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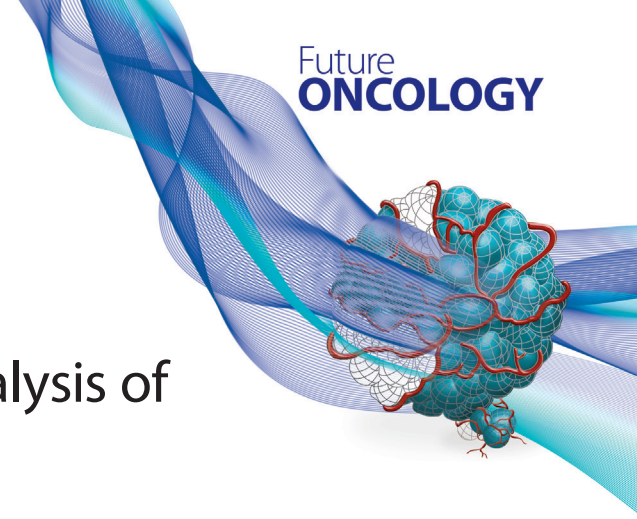

Capecitabine plus gemcitabine in thymic epithelial tumors: final analysis of a Phase II trial

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ABSTRACT **Background:** A multi-institutional Phase II trial was initiated in 2005 to test the combination gemcitabine and capecitabine in patients with thymic epithelial malignancies (TETs). **Patients & methods:** Patients with histologic confirmation of TET diagnosis by central review who had received >1 systemic chemotherapy treatment were included. Patients received oral capecitabine (650 mg/mq twice daily on days 1–14) and intravenous gemcitabine (1000 mg/mq on days 1 and 8 every 3 weeks). **Results:** Of the 30 patients included (18 men, 12 women; median age: 57 years, range: 48–61 years), the majority (73%) had thymoma, and the remaining thymic carcinoma. Eight patients developed grade 3–4 neutropenia. A total of 12 patients had a response. Median progression-free survival was 11 months (range: 6.5–16.5). **Conclusion:** Capecitabine and gemcitabine is highly active in TETs.

KEYWORDS
• capecitabine • gemcitabine • thymic epithelial tumors • thymomas

The estimated incidence of thymic epithelial tumors (TETs) is approximately three cases per 100,000 inhabitants [1]. Six distinct histologic types of thymic tumors (A, AB, B1, B2, and B3 and thymic carcinomas) showing increased clinical aggressiveness are included in the WHO classification [2]. Staging of thymic tumors is performed according to the Masaoka staging system, although an international effort to provide a better staging classification is ongoing [3].

Thymic epithelial malignancies pose a great challenge for the medical community because of their anatomic site of origin and contiguity with vital organs, as well as because of their association with a number of autoimmune diseases, and peculiar biological behavior [4]. Even in the context of advanced disease not amenable to radical surgery or radiotherapy, treatment with chemotherapy has been associated to a prolonged disease stabilization [4], although the magnitude of the effect of chemotherapy on survival is difficult to be ascertained given the lack of randomized controlled clinical trials in patients with TETs [5]. While uniform consensus supports the use of cisplatin-based first-line chemotherapy, no standard treatment is available for recurrent disease [4]. Re-challenge with the same chemotherapy agents is feasible in selected patients, according to prior response and time to progression, as well as cumulative toxicity [4]. The use of octreotide and prednisone is also a valuable option [4], especially in patients not eligible for cytotoxic chemotherapy.

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In 2005, a multi-institutional Phase II trial was started on the combination of gemcitabine and capecitabine in pretreated patients with TETs. After a high response rate was observed in the first 15 patients enrolled [6], accrual was continued until 2013. Final results of this Phase II study are presented.

Patients & methods

• Patients

Main inclusion criteria for participation in the study were adult age, histologic confirmation of TET diagnosis; more than one prior systemic chemotherapy treatment, including at least one platinum-based regimen; ≥1 measurable lesion on CT scan performed within 1 month since study inclusion; disease progression according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria [7]. Central histological review was performed at the Department of Pathology, Regina Elena National Cancer Institute (Rome, Italy) by Marino and 2004 WHO classification of thymus tumors was used [2]. Uncontrolled concomitant medical illnesses or prior systemic anticancer treatment received within 4 weeks of enrollment; pregnancy and lactation were exclusion criteria. As previously published, the study was conducted at six centers and was approved by the institutional review board of the participating institutions. It was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients before study entry.

• Assessment of activity & safety

All eligible patients had a complete medical history, a physical examination, a complete blood count and other laboratory tests (serum creatinine, calcium, aspartate aminotransferase, alanine aminotransferase and total bilirubin) performed within 1 week before study entry. Treatment consisted of oral capecitabine (650 mg/mq twice daily on days 1–14) and intravenous gemcitabine (1000 mg/mq on days 1 and 8) every 3 weeks (first cycle). Patients were seen on weeks 1 and 2 of each 3-week cycle. A complete blood count analysis and hepatic and kidney laboratory tests were performed every week. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (version 3.0) [8]. Grade 2 nonhematologic 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 (third) grade 2 nonhematologic toxicity, the drugs were reduced by 25% (50%). Grade 3 or 4 hematologic and nonhematologic toxic effects were managed through treatment suspension, followed by 50% dose reduction. Treatment was permanently discontinued if a grade 3 or 4 toxicity did not resolve within 3 weeks or if recurrent grade 2–4 toxicity required a greater than 50% dose reduction. A whole-body CT scan was performed a maximum of 30 days before enrollment in the trial and was repeated every three cycles. Measurable target lesions were evaluated using the RECIST criteria 1.0 for CT scans [7].

• Study design & statistical analysis

Characteristics of the population were presented using descriptive statistics and frequency counts. Median numbers were reported with interquartile ranges. The primary end point was radiographic response rate. Progression-free survival (PFS), toxicity and overall survival were secondary end points. PFS was computed from the time of inclusion to the time of progressive disease or death from any cause, whichever the first. Progressive disease was ascertained on CT scan by RECIST criteria applied by a qualified independent radiologist at each participating Institution. Patients who permanently discontinued study therapy for reasons other than death or progression were censored in the analysis.

The expected response rate was 25%. Calculation of the sample size was based on a minimax two-stage design to test the null hypothesis that the true response rate was <15% against the alternative hypothesis that the true response rate was more than 35%, with type I and II errors equal to 5 and 20%, respectively. A total of 15 patients had to be recruited for the first stage. If at least three patients showed response, accrual was continued for a total of 35 patients. If at least eight patients were considered to be responsive to treatment, the combination was considered to be active.

Results

• Patients' characteristics

A total of 30 patients (18 men, 12 women; median age: 57 years, range: 48–61 years) were enrolled in this Phase II trial from November 2005 to June 2013. The majority of patients (73%) had thymoma and presented stage IVB disease. All patients presented pleural metastases. Of note, 63% of patients showed disease

progression within 2 months from the last dose of the last systemic therapy received. All patients' characteristics are detailed in **Table 1**.

• Treatment & tolerance

Patients received at total of 301 cycles. Each patient received a median number of eight cycles (range: 5–17 cycles). There was no toxicity-related death. Neutropenia was the most important grade 3 (eight patients) and grade 4 (two patients); two patients showed grade 3 diarrhea. Patients required a 25% dose reduction in 39 cycles and a 50% dose reduction of 50% in 25 cycles, while treatment was delayed in 31 cycles. Most meaningful toxic effects are reported in **Table 2**.

• Efficacy

A total of 12 patients had a response (three complete responses and eight partial responses) **(Table 3)**. Among eight thymic carcinoma patients, we observed three partial responses. Responsive patients showed no significant change of the associated paraneoplastic syndromes (mainly B lymphopenia, hypogammoglobulinemia and myasthenia gravis). In patients with response versus stable disease versus progressive disease as best response, median duration of study treatment was 3, 12 and 4 months, respectively, while median duration of the last systemic treatment received prior to study treatment was 3, 5 and 4 months, respectively. After a median follow-up time of 18 months (range: 15–22 months), 13 patients have died. Median PFS was 11 months (range: 6.5–16.5 months) **(Figure 1)**. The PFS for patients with thymoma and thymic carcinoma was 11 months (range: 8.5–16.5 months) and 6 months (range: 3–10 months), respectively. The 1-year and 2-year survival rate was 90 and 66%, respectively **(Figure 2)**.

Discussion

The combined use of gemcitabine and capecitabine, which is enzymatically converted *in vivo* into 5-fluorouracil (5-FU), has a solid biochemical foundation. Once gemcitabine has been converted into its diphosphate intermediate, intracellular pools of deoxyuridine monophosphate are depleted and binding of 5-fluorodeoxyuridine monophosphate, the active metabolite of 5-FU, to thymidylate synthase is enhanced [8]. Synergism of 5-FU and gemcitabine has been shown in preclinical models [8]. In one meta-analysis involving 935 patients with pancreatic

Table 1. Patients' characteristics at baseline.

Characteristics	Absolute number
Patients (n)	30
Gender:	
– Male	18
– Fermale	12
Median age (range), years	54 (48–61)
Histology:	
– Thymoma:	22
• B1	3
• B1/B2	1
• B2	9
• B2–B3	3
• B3	6
– Thymic carcinoma:	8
• Stage IVA	8
• Stage IVB	22
ECOG performance status:	
– 0	16
– 1	11
– 2	3
Prior therapy:	
– Thymectomy	13
– Mediastinic radiotherapy	13
– Neo-adjuvant chemotherapy	6
– Chemotherapy for metastatic disease	30
– Median number of previous lines of systemic therapy (range)	3 (2–3)
Previous first-line chemotherapy:	
– Cisplatin–adriamicin–prednisone–cyclophosphamide	20
– Carboplatin–adriamicin–prednisone–cyclophosphamide	3
– Carboplatin–etoposide	5
– Cisplatin–adriamicin–cyclophosphamide	2
Previous second-line therapy:	
– Carboplatin–etoposide	11
– Cetuximab	1
– Imatinib	8
– Octreotide + prednisone	10
Interval from the end of the previous chemotherapy to disease relapse:	19
– ≤2 months	11
– >2 months	
Current site of metastases:	
– Pleura	30
– Lung	20
– Lymph nodes	18
– Soft tissues	6
– Liver	6
– Bone	5
– Myocardiac tissue	3
– Brain	1
Paraneoplastic syndrome:	
– Blymphopenia	19
– Hypogammaglobulinemia	20
– Myastenia gravis	14
– Autoimmune diabetes	2
– Psoriasis	1
– Pure red cellaplasia	1

Table 2. Toxicity data experienced per patient (n = 30).

Toxicity	Grade 1–2 (n)	Grade 3 (n)	Grade 4 (n)
Neutropenia	23	8	2
Anemia	13	5	–
Thrombocytopenia	13	5	–
Nausea/vomiting	7	2	–
Diarrhea	9	2	–
Alopecia	4	–	–
Hand–foot syndrome	9	4	–

cancer, combination of capecitabine and gemcitabine appeared to be associated to a significant survival benefit with respect to gemcitabine alone. A favorable toxicity profile was shown in Phase III trials in pancreatic cancer, with the main severe toxicity being bone marrow suppression and only <10% of patients showing grade 3–4 hand–foot syndrome [9]. A similar toxicity profile was also recorded in patients with biliary cancers [10]. Given the need of effective therapeutic options as salvage treatment for pretreated TET patients, we hypothesized that the demonstrated synergism of capecitabine and gemcitabine could yield clinical benefit in such chemo-sensitive neoplasms. Furthermore, their indolent clinical course may benefit from a prolonged treatment duration, which appeared to be feasible with such schedule, given the lack of a known cumulative toxicity of both agents and the metronomic administration of capecitabine [11].

In this Phase II study, we obtained a high response rate coupled with a prolonged disease stabilization and an excellent toxicity profile despite long-term administration. In our study, there were no cases of febrile neutropenia, although 66% of patients had some degree of hypogammaglobulinemia, which is far higher than that previously reported [12], but similar to that reported in a Phase II study previously published by our work group [13]. In this regard, we believe that our higher incidence is the result of the selection of highly pretreated patients with advanced disease, as most of our patients have shown a decrease in immunoglobulins over the course of the disease. All patients were clinically immunocompetent, which is the reason why patients with hypogammaglobulinemia were allowed to enter this trial. Furthermore, in 83% of cases, gammaglobulins G were only slightly decreased (> 0.75 × lower limit of normal). Our experience compares favorable with results obtained with other agents in the salvage setting after platinum-based chemotherapy. A 30.3% response rate was obtained with octreotide with and without prednisone in 38 TET patients (32 with thymoma and six with thymic carcinoma or carcinoid). The PFS for patients with thymoma and thymic carcinoma was 8.8 months (95% CI: 3.7–12.3 months) and 4.5 months (95% CI: 1.9–9.5 months), respectively [14]. A lower response rate was observed in a more recent clinical study conducted with histone deacetylase inhibitor belinostat in 41 previously pretreated TETs patients (25 with thymoma and 16 with thymic carcinoma), although biological activity of the drug was demonstrated in all patients, who responded with global protein hyperacetylation. Of note, time to disease progression in patients with thymoma was 11.4 months, which compares favorable with the results obtained in other trials, but

Table 3. Efficacy measures (n = 30).

Best response	Patients (n)
Complete response	3
Partial response	9
Stable disease	15
Progressive disease	3
Median number of cycles	8
Overall survival:	
– 1-year survival rate	27/30
– 2-year survival rate	20/30

is of unknown clinical meaningfulness given the indolent course of the disease. In fact, despite all patients had progressive disease at the time of study entry, the timeframe of assessment of progressive disease (e.g., 12 months) was not specified [15]. In our patient population, all patients had progressive disease and the majority had received a systemic chemotherapy agent within 2 months prior to enrollment. Everolimus and cetuximab are also promising agents in TETs, but no results from prospective trials are available [16,17].

A number of limitations apply to our trial. Like all prospective evaluations of pharmaceutical agents in TETs, it was a single-arm study, so the magnitude of the effect of the combination on survival cannot be established. Second, no explorative analysis on serum or histological biomarkers was performed to identify putative predictive factors. Third, quality of life and symptomatic improvement were not properly evaluated. Fourth, the recruitment period was prolonged, which was attributed to the rarity of the disease and the inclusion criteria selecting heavily pretreated patients. The median follow-up time of 18 months was sufficient to assess PFS, which we believe is a reliable indicator of therapy effectiveness in a population of progressive, highly pretreated patients. Nevertheless, we believe that the high response rate achieved and the excellent tolerance to treatment measured in a rigorous prospective fashion is sufficient to allow use of such combination in clinical practice after platinum-based therapy. Capecitabine–gemcitabine may also be investigated as neoadjuvant treatment in patients unfit to receive cisplatin and/or anthracyclines. Furthermore, given the frequent expression of EGF receptor in TETs [18] and the tolerability of capecitabine, gemcitabine and cetuximab [19], such three-drug combination may be highly active in TETs. In our trial, capecitabine and gemcitabine showed satisfactory activity in both thymic carcinomas and thymomas, with a median PFS of 11 and 6 months, respectively. Conversely, sunitinib yielded encouraging results in thymic carcinomas only, with three partial responses and a PFS of approximately 6 months recorded in 19 evaluable patients with thymic carcinomas enrolled in a Phase II trial [20]. In our view, the safety profile of sunitinib appeared to be less favorable with respect to capecitabine–gemcitabine, with grade 3 or 4 fatigue and mucositis occurring in approximately a third of the patients [20].

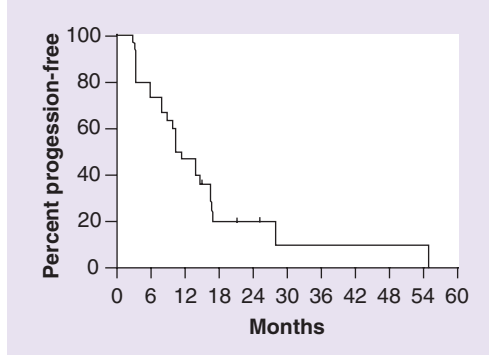

Figure 1. Progression-free survival of the population.

Encouraging results were also obtained with carboplatin–paclitaxel in a cohort of 40 patients with thymic carcinomas, with a median PFS of 7.5 months [21]. Presently, both sunitinib and carboplatin–paclitaxel can be considered as valuable therapeutic options in thymic carcinomas, in addition to the capecitabine–gemcitabine regimen tested in this trial.

Conclusion

In conclusion, given the rarity of the disease, we provided sufficient evidence to allow use of capecitabine–gemcitabine as salvage therapy in a nonexperimental setting. Additional trials are required to further explore the use of such highly active combination in TETs.

Future perspective

The rarity of thymic epithelial tumors demands an international effort to improve our knowledge about epidemiology, histology, disease course, associated syndromes and treatment of this indolent, yet deadly disease. The International Thymic Malignancies Interest Group has recently led an international effort to assemble

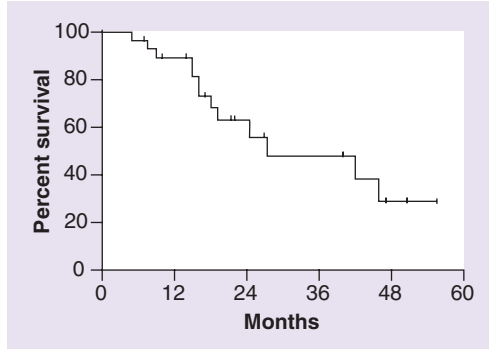

Figure 2. Overall survival of the population.

a database of more than 10,000 cases worldwide in order to provide a more accurate staging classification of thymic epithelial malignancies. A consensus International Thymic Malignancies Interest Group document on histologic classification of thymic malignancies has recently been published. As our knowledge of the biology of thymic epithelial tumors grows, an increasing number of druggable pathways will be identified. International cooperation is mandatory to ensure rapid patient accrual in this rare disease.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

- Capecitabine–gemcitabine combination has shown promising activity in heavily pretreated thymic epithelial tumors.
- A relatively high response rate was recorded in both patients with thymic carcinomas and thymomas.
- The excellent safety profile allowed long-term administration of this regimen.

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