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ORIGINAL ARTICLE

Imatinib mesylate in thymic epithelial malignancies

Giovannella Palmieri · Mirella Marino · Carlo Buonerba · Piera Federico · Salvatore Conti · Michele Milella · Luigi Petillo · Amelia Evoli · Maurizio Lalle · Anna Ceribelli · Gerardina Merola · Elide Matano · Stefano Sioletic · Sabino De Placido · Giuseppe Di Lorenzo · Vincenzo Damiano

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Abstract
Purpose Thymic epithelial tumors (TETs) are rare tumors of the mediastinum, with an estimated incidence of about 3 cases per 100,000 inhabitants. Although anthracycline- and platinum-based chemotherapy is an active treatment for TETs, novel systemic therapeutic options are especially needed for metastatic disease, which is virtually incurable. On the basis of the radiographic response obtained with imatinib (Novartis Pharma, Basel, Switzerland) in a patient with thymic carcinoma harboring the V560del c-KIT mutation, a phase II trial was initiated at the Department of Molecular and Clinical Oncology and Endocrinology of University "Federico II of Naples" with the purpose to test imatinib in TETs.
Methods Imatinib was daily delivered at the dose of 400 mg to patients affected by TETs, who had progressed after at least one chemotherapy regimen. Positivity of c-KIT on immunohistochemistry was not mandatory for study entry. Radiographic responses were measured by CT scans performed every 3 months, according to the RECIST criteria. Toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0.
Results Fifteen patients with advanced TETs were enrolled from March 2008 to May 2010. Three patients presented with thymic carcinomas. Two of these three patients presented c-kit expression on immunohistochemistry. No patient harbored a known c-kit activating mutation. Imatinib was very well tolerated, with no toxicity-related death. Diarrhea and migraine were the most frequent events, occurring both in 20% of patients, but were manageable and mild. No radiographic responses were recorded. Median progression-free survival was 3 months (interquartile range, 2.5–4). Median overall survival was not reached. The study was terminated before it reached its target accrual of 42 patients, because of the lack of responses and low accrual rate.
Conclusions This trial indicates the lack of effectiveness of imatinib in unselected patients with thymic epithelial tumors. Nevertheless, imatinib may represent a valuable option in selected patients with TETs, such as those harboring the V560del c-KIT mutation.

Keywords Thymic tumors · Imatinib · c-KIT · Thymic carcinomas

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G. Palmieri (✉) · C. Buonerba · P. Federico · G. Merola · E. Matano · S. De Placido · G. Di Lorenzo · V. Damiano
Molecular and Clinical Endocrinology and Oncology Department, University Federico II, Via Pansini 5, 80128 Naples, Italy
e-mail: giovpalm@unina.it

M. Marino · S. Conti · S. Sioletic
Department of Pathology, Regina Elena National Cancer Institute, Rome, Italy

A. Evoli
Neuroscience Department, Catholic University, Rome, Italy

M. Lalle
Medical Oncology, S. Eugenio Hospital, Rome, Italy

M. Milella · A. Ceribelli
Medical Oncology Division A, Regina Elena National Cancer Institute, Rome, Italy

G. Palmieri · L. Petillo · S. De Placido · G. Di Lorenzo · V. Damiano
CRTR-Centro Regionale Tumori Rari (Regional Center for Rare Tumors), University Federico II, Naples, Italy

Introduction

Thymic epithelial tumors (TETs) are rare malignancies, with an estimated incidence of about 3 cases per 100,000 inhabitants [1].The world health organization (WHO) classification identifies six distinct histologic types of thymic tumors that differ from one another on the basis of the predominant cell type [2]. Histologic types A, AB, B1, B2, and B3 present a less aggressive clinical behavior than thymic carcinomas. Staging of thymic tumors is performed according to the Masaoka staging system [3]. Treatment modalities comprise surgery [1], radiotherapy [4], and chemotherapy [4]. Chemotherapy can be administered as neoadjuvant therapy for locally advanced, inoperable tumors or as palliative, non-curative treatment for metastatic disease. Platinum compounds and anthracyclines, as well as somatostatin analog combined with prednisone, are active agents [4]. Recently, combination of gemcitabine and capecitabine has proved to be a tolerable and efficacious regimen for pre-treated patients with metastatic thymic tumors [5], but the therapeutic options in this setting are limited and most of these patients eventually die of the disease. Imatinib (Novartis Pharma, Basel, Switzerland) is a competitive inhibitor of BCR-ABL, KIT, PDGFRA, and PDGFRB tyrosine kinases [6]. These tyrosine kinases play a crucial role in the pathogenesis of malignancies for which imatinib is highly effective, such as chronic myeloid leukemia and gastrointestinal stromal tumors [7]. As the greatest majority of GISTs strongly express c-KIT on immunohistochemistry, research has been directed to establish whether other c-KIT positive solid tumors, such as small cell lung cancer [7] and thymic carcinomas [8, 9], are sensitive to imatinib. Importantly, a 6-month response to imatinib was obtained in a patient presenting with a thymic carcinoma overexpressing c-KIT on immunohistochemistry [10].

This single-center phase II study (TETIMAX trial) was conducted to evaluate the effectiveness of single-agent imatinib in a population of pre-treated patients with advanced TETs. Despite thymic epithelial tumors other than thymic carcinomas generally lack c-KIT expression [8, 9], the low predicted accrual of patients with thymic carcinomas induced us to include patients with all histologic types of thymic epithelial neoplasms, also in view of the potential for imatinib to be effective in tumors negative for c-KIT on immunohistochemistry [11].

Patients and methods

Patients

Eligibility criteria for the study are detailed in Table 1 and were mainly the following: adult age; histologic diagnosis of TET by central review; at least one measurable lesion, detected by whole-body CT scan, a maximum of 30 days before study entry; progressive disease, defined as enlargement of target measurable lesions on CT scan, according to the RECIST criteria [12]; at least one prior systemic chemotherapy treatment; adequate heart, bone marrow, renal, and hepatic function. A FDG-PET ([18F]2-fluoro-2-deoxy-D-glucose positron emission tomography) scan was required for inclusion for patients with thymic carcinomas only and was allowed for other patients at the investigator's discretion. Patients were excluded if they had uncontrolled concomitant medical illnesses or if they had received systemic anticancer treatment within 4 weeks of enrollment. Patients who were pregnant or lactating were also excluded. The study was conducted at Department of Molecular and Clinical Endocrinology and Oncology of University Federico II of Naples and was approved by the institutional review board of the participating institution. 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. The study was supported by "Agenzia Italiana del Farmaco" (AIFA code, FARM6HJ7CA).

Treatment

Imatinib mesylate was orally administered at the dose of 400 mg every day for a 30-day cycle. This study adopted the same protocol for dose modification and treatment suspension previously employed for GISTs [13]. Dose was reduced up to 200 mg daily, and treatment was suspended up to 2 weeks; if greater dose reduction or longer treatment suspension were required, the patient was taken off the study. Treatment was administered until unacceptable toxicity or radiographic or clinical progressive disease or completion of 12-month course of therapy, whichever came first.

Clinical, laboratory, and radiographic assessments

All patients eligible for inclusion 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.

A complete blood count analysis and hepatic and kidney laboratory tests were performed every other week. All adverse events were graded according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0. A whole-body CT scan was performed a maximum of 30 days before enrollment in the trial and was repeated every 12 weeks. If disease progression was clinically suspected, CT scan could be anticipated at physician's

Table 1 Inclusion and exclusion criteria for study entry

Inclusion criteria
Signed informed consent
Histological diagnosis of TET by central review
Patients with advanced disease not amenable to local treatment, pre-treated with at least one prior line of chemotherapy
WHO performance status of 0–1
At least one measurable lesion detected by CT scan (greatest diameter ≥1 cm)
Adequate bone marrow function
Absolute neutrophil count ≥ 1.5 × 10 ^ 9/l
Platelets ≥ 100 × 10 ^ 9/l
Hemoglobin ≥ 10 g/dl
Adequate liver function
Total bilirubin levels < 1.25 × unl
AST, ALT < 1.5 × uln
Adequate kidney function
Creatinine levels < 1.5 × unl
Whole-body PET scan (if thymic carcinoma)
Exclusion criteria
Lack of consent to protocol
Pregnancy or absence of contraception in sexually active fertile women
Major uncontrolled comorbidities (e.g., uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction <6 months before registration, uncontrolled cardiac arrhythmia)
Concurrent or recent (<30 days) chemotherapy or radiotherapy
Recent (<30 days) surgery

TET thymic epithelial tumors, *uln* upper limit of normal

discretion. A PET-FDG was required for all patients with thymic carcinomas and was allowed for the rest of accrued patients and was repeated every 12 weeks. Measurable target lesions were evaluated using the RECIST criteria 1.0 for CT scans [12] and the European Organization for Research and Treatment of Cancer (EORTC) criteria for PET scans [14]. Progressive disease was defined on the findings of CT scans only. Progression-free survival was calculated from the time of enrollment to disease progression or death from any cause, whichever came first. Patients who interrupted treatment for toxicity or reasons other than progression or death were censored in the analysis.

Histology review

Histological diagnosis of patients enrolled in the TETIMAX study was centrally revised at Department of Pathology, Regina Elena National Cancer Institute, Rome, Italy. All specimens were examined after routine H&E stain and classified according to the 2004 WHO classification of thymus tumors [2]. Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue. Expression of c-KIT was measured by employing anti-CD117 (clone T595) antibody from Novocastra (Menarini, Florence, Italy) at a typical dilution 1:20–1:40, incubated at 25C° for 60 min. Unmasking of antigenic sites was performed by treatment of the sections in a thermostatic bath at 96°C for 40 min in citrate buffer (pH 6). Immunostaining was revealed by a streptavidin–biotin enhanced immunoperoxidase technique (Super Sensitive MultiLink, Novocastra, Menarini Florence, Italy) in an automated stainer (Bond Max, Menarini). Diaminobenzidine (Menarini) was used as a chromogenic substrate.

Mutational analysis—sequencing of *c-kit* exons 9, 11, 13, and 17

DNA was extracted from formalin-fixed, paraffin-embedded tissue (FFPE) samples on histological sections. For microdissection, appropriate tissue blocks were selected and multiple serial sections were stained with H&E, and visualized with an inverted microscope. Under an operating microscope, tumoral tissues were microdissected from non-tumoral tissue by using a sterilized needle. Dissected tumoral tissues were collected, deparaffinized, and digested with proteinase K overnight in lysis buffer before DNA isolation with the QIAamp DNA FFPE Tissue Kit (QIAGEN, USA). The DNA was eluted in a volume of 50–150 µl of water. DNA concentrations were measured by Nanodrop, and the amount of isolated DNA ranged from 50–300 ng/µl. About 50–100 ng of genomic DNA was used for three PCR reactions to amplify the region of *c-kit* exons 9, 11, 13, and 17. Primers were designed to amplify four DNA regions (Table 2). All PCR reactions were in a volume of 50 µl containing, 10 pmol of each primer, 0.25 mM each dNTP, 2.5 mM MgCl2, 3 units of AmpliTaq Gold (Applied Biosystems, USA), 1X Taq Gold buffer (Applied Biosystems), and the appropriate volume of H_2O. Thermocycle PCR protocol was as follows: 10 min at 95°C, 35 cycles at 95°C for 30 s, 56°C for 30 s, and 72°C for 30 s, followed by 72°C for 10 min. PCR amplicons obtained from DNA were purified with NucleoSpin Extract II kit (Macherey–Nagel, Germany) and eluted with water. About 10 ng of PCR products were sequenced directly by using the Big Dye V3.1 Cycle-Sequencing kit (Applied Biosystems) with proper reverse primers (Table 2). After sequencing reaction, 1 µl of every mixture was purified by BigDye XTerminator Purification Kit (Applied Biosystems) and analyzed on a 3130 Genetic Analyzer (Applied Biosystems).

Statistical analyses

Descriptive statistics and frequency counts were used to summarize characteristics of the study population. Median

Table 2 Patients' characteristics ($n = 15$)

Patients' characteristics	Patient no. (%)
Male	10 (66%)
Female	5 (33%)
Pathological diagnosis	
Type B2	4 (26%)
Combined type B2/B3	2 (13%)
Type B3	6 (40%)
Thymic carcinoma	3 (20%)
Associated syndromes	
Myasthenia gravis	6 (66%)
Hypogammaglobulinemia/B lymphopenia	12 (66%)
Anatomical sites of disease	
Mediastinum	7 (46%)
Pleura	10 (66%)
Lymph node	4 (26%)
Lung	3 (20%)
Liver	3 (20%)
Bone marrow	1 (6%)
Prior local treatment	
Surgery	8 (53%)
Radiotherapy	5 (23%)

numbers were presented with interquartile ranges. The radiographic response rate was chosen as primary end point and employed to calculate the study sample. Secondary end points were time to progression, toxicity, and overall survival. Drug activity was evaluated following an exact binomial design for determination of response rates based on a single-treatment group [15]. A sample size of 38 patients was estimated assuming one-tailed α equal to 0.05, (1-β) equal to 0.9, and $\pi<0.05$ (null hypothesis) versus $\pi \geq 0.20$ (alternative hypothesis), where π was the radiographic response rate according to the RECIST criteria. Supposing that 10% of patients were not evaluable for response, the total target accrual was set to be 42 patients. If at least five patients were evaluated as responsive, it was assumed that the drug was active.

Results

Patients' characteristics

Fifteen patients with a histologic diagnosis of thymic epithelial tumor were recruited at the Department of Molecular and Clinical Oncology and Endocrinology of University "Federico II of Naples" from February 2008 to June 2010. Twelve patients were males, three were females. Median age was 51 years (range, 42–54 years). All patients had received at least one prior line of chemotherapy for metastatic or locally advanced disease and presented metastatic disease at the time of enrollment, with pleura being the most common site of metastasis. Patients' characteristics are detailed in Table 3.

Table 3 Primers for *c-kit* exons 9, 11, 13, and 17 amplification and sequencing analysis

c-Kit exon 9	
Fw	5′AGCCAGGGCTTTTGTTTTCT3′
Rv	5′CAGAGCCTAAACATCCCCTTA3′
c-Kit exon 11	
Fw	5′CCAGAGTGCTCTAATGACTG3′
Rv	5′ACCCAAAAAGGTGACATGGA3′
c-Kit exon 13	
Fw	5′CATCAGTTTGCCAGTTGTGC3′
Rv	5′AAAAGGCAGCTTGGACACGG3′
c-Kit exon 17	
Fw	5′TGGTTTTCTTTTCTCCTCCAAC3′
Rv	5′GCAGGACTGTCAAGCAGAGAATG3′

Histology review, c-kit expression, and mutational status

All centrally reviewed specimens were collected from primary tumor and/or local relapse, expect for one sample, which was collected from a bone marrow metastasis. All patients had either type B2 or B3 TETs, except for 3 patients who presented thymic carcinoma. Two patients with thymic carcinoma were positive by immunohistochemistry for c-kit. The other thirteen patients were all negative for c-kit. By mutational analysis, all cases tested were negative for known c-kit mutations in exons 9, 11, 13, and 17.

Tolerance and efficacy

A total of 61 cycles of imatinib mesylate were administered to patients, and each patient received a median of 3 cycles (interquartile range, 2–4). Dose reduction was required in two patients only. All of the patients were evaluable for toxicity. As shown in Table 4, diarrhea and migraine were the most frequent events, occurring both in 20% of patients, but were manageable and mild. No grade 3–4 event was recorded. All patients underwent periodical CT scans, and nine patients also underwent periodical PET scans. No response was detected by CT scan, while one patient showed a partial response by PET scan after 6 months of treatment, which was discordant with CT findings indicating progressive disease. PET results were concordant with CT findings in six patients, all of whom presented progressive disease after 3 months. CT scan was anticipated in seven patients because of clinically suspected disease

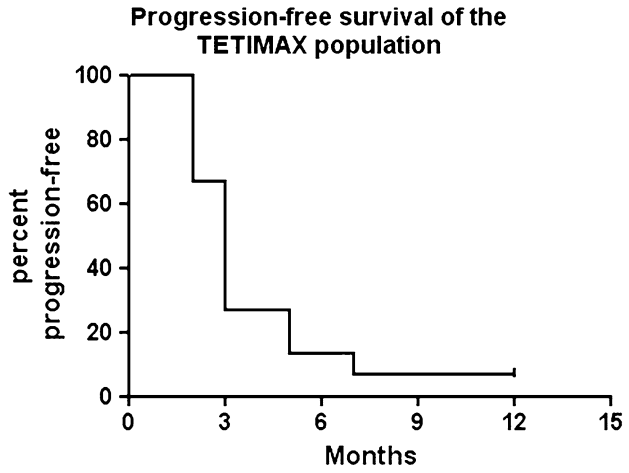

Fig. 1 Progression-free survival of patients enrolled in the TETIMAX trial

Table 4 Adverse events (CTCAE v.3) ($n = 15$)

Adverse events	Patient no. (%)	
	Grade 1 events	Grade 2 events
Asthenia	1 (6%)	
Bone pain	1 (6%)	1 (6%)
Conjunctivitis	1 (6%)	
Diarrhea	2 (13%)	1 (6%)
Dispepsy	1 (6%)	
Transaminasis elevation	2 (13%)	
Dyspnea	1 (6%)	
Esophthalmos	1 (6%)	
Headache	3 (20%)	
Inferior limb edema	2 (13%)	
Nausea	2 (13%)	

progression, which was confirmed by CT scan in all cases. As shown in Fig. 1, median progression-free survival was 3 months (interquartile range, 2–4). A single patient with B3 TET, negative for c-kit expression by immunohistochemistry, presented stable disease for 12 months. Four patients were dead at the time the study was closed, the others were alive. Median overall survival was not reached. Accrual was formally stopped on October 31, 2010, before the planned study numerosity was reached, due to slow accrual, absence of objective response to treatment, and low progression-free survival.

Discussion

As shown in murine models carrying inactivating mutations of c-KIT, CD117 plays a physiological role for the development of several cellular lines, such as melanocytes, germ cells, mast cells, hematopoietic stem cells, as well as the interstitial cells of Cajal, which are responsible for pacemaker activity in the mammalian gut [16]. GIST tumors probably originate from self-regenerating progenitor cells that normally differentiate into Cajal cells [17]. In view of the effectiveness of imatinib in GISTs, which dramatically changed the natural course of this chemo-refractory disease [13] and of the nearly constant expression of c-KIT of these tumors [7], the status of c-kit on immunohistochemistry analysis was hypothesized to be predictive of imatinib effectiveness in other tumors as well. On such basis, imatinib was experimented in a series of solid malignancies overexpressing c-KIT. In a sample of 12 patients with small cell lung cancer treated with imatinib, 78% showed c-KIT expression on immunohistochemistry, but no radiographic responses were detected and all patients progressed within a month since enrollment [18]. Similarly, the lack of activity of imatinib was reported by small trials in other c-kit positive tumors, such as adenoid cystic carcinoma of salivary glands [19] and uterine carcinosarcoma [20]. As far as thymic malignancies are concerned, several studies concordantly indicated a very low expression on immunohistochemistry of c-kit in thymic epithelial malignancies (around 2%), with the exclusion of thymic carcinomas, which showed c-kit expression in 79% of cases [21]. The first report of a patient with thymic carcinoma metastatic to the liver showed that treatment with imatinib resulted in stabilization of the mediastinal mass with symptomatic improvement and shrinkage of the liver lesions, with a progression-free survival of about 6 months. Of note, *KIT* mutational analysis demonstrated an in-frame deletion in exon 11 that causes the loss of valine at position 560 (V560del) and is frequently identified in GISTs [10]. This promising result paved the way for experimentation of imatinib in the context of a clinical trial. In a small, prematurely closed phase II trial, seven patients with thymic epithelial tumors received imatinib at a dose of 600 mg/die, which could be increased to 800 mg, if well tolerated [22]. These doses are higher than the one employed in the present study. Similarly to the present study, positivity of c-KIT was not mandatory for study entry and patients with all histologic types of TETs were enrolled in this study, on the basis of the rarity of thymic carcinoma. The results of this small trial [22], which had not been published in full form at the time our trial was started, are consistent with those obtained here, with no signal of imatinib effectiveness either in response rate or in progression-free survival. All of these negative experiences unequivocally showed that immunohistochemistry has no predictive role for imatinib efficacy. On the contrary, such a role is played by the particular c-KIT mutation, as it has been demonstrated for GISTs. As example, GISTs with KIT exon 11 mutations are those which are most likely to respond to imatinib, with a

nearly 85% response rate, while GISTs with the *PDGFRA* D842V mutation show no response to imatinib [7]. In our series, no known c-kit mutations have been identified. One female patient presented stable disease for 12 months, but she did not harbor a c-kit mutation, and she did not present c-kit expression by immunohistochemistry. We are unable to provide any explanation for this finding, even at a hypothetical level. This case supports the hypothesis that imatinib may be employed in selected subgroup of patients with TETs, and that the presence of KIT mutation may be a sufficient, but not necessary condition for imatinib effectiveness. There is the possibility, however, that the clinical relevance of such use of imatinib may be low, since *KIT*-mutant thymic carcinomas are about 7% of thymic carcinomas [21]. Furthermore, other c-KIT targeting biological agents, such as sorafenib or sunitinib, both of which have been administered to patients with thymic carcinomas [23, 24], may inhibit c-KIT and other tyrosine kinases receptors more effectively than imatinib [25]. In a series of 45 TETs analyzed for KIT expression and mutational status, KIT was found to be mutated in two tumors only, both of which were thymic carcinomas. One tumor showed the deletion of valine at position 560 (V560del), while the other tumor showed a KIT mutation in exon 14, which resulted in the substitution of a tyrosine for a histidine aminoacid at position 697 (H697Y). Interestingly, while sunitinib resulted to inhibit effectively both of KIT mutants, imatinib was less efficient than sunitinib in inhibiting the H697Y KIT mutant [25].

In conclusion, this study adds further evidence indicating the lack of effectiveness of imatinib in unselected patients with thymic epithelial tumors. Nevertheless, imatinib is likely to represent a valuable option in selected patients with TETs, that is to say those harboring the V560del c-KIT mutation. Such hypothesis should be tested in a clinical trial, with the obvious difficulty of enrolling patients presenting both a rare tumor and a rare gene mutation.

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Conflict of interest The authors declare no potential conflicts of interest.

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