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Pemetrexed in patients with thymic malignancies previously treated with chemotherapy☆

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ABSTRACT

Purpose: Thymic malignancies are rare, with limited published trials of chemotherapy activity. We performed a retrospective analysis of pemetrexed activity in patients with thymic malignancies.
Methods: Patients with unresectable histologically confirmed invasive, recurrent, or metastatic thymoma or thymic carcinoma seen at the Stanford Cancer Center between January 2005 and November 2013 were identified, and those who were treated with pemetrexed in the second-line setting and beyond were included in this analysis.
Results: A total of 81 thymic malignancy patients were identified, of whom 16 received pemetrexed alone ($N = 14$) or in combination ($N = 2$). There were 10 patients (62.5%) with thymic carcinoma and 6 patients (37.5%) with thymoma. Among the 6 patients with thymoma, best response was 1 (17%) with a partial response (PR) and 5 (83%) with stable disease (SD). At a median follow-up of 21.2 months, the median PFS in the thymoma patients was 13.8 months (95% CI, 4.9–22.6 months) and the median OS was 20.1 months (95% CI, 16.4–23.9 months). Among the 10 patients with thymic carcinoma, best response to treatment was 1 (10%) PR, 5 (50%) SD, and 4 (40%) progressive disease (PD). At a median follow-up of 13.5 months, the median PFS in patients with thymic carcinoma was 6.5 months (95% CI, 0.2–12.8 months) and the median OS was 12.7 months (95% CI, 2.9–22.5 months).
Conclusions: This small retrospective study demonstrates modest pemetrexed activity and disease stabilization in thymic malignancies with a clinically meaningful duration, and supports previous reports of pemetrexed efficacy in these rare diseases.

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1. Introduction

Thymoma (THY) and thymic carcinoma (TC) are rare neoplasms, with an incidence in the United States of 0.15 per 100,000 person-years [1]. Approximately 30% of patients with thymoma and 50–60% with thymic carcinoma are diagnosed with locally advanced or metastatic inoperable disease, including invasion into neighboring organs, pericardial or pleural dissemination, distant metastases or recurrent disease after primary therapy [2–4]. Systemic chemotherapy plays an important role in the treatment of thymic malignancies. Because of the rarity of thymic malignancies, there are limited prospective published trials with chemotherapy and a lack of randomized studies. However, retrospective studies and prospective clinical trials have demonstrated efficacy of some palliative chemotherapy regimens. The most common first-line therapy regimens include cisplatin, doxorubicin, and cyclophosphamide (CAP) for thymoma [5,6] and carboplatin/paclitaxel for thymic carcinoma patients and thymoma patients who are not fit for anthracycline-based regimens [7]. At the time of disease progression after first-line chemotherapy, many single agents may be effective. Pemetrexed, a multitargeted antifolate, was shown to have single agent activity in a prospective phase II trial [8] for

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Table 1
Individual patient, treatment, and outcome characteristics.

Pt No.	Sex	Age (yr)	PS	Path	Prior Chemo	Disease extension	Chemo	No. of cycles	Best response (RECIST 1.1)	PFS (mo)	OS (mo)
1	F	48	1	THY[a]	CAP	Lung, pericardium, diaphragm	Pem	6	SD	16.5	47.6
2	F	55	1	THY[b]	CAP, EP, AZD0530	Lung	Pem	7	SD	6.3	15.7[g]
3	M	39	2	THY[c]	Car/Tax, CAP, AZD0530	Mediastinum, pleural, lung	Pem	16	PR	14.4	20.1
4	M	64	1	THY[d]	CAP, Car/Tax	Pleural, lung	Pem/Car	3	SD	6.6	6.6
5	M	79	1	THY[c]	CAP, EP Capecitabine,	Lung, adrenal	Pem	6	SD	13.8	17.9
6	M	43	0	THY[b]	CAP	Mediastinum, pleura, lung	Pem	8	SD	14.0	16.7[g]
7	M	85	2	TC[b]	Car/Tax	Chest wall, pericardium, pleura	Pem	1	PD	2.5	3.4
8	F	42	2	TC[e]	CAP, EP, Car/Tax	Mediastinum, pleura, lung	Pem	10	SD	8.7	8.7
9	F	41	1	TC[b]	CAP	Mediastinum, Lung	Pem	6	SD	33.8	81.9
10	M	48	2	TC[b]	CAP, Car/Tax	Mediastinum, pleura, lung	Pem	4	SD	2.8	3.1
11	M	40	1	TC[f]	CAP, Car/Tax, FOLFIRINOX	Mediastinum, diaphragm, lung	Pem/Car	2	PD	1.1	7.2[g]
12	M	59	2	TC[b]	Car/Tax, amrubicin	Mediastinum, LN, liver, bone, brain	Pem	1	PD	0.8	4.7
13	F	64	1	TC[b]	CAP, CAV	Mediastinum, pleura, LN	Pem	6	SD	7.3	7.3[g]
14	M	58	1	TC[b]	Car/Tax	Mediastinum, pleura, LN	Pem	2	PD	1.3	20.5[g]
15	M	57	1	TC[f]	CAP, amrubicin	Pleura, chest wall	Pem	10	PR	6.5	12.7
16	M	68	1	TC[f]	CAP, Car/Tax	Lung, rib	Pem	16	SD	13.0	31.2[g]

Abbreviations: Pt, patient; PS, performance status; Path, pathology; Chemo, Chemotherapy; PFS, progression free survival; OS, overall survival; Mo, months; F, female; M, male; THY, thymoma; NOS, not otherwise specified; CAP, cyclophosphamide + doxorubicin + cisplatin; Pem, pemetrexed; EP, etoposide + platinum; Car, carboplatin; Tax, Paclitaxel; TC, thymic carcinoma; LN, lymph node.

[a] Histology subtype B1.
[b] Histology subtype NOS.
[c] Histology subtype B3.
[d] Histology subtype AB.
[e] Histology subtype large cell neuro-endocrine carcinoma.
[f] Histology subtype squamous cell carcinoma.
[g] Alive as of data cutoff.

previously treated thymoma and thymic carcinoma patients with a median time to progression of 45 weeks (THY 45.4 weeks vs. TC 5.1 weeks). In this trial, two complete responses (CR) and two partial responses (PR) were noted in 23 fully evaluable patients with all four responding patients having stage IVA thymoma. There is also a case report of a single thymoma patient response in a phase I trial in Japan [9]. Given the limited literature available, we designed this retrospective study to examine pemetrexed activity and safety in unresectable locally advanced or metastatic previously treated thymoma and thymic carcinoma patients at Stanford University Medical Center.

2. Patients and methods

2.1. Patient selection

Patients seen between January 2005 and November 2013 with unresectable histologically confirmed invasive, recurrent, or metastatic thymoma or thymic carcinoma were retrospectively identified using ICD-9 codes and pathology reports from the Stanford Cancer Institute Research Database (SCIRDB). This study protocol was approved by the Stanford Institutional Review Board. Patients treated with pemetrexed alone or in combination were included in this analysis if they had received at least one prior systemic chemotherapy regimen for inoperable disease excluding first-line pemetrexed therapy. All patients were deemed medically fit for pemetrexed therapy by the treating oncologist at the time therapy was initiated as part of routine clinical care. Clinical and pathological characteristics were collected from retrospective chart review. Data were collected according to the Standard Definitions and Policies of the International Thymic Malignancy Interest Group (ITMIG)[10].

2.2. Treatment methods

As per standard of care with the agent, patients received pemetrexed 500 mg/m^2 over 10 min as an intravenous infusion every 3 weeks along with adequate folate and B12 supplementation and supportive therapy such as dexamethasone and anti-emetics. Per our standard practice, tumor responses were assessed every two cycles. Adverse event (AE) information including laboratory data performed as part of routine care was collected retrospectively from the medical chart at each cycle and assessed according to the National Cancer Institute Common Terminology Criteria version 3.0.

2.3. Statistical analyses

All statistical analyses were performed using SPSS (Solutions Statistical Package for the Social Sciences software) version 19.0 (IBM SPSS, Chicago, IL). Progression free survival (PFS) was measured from the date of first pemetrexed infusion until either first documented progressive disease (PD) or death from any cause, whichever occurred earlier. Overall survival (OS) was measured from the date of first pemetrexed infusion to the date of death from any cause or was censored at the date of data cutoff (Apr 15, 2014). Survival functions were estimated by the Kaplan–Meier method. Two-sided significance level was defined as $P < 0.05$.

3. Results

3.1. Patient characteristics

We identified 81 patients with thymoma or thymic carcinoma seen at the Stanford Cancer Center between January 2005 and November 2013. Of these, 16 were previously treated recurrent or metastatic thymoma or thymic carcinoma patients who received pemetrexed after first-line, either as monotherapy or in combination with carboplatin. Characteristics of the patients are shown in Tables 1 and 2. The median age was 56 years (range, 39–85 years) and the majority were men (68.8%) and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1. There were three patients who had a history of other malignancies (testicular cancer, ovarian cancer, and renal cell carcinoma) before their diagnosis of thymic carcinoma, but in all cases the pathologist confirmed a primary thymic malignancy. There were 10

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