original article

Annals of Oncology 21: 1168–1172, 2010
doi:10.1093/annonc/mdp483
Published online 30 October 2009

Preliminary results of phase II study of capecitabine and gemcitabine (CAP-GEM) in patients with metastatic pretreated thymic epithelial tumors (TETs)

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Received 15 May 2009; revised 1 September 2009; accepted 4 September 2009

Background: No previous prospective trials have been reported with capecitabine and gemcitabine (CAP-GEM) in patients with metastatic thymic epithelial tumors (TETs). We conducted a multicenter study to determine the activity and tolerability of this regimen in pretreated TETs.

Patients and methods: A total of 15 patients were enrolled in the first stage of phase II study. All patients received CAP-GEM every 3 weeks. The primary end point was objective response rate (RR); secondary end points were toxicity, progression-free survival (PFS) and overall survival.

Results: Complete responses (CR) and partial responses were observed in three (20%) and three (20%) patients for a 40% RR, respectively. Grade 1–2 neutropenia, anemia and thrombocytopenia were the most common side-effects, noted in seven (46.7%), five (33.3%) and five (33.3%) patients, respectively. The most common grade 3 toxicity was neutropenia in three patients (20%). Median PFS was 11 months (95% confidence interval 4–17). The 1- and 2-year survival rates were 80% and 67%, respectively.

Conclusion: We have decided to publish the preliminary results because this regimen was more active than that expected. Although our results are preliminary, CAP-GEM shows activity and safety in pretreated TETs. Furthermore, multicenter trials, also in first-line setting, are necessary to confirm our results.

Key words: capecitabine, gemcitabine, pretreated patients, thymic epithelial tumor

introduction

Thymic epithelial tumors (thymoma and thymic carcinoma, TETs) are the most common tumors of anterior mediastinum in adults. Surgical resection of early-stage TET is a standard approach and >90% of patients with localized TETs are cured with complete surgical resection [1]. For patients with locally advanced disease, combination chemotherapy with additional local therapy (radiation therapy or surgery) is the treatment of choice. Systemic chemotherapy including cisplatin, doxorubicin and cyclophosphamide (PAC) is associated with a 50%–90% objective response rate (RR) [2, 3] but ∼50% of patients with locally advanced or metastatic TETs will be candidates for second-line therapy [1]. Several studies have documented 10%–30% of objective RRs with various drugs, such as ifosfamide, octreotide, fluorouracil and biological agents in recurrent TETs [1, 4, 5].

Various studies, especially in gastrointestinal tumors, showed that capecitabine and gemcitabine (CAP-GEM) combination was active and well tolerated [6–10].

To our knowledge, the effect of combining these agents in pretreated metastatic TETs is not known. We have evaluated the activity and safety of CAP-GEM for pretreated TET patients in a muticenter phase II clinical trial.

patients and methods

patient selection

All patients were adults with histologically confirmed TET that was metastatic and measurable according to RECIST [11].

All TETs were independently reviewed by a pathologist (MM).

Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of two or less; previous chemotherapeutic regimens, including platinum agent as first line; disease progression after previous treatment; hemoglobin >9 g/dl; absolute neutrophil count >1.5 ×

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10^9/l; platelets >100 × 10^9/l; and normal renal, cardiac and liver functions. All patients gave informed consent for their treatment. The study complied with the provisions of the Declaration of Helsinki, Good Clinical Practice Guidelines and local laws.

study design

The study was an open-label, nonrandomized, Italian multicenter, phase II study approved by the institutional review boards at six participating centers. The primary end point was RR; secondary end points were safety, progression-free survival (PFS) and overall survival (OS).

Treatment consisted of oral capecitabine (650 mg/mq twice daily on days 1–14) and i.v. gemcitabine (1000 mg/mq on days 1 and 8) every 3 weeks (first cycle). In case of an objective partial response (PR) or stable disease (SD) (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions), the patients could receive additional cycles until disease progression. Patients were seen on weeks 1 and 2 of each 3-week cycle; they had blood tests to check renal and hepatic functions and blood counts every week.

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (version 3.0) [12]. Grade 2 non-hematologic toxic effects were managed by holding the drug until resolution to ≤grade 1 and then resuming without a dose reduction. If the patient experienced a second grade 2 non-hematologic toxicity, the drugs was reduced by 25%. Grade 3 or 4 hematologic and non-hematologic toxic effects were managed through dose interruption, followed by 50% dose reduction. Treatment was discontinued if a grade 3 or 4 toxicity did not resolve within 3 weeks or if a second dose reduction was required.

assessment of tumor response

Tumor measurements were obtained by computed tomography scan, including the brain, before the treatment and for every three cycles. Response and progression were assessed by the treating physicians, who carried out their evaluations on the basis of RECIST [11].

statistical design

For statistical considerations and study design, the primary end point was objective response. The RR was expected to be ∼25%; a total of 35 assessable patients were needed for a two-stage design with a type I error (alpha) of 0.05 and a type II error (beta) of 0.2. In the first stage, 15 patients were to be enrolled. If three or more responses were observed, the design called for an additional 20 eligible patients to be accrued.

We have decided to publish these interesting preliminary results of the first stage, and also if we have observed slow enrollment due to the rarity of those patients, we have planned to continue the trial to the second stage.

RR [complete response (CR) + PR] is reported with its exact 95% confidence interval (CI). Toxic effects are tabulated by type and grade. PFS was defined as the length of time during and after treatment in which a patient is living with a disease that does not get worse. OS was defined as the survival from registration until death. The 1- and 2-year survival rates were calculated from the date of registration to the 12th and 24th months.

Descriptive statistics were used to characterize patients at study entry. The Kaplan–Meier method was used to describe PFS and OS [13].

results

patient characteristics

Between November 2005 and August 2008, 15 patients (10 men, five women; median age 63 years, range 43–77 years) with TET were entered into this phase II trial (Table 1). Fourteen patients (93.3%) had an ECOG PS score of zero to one, while

Table 1. Patients characteristics

No. of patients (%)	15
Gender	
Male	10 (66.7)
Female	5 (33.3)
Median age (range), years	63 (43–77)
Histology	
Thymoma	12 (80)
B2	6 (40)
B2-B3	3 (20)
B3	3 (20)
Thymic carcinoma	3 (20)
Stage IVB	15 (100)
ECOG performance status	
0	8 (53.3)
1	6 (40)
2	1 (6.7)
Prior therapy	
Thymectomy	7 (46.7)
Mediastinic radiotherapy	8 (53.3)
Neo-adjuvant chemotherapy	2 (13.3)
Chemotherapy for metastatic disease	15 (100)
Two prior chemotherapeutic regimens	15 (100)
Two prior regimens	8 (53.3)
Previous chemotherapy	
Cisplatin	15 (100)
Anthracyclines	15 (100)
Cyclophosphamide	15 (100)
Somatostatin analogue	14 (93.3)
Prednisone	14 (93.3)
Etoposide	13 (86.7)
Carboplatin	6 (40)
Imatinib	5 (33.3)
Cetuximab	4 (26.7)
Oxaliplatin	3 (20)
Paclitaxel	2 (13.3)
Ifosfamide	2 (13.3)
Zoledronic acid	2 (13.3)
Vinblastine	1(6.7)
Vincristine	1 (6.7)
5-Fluorouracil	1 (6.7)
Interval from the end of the previous chemotherapy to disease relapse	
≤2 months	12 (80)
>2 months	3 (20)
Current site of metastases	
Pleura	15 (100)
Lung	12 (80)
Lymph nodes	12 (80)
Soft tissues	4 (26.7)
Liver	5 (33.3)
Bone	4 (26.7)
Myocardiac tissue	2 (13.3)
Brain	1 (6.7)
Paraneoplastic syndrome	
B lymphopenia	13 (86.7)
Hypogammaglobulinemia	11 (73.3)
Myastenia gravis	7 (46.7)
Autoimmune diabetes	2 (13.3)
Psoriasis	1 (6.7)
Pure red cell aplasia	1 (6.7)

Histology: World Health Organization grading; stage: Masaoka staging system.

ECOG, Eastern Cooperative Oncology Group.

one patient (6.7%) had an ECOG PS score of two. The majority of patients had thymoma (12 patients), histologically classified according World Health Organization grading, while three patients had thymic carcinoma. All patients were stage IVB according Masaoka staging system [14], while the most common site of metastases was the pleura (100%).

All patients had received at least two prior chemotherapeutic regimens, including cisplatin regimen, while eight patients (53.3%) had received three previous treatments. Median time between interruption of previous regimen and start of CAP-GEM was 5 weeks (range 3–12 weeks).

Most common paraneoplastic syndromes were lymphopenia, hypogammaglobulinemia and myasthenia gravis presented in 13, 11 and seven patients, respectively (Table 1).

therapy administration

At total of 105 cycles were administered. The mean number of cycles per patient was 7 (median 6, range 3–9). The schedule resulted in a mean received dose intensity of 617.5 mg/mq twice, on days 1–14, for capecitabine; and 950 mg/mq, on days 1 and 8, for gemcitabine; or 95% of the planned dose intensity.

A dose reduction of 25% was adopted in six cycles (5.7%) due to grade 2 non-hematologic and hematologic toxicity. A dose reduction of 50% was adopted in six cycles (5.7%) due to grade 3 hematologic and non-hematologic toxic effects. Treatment was delayed in six cycles (5.7%). Reasons for delay were patient's request (four cycles) and investigator's decision (two cycles).

response and survival

All patients were included in analyses. Table 2 shows responses and survival rates in 15 patients. After six cycles, three patients each showed CR and PR (95% CI 10–35) for an overall RR of 40%. Six patients had SD for at least six cycles (40%). Figure 1 shows a CR in liver metastasis after six cycles.

Among three thymic carcinoma patients, we have observed one PR, one SD and one PD.

All six responder patients showed no change in paraneoplastic syndromes (stable B lymphopenia and hypogammaglobulinemia without increase of recurrent infections during chemotherapy and stable symptoms by myasthenia gravis).

Median follow-up was 22 months (range 8–28 months). Median PFS was 11 months (95% CI 3–17 months) (Figure 2).

Table 2. Responses and survival rates according to the follow-up

Response (after six cycles)	No. of patients (%)
Complete response	3 (20) (95% CI 10–35)
Partial response	3 (20)
Stable disease	6 (40)
Progression	3 (20)
Median number of cycles	6 (3–9)
Progression-free survival	11 months (4–17)
1-year survival rate	12/15 (80%)
2-year survival rate	10/15 (67%)

Response criteria as reported in the 'Materials and methods' section.

The PFS for patients with thymoma and thymic carcinoma was 11 months (95% CI 6–17 months) and 6 months (95% CI 3–11 months), respectively. The median survival time has not been reached for the patients to date. On the basis of Kaplan–Meier estimates, 1- and 2-year survival rates were 80% and 67%, respectively (Figure 3).

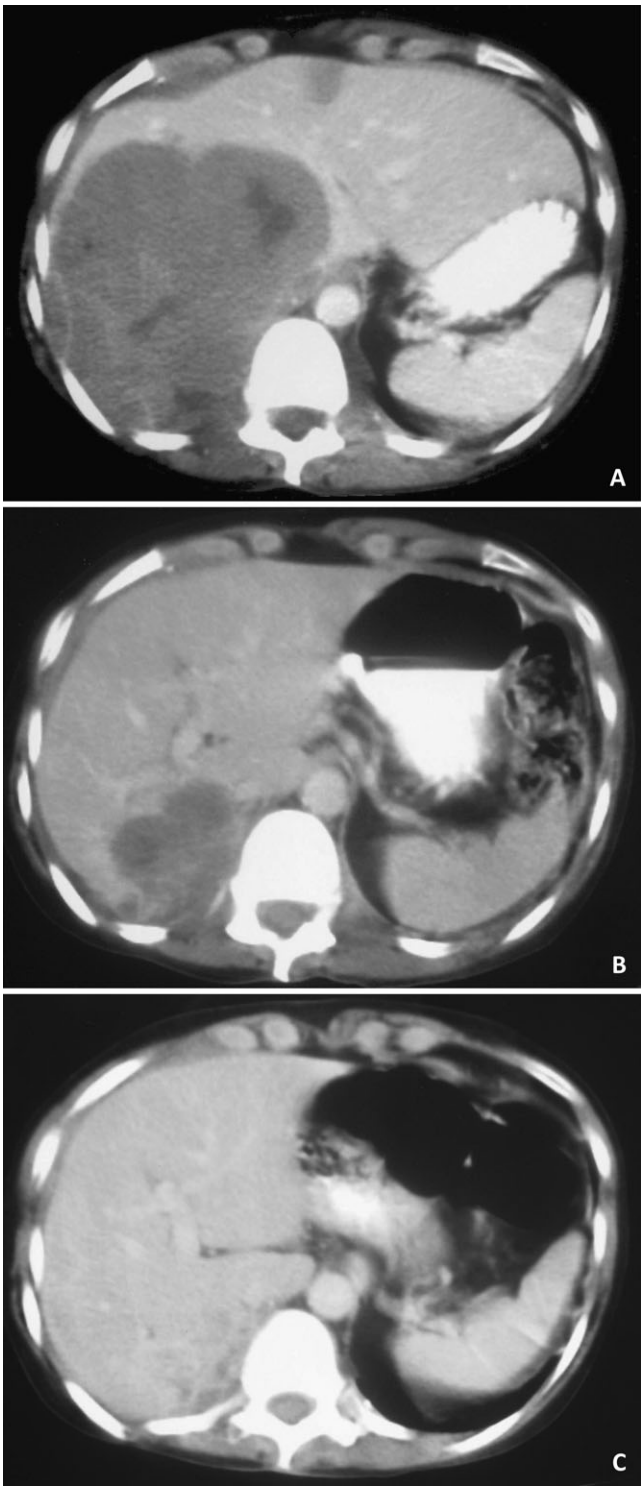

Figure 1. Liver metastasis (A) before the treatment; (B) after three cycles, partial response; (C) complete response after six cycles.

After disease progression with this regimen, 11 patients received only supportive care, while two patients each were treated with paclitaxel and docetaxel, respectively.

toxicity

In general, treatment was well tolerated. No toxic deaths occurred. Grade 1–2 nausea/vomiting, diarrhea, alopecia and hand-foot syndrome were the most common non-hematologic toxic effects, noted in four (26.7%), four (26.7%), three (20%), and three (20%) patients, respectively. The most important grade 3 hematologic toxicity was neutropenia in three patients (20%) and anemia in two patients (13%); grade 3 diarrhea was observed in one patient (6.7%). We did not observe grade 4 toxic effects (Table 3).

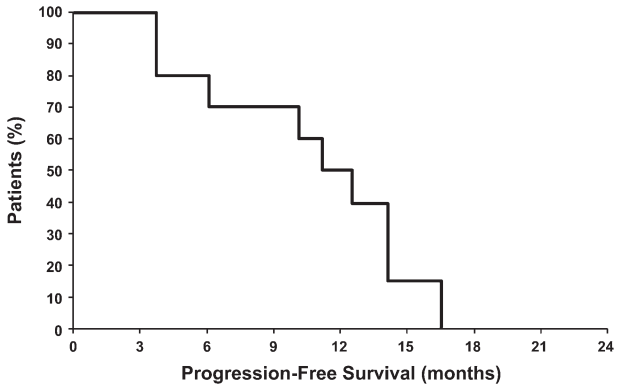

Figure 2. Kaplan–Meier curve for progression-free survival.

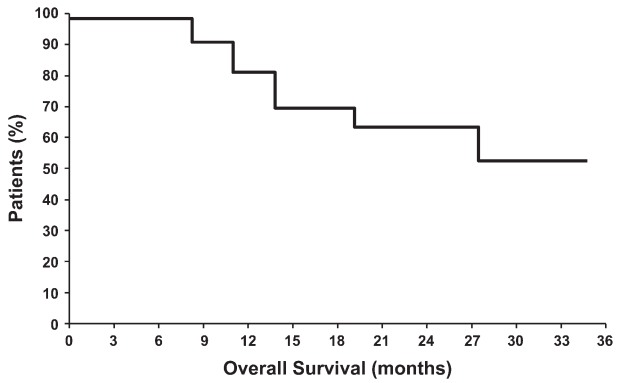

Figure 3. Kaplan–Meier curve for overall survival.

Table 3. Toxicity data experienced per patient ($n = 15$)

Toxicity	Grade 1–2	Grade 3	Grade 4
Neutropenia	7 (46.7%)	3 (20%)	–
Anemia	5 (33.3%)	2 (13.3%)	–
Thrombocytopenia	5 (33.3%)	2 (13.3%)	–
Nausea/vomiting	4 (26.7%)	1 (6.7%)	–
Diarrhea	4 (26.7%)	1 (6.7%)	–
Alopecia	3 (20%)	–	
Hand-foot syndrome	3 (20%)	1 (6.7%)	–

discussion

Multiagent chemotherapy inclusive of cisplatin plays an important role in the treatment of advanced TETs [1]. A study conducted by the Southwest Oncology Group was designed to evaluate PAC in patients with advanced-stage disease. This combination yielded an overall RR of 50% and median survival was 38 months [2]. The combination of doxorubicin, cisplatin, vincristine and cyclophosphamide (ADOC) reported an overall RR of 92% and median survival of 15 months [3].

Based on those results a chemotherapy regimen such as PAC or ADOC represents the standard first-line treatment in TETs.

Despite the high RR after first-line treatment, about 50%–70% will be candidates for second-line therapy [1, 4].

To our knowledge, this study represents the first prospective investigation of CAP-GEM in TETs, both in first-line and in pretreated patients.

The preliminary findings show that CAP-GEM combination chemotherapy is active and well tolerated in pretreated TETs. The overall response rate (ORR) was 40% and an additional 40% of patients had SD.

It compares favorably with results previously reported for other combinations in pretreated patients, although it is impossible to directly compare the results.

It is also important to note that not many trials have been published in pretreated TETs with chemotherapy and the most active regimens, used in this setting, were octreotide and pemetrexed [15–17].

Our group has previously conducted a study in 16 patients with advanced pretreated TETs with octreotide associated with prednisone. The overall RR was 37%. One patient had CR and five had PR [15].

The octreotide activity was confirmed by an ECOG phase II that was conducted in patients with octreotide scan-positive TETs [16]. Out of 38 assessable patients, 32 had thymoma and 6 patients had thymic carcinoma or carcinoid; 82% had been exposed to prior chemotherapy. In the assessable patients, two CRs and 10 PRs were noted, yielding CR and PR rates of 5.3% and 25%, respectively. However, none of six patients with thymic carcinoma had objective response to therapy. Among those patients who received a combination of octreotide and prednisone, the ORR was noted higher at 31.6% but with increased toxicity [16].

Compared with the Loehrer et al. study [16], CAP-GEM combination appears more active (RR = 40%), also considering that our patients had received at least two prior regimens and were more pretreated than those in the previous study.

Results of the phase II study evaluating the role of pemetrexed in patients with recurrent TETs were reported in 2006 [17].

In 23 assessable patients, two CRs and two PRs were noted.

Median number of prior therapies was two. The median time to progression for patients with recurrent thymoma was 45.4 weeks and in patients with thymic carcinoma it was 5.1 weeks. If compared with those results, CAP-GEM combination shows higher response [17].

Considering that no standard treatment exists in second line for TETs and as there limited options in this setting, the physicians have tried to use the biological agents in pretreated

TETs. Preliminary results with those regimens, however, show poor activity and responses only in rare cases [18, 19].

Giaccone et al. reported two SD in seven patients receiving imatinib [18]. Bedano et al. treated 18 patients with erlotinib and bevacizumab, reporting 11 SD among those patients [19].

Our group has previously published a case report with two patients who were treated with cetuximab. Both the patients reported a PR, suggesting that cetuximab may be a useful therapeutic choice in advanced TETs [20].

In this scenario, CAP-GEM appears an attractive option in pretreated TETs.

Toxicity from treatment in our study was consistent with previous trials [8–10]. Grade 4 toxicity was not found and grade 2–3 toxicity was well controlled.

The study has several limitations. First, it is important to note that the responses in this study were investigator assessed and because independent review of scans can result in lowering of the RR relative to the investigator-assessed response, such an effect should be taken into consideration when interpreting the results.

Another limitation is that this was a nonrandomized study with limitations in determining the benefit of other agents such as cetuximab, bevacizumab or octreotide in second line.

It should be noted that our patients in some cases had received three previous regimens and could be useful to test this CAP-GEM in first line or second line.

Prospective randomized trials will be required to provide insight into the most effective option after disease progression with a cisplatin regimen.

Although our results are preliminary and limited by little number of enrolled patients, CAP-GEM combination appears active and well tolerated. Further clinical trials, also in first-line setting, are needed to confirm our important findings.

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