ORIGINAL ARTICLE

Efficacy and toxicities of gemcitabine and cisplatin combined with endostar in advanced thymoma and thymic carcinoma

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Abstract

Background: Thymoma and thymic carcinoma are rare thymic epithelial tumors. We investigated the efficacy of first-line gemcitabine and cisplatin (GP) chemotherapy versus gemcitabine and cisplatin chemotherapy combined with the anti-angiogenic drug endostar (GP + E) in advanced thymoma and thymic carcinoma.

Methods: The records of 45 patients with invasive metastatic thymomas or thymic carcinomas treated with GP as first-line therapy between August 2008 and July 2017 at the Department of Respiratory Medicine, Peking University Cancer Hospital and Institute were retrospectively reviewed.

Results: Eighteen patients (75%) in the GP + E group achieved a partial response and six (25%) had stable disease. In GP only group, nine (42.8%) patients achieved a partial response, 11 (52.4%) had stable disease, and one (4.8%) had progressive disease. The GP + E group had a significantly higher overall response rate (75% vs. 42.9%; $P = 0.028$), and median progression-free survival (PFS) and overall survival (OS) of 19 and 76 months, respectively. In the GP only group, median PFS and OS were 16 and 29 months, respectively. PFS and OS were not significantly different between the groups.

Conclusions: GP has moderate efficacy and could represent a suitable first-line therapy for thymic carcinoma and thymoma. Chemotherapy combined with endostar could improve the overall response rate, but did not prolong PFS or OS.

Introduction

Thymoma and thymic carcinoma, the most common anterior masses in the mediastinum, are rare thymic epithelial cancers. The annual incidence of thymoma is 1.4/1 000 000 and 1.3/1 000 000 in the United States and Europe, respectively.[1–3] Thymic carcinoma is rarer, significantly more aggressive, and less responsive to chemotherapy. According to the World Health Organization (WHO) histological classification, thymoma is classified as types: A, AB, B, B2, and B3[4] Although both originate from thymic epithelial cells, thymoma and thymic carcinoma exhibit different biological behaviors and have distinct prognoses:

five-year overall survival for type A thymoma is 88% compared to 38% for thymic carcinoma.[5]

Surgery remains the main form of treatment, while systemic chemotherapy is prescribed for unresectable, recurrent, or metastatic thymoma and thymic carcinoma. Because of their rarity, there is lack of randomized studies on chemotherapy for thymoma and thymic carcinoma. However, prospective and retrospective studies have indicated that anthracycline-based regimens may be effective. Anthracycline-based regimens, including cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) or cisplatin, doxorubicin, and cyclophosphamide (PAC), are commonly used, with overall response rates (ORRs) of 50–92% in thymoma[6–8] and 30% in thymic

carcinoma.[9] However, anthracyclines can accumulate in the body and are associated with heart failure.[10] Less intensive anthracycline-free regimens may be preferable for patients with risk factors for heart disease or those who cannot tolerate aggressive regimens. Gemcitabine, a third-generation antitumor agent nucleoside analogue, provides better outcomes with less toxicity when combined with cisplatin compared to multidrug regimens in various types of cancer.[11–13] Endostar, a recombinant human endostatin, has been proven to improve the treatment response rate in non-small cell lung cancer when combined with chemotherapy.[14–16]

This retrospective study evaluated the efficacy and toxicity of gemcitabine and cisplatin (CP) chemotherapy only versus gemcitabine and cisplatin chemotherapy combined with anti-angiogenesis drug endostar (GP + E), as first-line therapy for patients with invasive, metastatic, or recurrent thymoma or thymic carcinoma at a single institution in China.

Methods

Patient selection

This was a retrospective review of 45 patients with histologically confirmed invasive metastatic thymoma or thymic carcinoma who received GP as first-line treatment between August 2008 and July 2017 at the Department of Respiratory Medicine, Peking University Cancer Hospital and Institute. Twenty-four patients received GP + E, while 21 received GP only. Pathological diagnosis was independently confirmed by two pathologists using the 2004 WHO classification and the Masaoka–Koga staging system. Institutional ethics review board approval for the study was obtained in advance.

Treatment methods

Gemcitabine (1250 mg/m^2) was administered intravenously over 30 minutes on days 1 and 8 every three weeks. Cisplatin (75 mg/m^2) was administered intravenously over days 1 and 2 (dose divided equally) every three weeks. Endostar (7.5 mg/m^2) was injected on days 1 to 14 every three weeks. Computed tomography scans were performed after two cycles. Treatment responses were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1. Adverse events were classified using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

Descriptive statistics were employed to describe baseline clinicopathological characteristics. Fisher's exact or χ^2 tests were used to examine the differences between variables. Overall

survival (OS) and progression-free survival (PFS) were determined using the Kaplan–Meier method. OS was measured from the initiation of gemcitabine plus cisplatin until death from any cause or the final follow-up examination (31 May 2018). PFS was measured from the initiation of treatment to the first documented progressive disease (PD) or death from any cause. All tests were two-sided and significance was defined as $P < 0.05$. All analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). GraphPad Prism7.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used to plot survival analysis curves.

Results

Patient characteristics

Between August 2008 and July 2017, 45 patients with advanced thymoma (16, 35.6%) or thymic carcinoma (29, 64.4%) received GP as a first-line regimen. The characteristics of the patients are summarized in Table 1. The median patient age was 50 years (range: 19–71), 24 (53.3%) patients were male, and 43 (95.6%) had an Eastern Cooperative Oncology Group performance status score of 0 or 1. Of the 29 patients with thymic carcinoma, 28 (96.6%) had squamous-cell carcinoma or an uncategorized histological type. Based on the Masaoka–Koga staging system, 10 (22.2%) patients had stage III disease, five (11.1%) had stage IVa disease, and 30 (66.7%) had stage IVb disease. The most common locations for metastasis were: lymph nodes (21), lung (13), pleura (10), bone (4), pericardium (3), soft tissue (3), and liver (3).

Of the 17 (37.8%) patients who underwent surgery, 13 had postoperative recurrent or metastatic disease, and four (all thymoma), underwent extended thymectomy after treatment with GP. In total, 33 (73.3%) patients received radiotherapy, 26 received radiotherapy after GP for further treatment, and seven received GP after radiotherapy because of recurrence or metastasis. Seventeen (37.8%) patients received second-line chemotherapy: docetaxel plus oxaliplatin (15), pemetrexed (1), and apatinib (1).

Treatment efficacy and survival outcomes

All 45 patients were evaluable; the treatment responses are summarized in Table 2.

Twenty-four (53.3%) patients received GP + E, including 10 (22.2%) thymoma and 14 (31.1%) thymic carcinoma patients. Eighteen (75%) achieved a partial response (PR), 6 (25%) had stable disease (SD) and none had progressive disease (PD) or achieved a complete response (CR). The objective response rate (ORR = CR, PR, or PR) was 75% (95% confidence interval [CI] 57.68–92.32%) and the disease control rate (DCR = ORR and SD) was 100%.

Table 1 Baseline characteristics of the patients

Characteristics	Thymoma (*n* = 16)	Thymic carcinoma (*n* = 29)	Total (*n* = 45)
Age (years)	48.5 (25–71)	50 (19–67)	50 (19–71)
Gender			
Male	7	17	24
Female	9	12	21
ECOG PS			
0	9	20	29
1	7	7	14
2		2	2
Histological type, thymoma			
B1	4	—	4
B2	5	—	5
B3	2	—	2
Uncategorized	5	—	5
Histological type, thymic carcinoma			
Squamous cell	—	21	21
Uncategorized	—	7	7
Neuroendocrine	—	1	1
Masaka–Koga staging			
III	4	6	10
IVa	4	1	5
IVb	8	22	30
Postoperative recurrence			
Initial metastasis site			
Lung	3	10	13
Lymph node	4	17	21
Pleura	6	3	9
Pericardium	3	2	5
Bone	0	4	4
Soft tissue	3	1	4
Liver	0	3	3
Endostar			
Yes	10	14	24
No	6	15	21
Number of cycles			
Median	3	4	4
Range	2–6	1–7†	1–7

†A thymic carcinoma patient switched to paclitaxel chemotherapy because of grade 4 thrombocytopenia and grade 2 erythra after one cycle of gemcitabine and cisplatin. ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 Response to GP + E and GP chemotherapy only in T and TC patients

|	GP + E (*n* = 24)			GP only (*n* = 21)			All Patients (*n* = 45)
	Patients (%)	Thymoma (%)	Thymic carcinoma (%)	Patients (%)	Thymoma (%)	Thymic carcinoma (%)	Patients (%)
ORR†	18 (75%)	8 (33.3%)	10 (41.7%)	9 (42.9%)	2 (9.5%)	7 (33.3%)	27 (60%)
SD	6 (25%)	2 (8.3%)	4 (16.7%)	11 (52.4%)	4 (19%)	7 (33.3%)	17 (37.8%)
PD	0	0	0	1 (4.8%)	0	1 (4.7%)	1 (2.2%)
DCR	24 (100%)	10 (41.7%)	14 (58.3%)	20 (95.3%)	6 (28.6%)	14 (66.7%)	44 (97.5%)

†As no patients achieved a complete response, the overall response rate (ORR) was defined as a partial response in this study. Chemo, chemotherapy; DCR, disease control rate; GP, gemcitabine and cisplatin; GP + E, gemcitabine and cisplatin with endostar; PD, progressive disease; SD, stable disease.

Of the 21 patients in GP only group, 9 (42.9%) achieved a PR, 11 (52.4%) had SD, one (4.8%) had PD, and none achieved a CR. The ORR was 42.9% (95% CI 21.69–64.02%), and the DCR was 95.3% (95% CI 86.13–100%). The GP + E group had a significantly higher ORR (75% vs. 42.9%; *P* = 0.028).

Overall, the median follow-up was 55 months (until May 2018), the median PFS was 18 months (95% CI 13.7–22.3), and the median OS was 41 months (95% CI 13.3–68.7). In thymic carcinoma patients, the median PFS was 18 months (95% CI 12.1–23.9) and the median OS was 33 months (95% CI 17.9–48.1) (Fig 1). In thymoma patients, the median PFS was 19 months (95% CI 17.2–20.8) and the median OS was 76 months (95% CI 24.7–127.3) (Fig 1). PFS and OS were not significantly different between thymic carcinoma and thymoma patients ($P = 0.476$ and $P = 0.553$, respectively). In the GP + E group, the median PFS was 19 months (95% CI 15.7–22.3) and the median OS was 76 months (Fig 2). In the GP only group, the median PFS was 16 months (95% CI 9.5–22.5) and the median OS was 29 months (95% CI 16.8–41.2) (Fig 2). PFS and OS were not significantly different between the GP + E and GP only groups ($P = 0.645$ and $P = 0.348$, respectively).

Toxicities

All patients were included in toxicity evaluations (Table 3). Grade 3/4 adverse events included neutropenia in 11 (24.4%) patients, thrombocytopenia in five (11.1%), and vomiting in one (2.2%). Five (11.1%) patients required dose reductions because of grade 4 toxicities (3 with neutropenia and 2 with thrombocytopenia), and one patient switched to paclitaxel chemotherapy because of grade 4 thrombocytopenia and grade 2 erythema after one cycle of gemcitabine and cisplatin. No febrile neutropenia or treatment-related deaths occurred. Non-hematological toxicities included nausea, vomiting, fatigue, rash, and alopecia, all of which were mild. Endostar did not significantly increase the total (91.7% vs. 76.2%; $P = 0.225$) or grade 3–4 (37.5% vs. 23.8%; $P = 0.356$) toxicities.
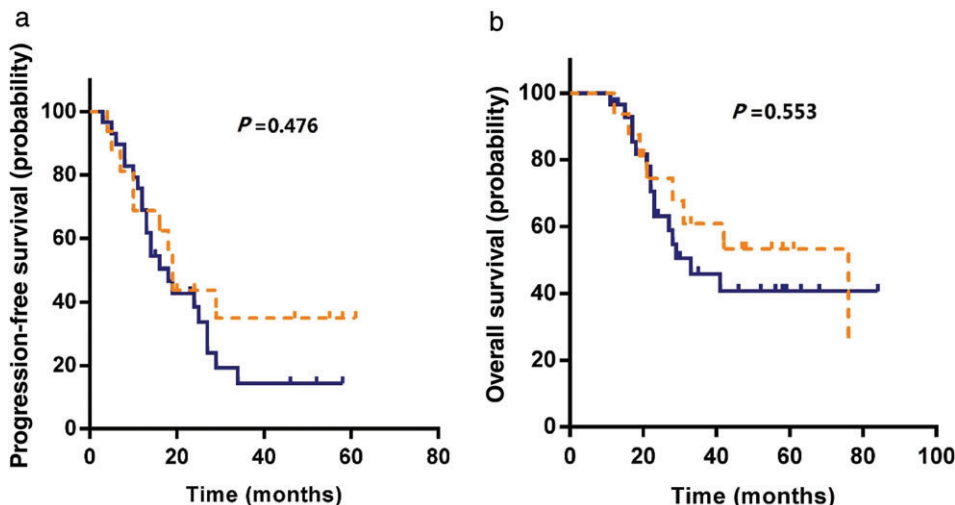
Figure 1 (**a**) Progression-free survival and (**b**) overall survival of thymoma and thymic carcinoma patients. (-----) Thymoma (10/16 failed), (——) Thymic carcinoma (22/29 failed), (-----) Thymoma (8/16 failed), and (——) Thymic carcinoma (15/29 failed).
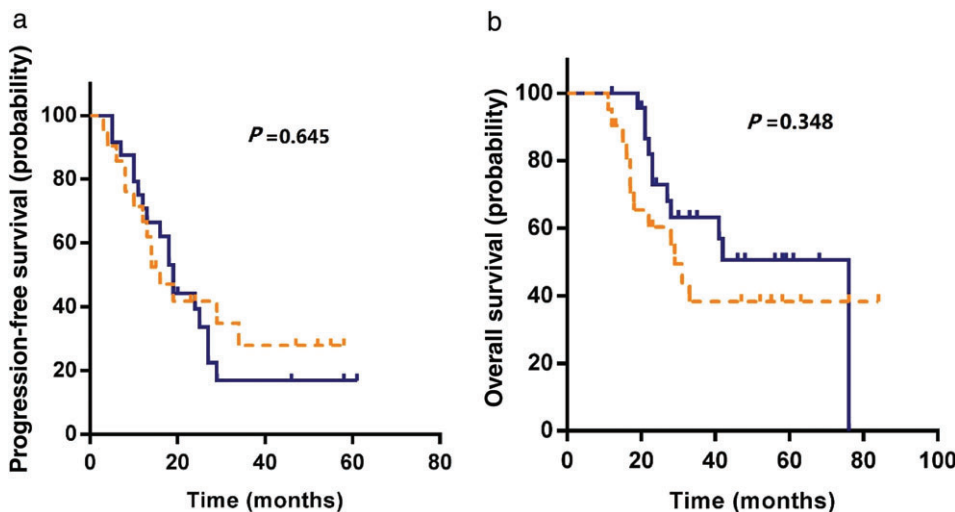
Figure 2 (**a**) Progression-free survival and (**b**) overall survival of patients in chemotherapy combined with endostar and chemotherapy only groups. (-----) Chemotherapy only (14/21 failed), (——) Chemotherapy combined with endostar (22/24 failed), (-----) Chemotherapy only (12/21 failed), and (——) Chemotherapy combined with endostar (11/24 failed).

Table 3 Treatment related adverse events

	Grade 1–2	Grade 3	Grade 4	Total
Neutropenia	17	8	3	28
Thrombocytopenia	5	2	3	10
Anemia	3	0	0	3
Fatigue	5	0	0	5
Nausea/vomiting	17	1	0	18
Stomatitis	4	0	0	4
Rash	2	0	0	2
Diarrhea	2	0	0	2
Liver dysfunction	2	0	0	2

The highest grade per event per patient is shown.

Discussion

In the 1990s, Fornasiero *et al.* reported that the ADOC regimen was clinically effective in thymoma patients (response rate 91.8%, OS 15 months)[17] these results were subsequently confirmed in retrospective and prospective studies of thymoma and thymic carcinoma.[18,19] Another study demonstrated that the PAC regimen led to a response rate of 50% and survival of 37.7 months in thymoma patients.[6] A meta-analysis of anthracycline-based and anthracycline-free regimens in thymoma and thymic carcinoma patients emphasized the importance of anthracyclines: anthracycline-based regimens led to significantly higher response rates in thymoma, but not in thymic carcinoma patients.[20] Because thymoma and thymic carcinoma often occur in middle-aged and elderly patients and a considerable number of such patients receive radiotherapy, attention needs to be paid to the cardiotoxicity of anthracyclines. For patients with a cardiac history or risk factors who require radiotherapy, anthracycline-free regimens may be preferable. A phase II trial of a cisplatin plus etoposide in 16 patients with thymoma reported an ORR of 56% and PFS of 2.3 years.[21] Carboplatin plus paclitaxel provided an ORR of 42.9% in thymoma and 21.7% in thymic carcinoma,[22] with PFS of 16.7 and 5.0 months, respectively. Carboplatin plus paclitaxel is recognized as the preferred regimen for thymic carcinoma because of its high response rate and low toxicity.

Gemcitabine plus cisplatin is recommended as the first line treatment for advanced or metastatic squamous cell lung cancer,[11] and is widely used in cervical[23] and bladder cancers.[12] In a prospective phase II trial of 30 patients with stage IV thymic epithelial tumors (22 thymoma, 8 thymic carcinoma) treated with gemcitabine plus capecitabine, Giovannella *et al.* reported an ORR of 40% (12/30) and median PFS of 11 months.[24] A retrospective study of 13 patients indicated GP provided a high response rate (61.5%) with manageable toxicities in advanced thymic squamous cell carcinoma; although no patients achieved complete remission and median survival was 50.7 months.[25]

Moreover, case reports have indicated that GP is effective in thymic carcinoma.[26,27] To our knowledge, no studies have reported the therapeutic efficacy and toxicity of GP in thymoma and thymic carcinoma. This is the first study to compare the effect of the anti-angiogenesis drug endostar combined with chemotherapy and chemotherapy alone in thymic tumors.

This retrospective analysis showed that GP was an effective regimen in thymoma and thymic carcinoma patients, with a total ORR of 60% (26/45), similar to the retrospective GP regimen (ORR 61.5%), and superior to anthracycline-based chemotherapy (ORR 50%)[6] and carboplatin plus paclitaxel (ORR ranging from 21.7–37%) in thymic carcinoma.[22,28] As the median number of treatment cycles in this study was relatively low (3 in thymoma, 4 in thymic carcinoma), increasing the number of treatment cycles may enhance the therapeutic effect.

The recombinant human endostatin endostar can inhibit angiogenesis and tumor growth.[29] Endostar in combination with chemotherapy is reported to exert synergic activity in squamous cell lung cancer.[30] This study showed that compared to GP chemotherapy alone, chemotherapy combined with endostar could improve the ORR (75% vs. 42.9%; $P = 0.028$) and may prolong the OS of patients with thymic carcinoma or thymoma (76 vs. 29 months); however, the results did not reach statistical significance ($P = 0.348$), which could be associated with the relatively small sample size. Vascular endothelial growth factor (VEGF), VEGR receptor-1, and VEGF receptor-2 are overexpressed in thymoma and thymic carcinoma.[31] Angiogenesis is associated with tumor invasion and stage in thymoma and thymic carcinoma. Sunitinib, a tyrosine kinase inhibitor that inhibits VEGFR1-3, KIT, and platelet-derived growth factor receptor, showed a therapeutic effect as second-line therapy in thymic carcinoma.[32] This anti-tumor response may be an anti-angiogenic effect, as the circulating endothelial progenitor cells decreased after sunitinib therapy and is associated with longer OS.

The grade 3/4 hematological toxicities documented in 17 patients (37.7%) were similar to rates observed in non-small cell lung cancer patients.[11] All non-hematological toxicities in this study were mild, and there was no significant difference between the GP only and GP + E groups.

The limitations of this study include its retrospective nature, small sample size, and analysis of patients treated at a single institution. Unfortunately, the rarity of thymoma and thymic carcinoma make it difficult to perform large-scale prospective trials.

Despite these limitations, this retrospective analysis indicates that GP could be a suitable first-line therapy in thymic carcinoma and thymoma, and adding the anti-angiogenesis drug endostar could improve the ORR, but did not prolong PFS and OS. Further prospective studies

of the gemcitabine plus cisplatin and endostar regimen in thymic carcinoma and thymoma are warranted.

Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1. The individual clinical endpoints for each thymoma and thymic carcinoma case.
Table S2. Response to endostar combined chemotherapy and chemotherapy only in thymoma.
Table S3. Response to endostar combined chemotherapy and chemotherapy only in thymic carcinoma.