Pemetrexed in patients with thymic malignancies previously treated with chemotherapy

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\textbf{A B S T R A C T}

\textbf{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.

\textbf{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.

\textbf{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).

\textbf{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.

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

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.

* Histology subtype B1.
* Histology subtype NOS.
* Histology subtype B3.
* Histology subtype AB.
* Histology subtype large cell neuro-endocrine carcinoma.
* Histology subtype squamous cell carcinoma.
* 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/m² 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
Table 2
Patients characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole group (n = 16)</th>
<th>Thymoma (n = 6)</th>
<th>Thymic Ca (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>51.5</td>
<td>57.5</td>
</tr>
<tr>
<td>Range</td>
<td>39–85</td>
<td>39–79</td>
<td>40–85</td>
</tr>
<tr>
<td>Number of prior chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (31.3%)</td>
<td>2 (33.3%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>2</td>
<td>5 (31.3%)</td>
<td>1 (16.7%)</td>
<td>4 (40.0%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (37.4%)</td>
<td>3 (50.0%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>Cycles of Pemetrexed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Range</td>
<td>1–16</td>
<td>3–16</td>
<td>1–16</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>2 (12.5%)</td>
<td>1 (16.7%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>SD</td>
<td>10 (62.5%)</td>
<td>5 (83.3%)</td>
<td>5 (60%)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (25%)</td>
<td>0</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Median OS (95%CI) (months)</td>
<td></td>
<td>20.1 (16.4–23.9)</td>
<td>12.7 (2.9–22.5)</td>
</tr>
<tr>
<td>Median PFS (95%CI) (months)</td>
<td></td>
<td>13.8 (4.9–22.6)</td>
<td>6.5 (0.2–12.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; PFS, progression free survival; CI, confidence interval; Ca, carcinoma.

(62.5%) patients with thymic carcinoma and 6 (37.5%) patients with thymoma. Among the 10 thymic carcinoma patients, the histological subtypes included squamous cell carcinoma (3 patients; 30%), large-cell neuroendocrine carcinoma (1 patient; 10%), and not otherwise specified (6 patients; 60%). Among the 6 thymoma patients, there was one each of type AB, B1, B2, and B3, and 2 patients with thymoma not otherwise specified because of limited material. Lungs (68.8%) and pleura (62.5%) were the most common sites of metastasis.

There were 5 (31.3%) patients who had received one prior chemotherapy regimen while the remaining received 2–3 prior chemotherapy regimens. The prior chemotherapy regimens included CAP; cyclophosphamide, doxorubicin, and vincristine (CAV); carboplatin and paclitaxel; amrubin (clinical trial); capecitabine; and etoposide + platinum (EP).

There were 2 patients (one thymoma and one thymic carcinoma) who received pemetrexed combined with carboplatin (AUC=6) and the remaining 14 patients received pemetrexed monotherapy. As of the last follow-up date, 16 patients had received a total of 104 cycles and the median number of cycles was 6 (range, 1–16). Subsequent post-progression treatments included gemcitabine, paclitaxel, carboplatin combined with etoposide, carboplatin combined with paclitaxel, amrubin (on a clinical trial), capecitabine, octreotide, or palliative radiotherapy.

3.2. Efficacy

Best response to treatment was evaluated for all patients. Among 6 patients with thymoma, there were no complete responses (CR), 1 (16.7%) partial response (PR), and 5 patients with stable disease (SD) after at least 2 cycles. Thymoma patients in our series had an overall response rate (ORR) of 16.7% and a disease control rate (DCR) of 100%. At a median follow-up of 21.2 months, the median PFS in patients with thymoma (Table 1 and Fig. 1) 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, there were no CRs, 1 (10%) PR, 5 (50%) SD and 4 (40%) PD. The ORR was 10% and the DCR was 60%. At a median follow-up time of 13.5 months, the median PFS (Table 1 and Fig. 1) 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). The OS between thymoma and thymic carcinoma patients was not significantly different (P=0.935).

Fig. 1. Progression free survival of the thymic malignancies patients who received pemetrexed chemotherapy.
The survival analyses above include the two patients (one thymoma and one thymic carcinoma) who received pemetrexed in combination with carboplatin. The thymic carcinoma patient had PD after two cycles and the thymoma patient had stable disease with a PFS of 6.6 months.

3.3. Safety

All 16 patients were evaluated for toxicity with detailed chart review of laboratory values and clinic notes. The most common side effects were fatigue, nausea, and constipation. There were no grade ≥3 hematologic AEs or chemotherapy-related deaths during pemetrexed treatment. To our knowledge only one patient was hospitalized during pemetrexed therapy; for a pneumonia that was not felt to be treatment related.

4. Discussion

In the first-line setting, cisplatin and doxorubicin combination regimens are preferred for thymoma and carboplatin/paclitaxel is a preferred regimen for thymic carcinoma [11,12]. Fornasier et al. [12] reported on 37 patients with stage III and IV thymoma who were treated with cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) combination chemotherapy with a response rate of 91.8% and a median survival time of 15 months. Loehrer et al. [5] conducted a trial in 29 thymoma patients and one thymic carcinoma patient with metastatic or locally progressive recurrent disease who were treated with CAP and had a response rate of 50% and a median survival time of 37.7 months. However, anthracyclines have cumulative dose-related cardiac toxicity, and patients frequently cannot receive them again after the first-line setting. The National Comprehensive Cancer Network (NCCN) guidelines [11] now list carboplatin/paclitaxel [7], cisplatin/etoposide (PE) [13], and etoposide/ifosfamide/cisplatin (VIP) [14] as alternative anthracycline-free regimens. After PD from first-line chemotherapy, single agents with modest efficacy include etoposide [13], ifosfamide [15], pemetrexed [8], octreotide ± prednisone [16,17], 5-FU and leucovorin [11], gemcitabine [11], or paclitaxel [11].

Pemetrexed is a multi-targeted antifolate cytotoxic agent against three major enzymes: thymidylate synthase (TS), dihydropyrimidine reductase (DHFR), and glycaminide ribonucleotide formyltransferase (GARFT). It is FDA approved for the treatment in non-small cell lung adenocarcinoma [18,19] and mesothelioma [20], with a favorable toxicity profile [18]. Loehrer et al. [8] reported a prospective phase II trial of pemetrexed in previously treated thymoma and thymic carcinoma patients. Sixteen thymoma and 11 thymic carcinoma patients were treated and among 23 evaluable patients, there were two CRs and two PRs in thymoma patients but none in thymic carcinoma patients. The median time to progression for all patients was 10.4 months (thymoma = 10.5 months vs. thymic carcinoma = 1.2 months), the OS date was not reported and the drug was well tolerated. Nakagawa et al. [9] performed a phase I study of pemetrexed in Japanese patients with solid tumors, and reported a partial response in the single thymoma patient included in the study. Beyond these trials, there are no other studies to our knowledge reporting the clinical activity of pemetrexed in the treatment of thymic malignancy. We conducted this retrospective study to analyze the efficacy and safety of pemetrexed chemotherapy in thymic malignancy patients seen at Stanford University.

In our retrospective analysis, we identified two responders, one with thymoma and one with thymic carcinoma. The PFS of patients with thymoma in our study was 13.8 months, which was similar to the prospective pemetrexed study [8] of 45.4 weeks (10.5 months). The PFS of thymic carcinoma patients in our study was 6.5 months, which is much longer than that reported in the prospective pemetrexed study [8] of 5.1 weeks (1.2 months). We also report OS data with pemetrexed therapy in this retrospective analysis (thymoma = 20.1 months vs. thymic carcinoma = 12.7 months, P = 0.935). Thymidylate synthase (TS) expression may be a predictive biomarker of pemetrexed sensitivity [21–23], with lower levels correlated to enhanced sensitivity. Recent data on TS levels in thymic carcinoma patients are intriguing. Yokota et al. [24] assessed TS protein expression levels in 24 thymic carcinoma patients and reported that TS protein expression of thymic carcinoma is similar to lung adenocarcinoma levels and significantly lower than that in lung squamous cell carcinoma (P = 0.0407). Recently, there have been several reports [25–27] of activity of the oral dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine agent S-1 in thymic carcinoma, with activity related to the intra-tumor expression of DPD and TS as salvage chemotherapy for advanced thymic carcinoma.

This is a retrospective analysis of a small cohort from a single institution of a rare disease with significant heterogeneity. This analysis included patients with either thymoma or thymic carcinoma and though the majority of patients (N = 14) were treated with pemetrexed as a single agent, two patients did receive combination therapy with carboplatin. However, the prolonged progression free survival with pemetrexed in thymoma and particularly thymic carcinoma patients confirms previous reports of its clinical activity and adds evidence to support its use in these rare diseases.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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