicity to heart, especially when thoracic irradiation is involved. In the previous decade, new regimen of paclitaxel and platinum has been proved efficient in TETs with low toxicities [4–6]. Meanwhile, a humanized monoclonal antibody-Bevacizumab (BV), was found to increase response rate and survival when added to standard chemotherapy in a series of cancers [7–9]. What the outcome would be, when paclitaxel and platinum plus BV are used to TETs, has not been explored yet. In this study, the efficacy and safety of this combination was retrospectively investigated.

2. Patients And Methods

2.1. Patient selection

All patients who were enrolled in this study should meet the following eligibility criteria: pathologically diagnosed TET; no indications for surgical resection; measurable lesions on computed tomography (CT), magnetic resonance imaging (MRI) or other radiological images; disease uncontrolled after previous chemotherapy; ECOG PS of ≤ 2 ; adequate bone marrow, hepatic and renal function. Patients were excluded if they had unsteady hypertension, or the lesions invaded major vessels or trachea. This retrospective study was approved by the Shanghai Chest Hospital Ethic Committee (ID: IS2162) and written informed consents were given by all patients.

2.2. Treatment methods

Patients intravenously received paclitaxel ($160\text{mg}/\text{m}^2$) and carboplatin (area under the curve, 6) plus BV at $7.5\text{mg}/\text{kg}$ on day 1. If carboplatin was applied in previous front-line chemotherapy, then in this study it would be replaced by cisplatin ($70\text{mg}/\text{m}^2$). The treatment cycle was repeated every 3 weeks until the disease progressed or intolerable toxicities occurred. The peripheral blood-count test was repeated at least once a week, while biochemistry once a cycle. Radiological examination was conducted every 2 cycles to assess the efficacy of the new regimen. Subsequent treatment after progression was determined by the attending physician.

2.3. Evaluation of response and toxicity

In general, responses were assessed using RECIST. When the target lesions appeared as pleural nodules or mass, however, evaluation would be made according to the modified RECIST advised by ITMIG [10]. Side effects were graded according to Common Terminology Criteria for Toxicity and Adverse Event reporting version 5.0.

2.4. Statistical analysis

Progression free survival (PFS) was defined from the start of three-component-chemotherapy to tumor progression, while overall survival (OS) was defined from the start of chemotherapy to patient's death or last follow up. The response rates were compared using the chi-square test. PFS and OS were estimated with the Kaplan-Meier method. The log-rank test was used to test differences between groups. Statistical

analysis was performed with SPSS 16.0, and p values of less than 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

From March 2018 to August 2020, 49 consecutive patients had been enrolled in this study in Shanghai Chest Hospital. The demographic descriptions of all patients are summarized in Table 1. There were 28 men and 21 women with a median age of 50 years (range: 21–73 years). The numbers of thymoma and thymic carcinoma were 21 and 28, respectively. Among 28 patients with thymic carcinomas, the subtypes were squamous cell carcinoma ($n = 21$), undifferentiated carcinoma ($n = 3$), lymphoepithelioma-like carcinoma ($n = 2$), basaloid carcinoma ($n = 1$) and mucoepidermoid carcinoma ($n = 1$), respectively. The most common failure sites were pleura ($n = 38$), lung ($n = 11$), liver ($n = 5$) and lymph node ($n = 3$). The most frequent regimens in front-line chemotherapy were paclitaxel/docetaxel + cisplatin/carboplatin (41%), CAP/ADOC (27%), etoposide + cisplatin (10%), pemetrexide + carboplatin (6%) and other uncommon combinations (16%). The ORRs of front-line chemotherapy in thymoma and thymic carcinoma were 4.8% and 25%, respectively.

Table 1
Patients' characteristics (n = 49)

Age median (range)	50 (21–73) y
Male/female	28/21
Histology	
B2	6
B3	15
C	28
Failure site	
Pleura	38
Lung	11
Liver	5
Lymph node	3
Chemo before TPB*	
One line	49
Two lines	11
Three lines	5
*TPB: paclitaxel + platinum + Bevacizumab	

3.2. Response and survival

In total, 161 cycles of the novel chemotherapy were given. The median number of cycles was 3 (range: 1–6) per patient. In all 49 patients, 21 (43%) achieved partial response (PR), 27 (55%) remained stable disease (SD) and one patient (2%) with squamous cell carcinoma showed progression disease (PD) of more than 50% after two cycles. For thymoma and thymic carcinoma, the ORRs were 24% and 57%, respectively. The best responses of each patient are shown in Fig. 1. Different response status of thymoma and thymic carcinoma is displayed in Fig. 2A and Fig. 2B. The detailed information about response status in each subgroup is shown in Table 2. Thymic carcinoma appears to be more sensitive to this regimen than thymoma. (57% vs 24%, $p = 0.02$)

Table 2
The objective response rate (%) in each subgroup

	ORR	P value
Gender		
Male	46% (13/28)	0.56
Female	38% (8/21)	
Histology		
Thymoma	24% (5/21)	0.02
Thymic carcinoma	57% (16/28)	
Failure site		
Pleura	39% (15/38)	0.41
Lung	64% (7/11)	
Liver	60% (3/5)	
Lymph node	67% (2/3)	
Platinum		
Cisplatin	41% (13/32)	0.67
Carboplatin	47% (8/17)	

The median PFS for all patients was 7 months (95% CI: 5.63–8.37, Fig. 3). The median PFS for thymoma and thymic carcinoma were 6months (95% CI: 5.13–6.87) and 8months (95% CI: 5.40-10.59), respectively. (Fig. 4)

3.3. Toxicity

The most common adverse events (AEs) were fatigue, neutropenia, vomiting and hemoptysis. Toxicities of more than grade 2 are listed in Table 3. Five patients had the treatment discontinued due to fatigue (n = 2), hemoptysis (n = 1), anemia (n = 1) and myasthenia gravis crisis (n = 1). No treatment related death occurred.

Table 3
Adverse events of more than grade 2 (n = 49)

	N		
	Grade 2	Grade 3	Grade 4
Fatigue	6	2	0
Vomiting	4	2	0
Neutropenia	13	4	1
Anemia	2	0	1
Hemoptysis	1	0	0
Hypertension	2	0	0
MG* deterioration	1	1	0
*MG: myasthenia gravis			

Discussion

Our retrospective, real-world study proved the high efficiency of paclitaxel and platinum plus BV in previously highly treated advanced TETs without life-threatening toxicity. The ORR for thymoma and thymic carcinoma were 24% and 57%; and the median PFS were 6months and 8months, respectively. To our knowledge, this is the first report evaluating the addition of BV to standard chemotherapy in TETs, although its superiority has been established in other malignancies through randomized trials. [8, 9, 11] Imbimbo et al registered a phase II trial, using similar antiangiogenic agent (ramucirumab) plus paclitaxel and carboplatin for thymic malignancies, while the results have not been revealed yet.[12]

There were 21 patients with thymoma in this study, and all of them received front-line chemotherapy before this trial. However, only one patient (4.7%) showed partial response. In Lemma et al's study, the ORR of paclitaxel-carboplatin regimen was 42.9% in thymoma.[4] Meanwhile, the ORR of anthracycline-containing regimen was approximately 73% in Lucchi et al's report.[13] All our 21 patients had pleural disseminations, and mainly showed resistance to routine chemotherapeutic regimens. To our delight, 5 out of 21 (24%) patients experienced tumor regression when BV was added to routine chemotherapy. At the same time, an ORR of 57% was observed in our 28 TC patients with the same regimen, which was much higher than that of the front-line chemotherapy (25%) in this cohort, as well as the ORRs in other large-sample reports.[14–15] As for the enhancement mechanism of BV, most authors agreed that it improves drug delivery to the tumor.[16–18] In addition, due to its anti-VEGF antibody nature, BV may also inhibit tumor angiogenesis, which is critical for tumor progression. Similarly, in our current study, the improvement in ORR was obvious in both thymoma and TC (24% vs 4.7, 57% vs 25%) compared with front-line chemotherapy.

Johnson et al reported in their phase II study that 6 out of 11 patients with squamous cell lung cancer developed severe pulmonary hemorrhage (4 were fatal) after receiving BV-containing chemotherapy. [19] Thus, squamous lung cancer was excluded from the candidates of BV target therapy. In our study, however, there were 28 cases of thymic squamous cell carcinoma. Only 1 patient developed grade 2 hemoptysis, and the treatment was discontinued thereafter. We reviewed the computed tomography of this patient and found that his tumor body was adjacent to the main trachea and showed a sign of invasion. As we know, a major portion of squamous cell lung cancers are centrally located, and have a tendency to involve hilar structure like main bronchia and vessel. When BV delivered, the necrotic cavity inside tumor is likely to form up, resulting in fatal bleeding. While the situations in thymic squamous carcinoma and cervical cancer are different, although the pathological types are also squamous cell, the risk of severe hemorrhage is relatively low. Therefore, they should not be viewed as contraindications of BV treatment despite of the pathology.

The dose of paclitaxel in the current study (160mg/m²) was lower than that in Lemma et al's study (225mg/m²)[4], because all our patients were heavily treated before they received the new regimen. Meanwhile, BV was prescribed at the dose of 7.5mg/kg based on the results of AVAiL study, in which similar clinical outcome was observed in either 7.5mg/kg group or 15mg/kg group. [11] These might explain the lower incidence of severe hematological toxicity and hypertension in this trial (Table 3) than that of previous studies. [8–9, 19] Whether higher dose of paclitaxel and BV could produce better outcome in TETs needs to be examined in further prospective trials.

In this study, the median PFS for thymoma was 6 months, shorter than that of 16.7 months in Lemma et al's study,[4] possibly due to the lower response rate (24%) in our thymoma cohort. While for thymic carcinoma, the median PFS was 8 months, consistent with previous reports. [5, 15] We did not take overall survival (OS) as a primary end point because there was great heterogeneity in the subsequent therapy after progression so that it is complicated to interpret OS. Thus, we took PFS as the primary end point like in most studies with BV. In ECOG 4599 study, BV single-agent maintenance treatment after chemotherapy was associated with better PFS, [20] so it may also be worthy of trying BV maintenance therapy in prospective trials for TETs.

There are some limitations in our study. First, it is a single-center retrospective study of small sample due to the rarity of TETs. Second, most of the target lesions in thymoma patients are pleural dissemination, while it is only one manifestation of late-staged thymoma. Third, there is inconsistency in chemotherapy regimen, such as cisplatin and carboplatin are both administered, although our limited cases showed there was no difference in the efficacy.

In conclusion, paclitaxel and platinum plus BV showed promising effect in refractory or relapsed advanced TETs without severe toxicity. Even applied as salvage therapy, this regimen resulted in better ORR than the front-line chemotherapy. Further prospective investigation in first-line setting for unresectable TETs is warranted.

Abbreviations

TET= thymic epithelial tumor; ORR= objective response rate; CAP= cisplatin+doxorubicin+cyclophosphamide; ADOC= cisplatin+doxorubicin+ vincristine +cyclophosphamide; EP= etoposide+cisplatin; ITMIG=International Thymic Malignancies Interest Group; BV= Bevacizumab; CT= computed tomography; MRI= magnetic resonance imaging; PFS= progression free survival; OS= overall survival; PR= partial response; SD= stable disease; PD= progression disease

Declarations

1 No funding or grants.

2 All authors declare no conflict of interests

3) Original data could be available on request

4) This study was approved by our institutional ethic committee.

5) All patients gave their consent for receiving this new chemotherapy regimen and the using of their information.

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Figures

Figure 2

Waterfall plot of the best response in (A) thymoma and (B) thymic carcinoma.

Figure 3

Progression free survival of all patients.

Figure 4

Progression free survival of thymoma and thymic carcinoma.