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Imatinib Mesylate in Patients with WHO B3 Thymomas and Thymic Carcinomas

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Abstract

Thymic malignancies are rare tumors of the mediastinum. c-KIT is highly expressed in thymic carcinomas (TC) but infrequently in thymomas. Anecdotal experience suggests activity of imatinib mesylate in TC. Patients with unresectable World Health Organization B3 thymomas or TC, performance status 0 to 2, good organ function, and measurable disease were enrolled in this study. Imatinib was administered at 600 mg PO daily. Seven patients were recruited at one institution: two World Health Organization B3 thymomas and five TC. Imatinib treatment was generally well tolerated. Two patients had stable disease and five progressed. Median survival was 4 months, and median time to progression was 2 months. c-KIT expression was found in one of four samples by immunohistochemistry. No mutations were detected in the c-KIT or PDGFRA genes in three samples analyzed. Imatinib has no major activity in this rare tumor. Given the small number of patients treated in this study, selection based on presence of c-KIT mutations might be warranted.

Keywords

Imatinib; KIT; Thymoma

Thymomas are rare malignancies of the anterior superior mediastinum and represent 0.2 to 1.5% of all malignancies.[1]

The World Health Organization (WHO) histologic classification reports a continuum of tumors from A to C.[2] Thymic carcinomas (TC) (WHO type C) represent less than 1% of thymic malignancies and seem to have a different molecular and clinical profile compared with thymomas.[3] In recent years, studies on molecular alterations in thymic malignancies

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have been published. c-KIT positivity by immunohistochemistry (IHC) has been observed in 73 to 86% of TC.[4,5]

Imatinib mesylate inhibits several receptor tyrosine kinases that are believed to play a role in the proliferation of tumor cells including those associated with Bcr-Ab1, PDGFR, and c-KIT. Striking activity has been observed with imatinib in chronic myelogenous leukemia[6] and gastrointestinal stroma cell tumors (GIST).[7,8]

We performed this study to evaluate response of highgrade thymic malignancies known to overexpress c-Kit to imatinib mesylate.

PATIENTS AND METHODS

Patients

This was an open-label phase II trial, to test the clinical activity and safety of imatinib in patients with TC. Because of the rarity of TC known to overexpress c-Kit, WHO B3 thymomas were also included in this study. Other inclusion criteria were age more than 18 years, presence of measurable and/or evaluable disease (by WHO Response Criteria), performance status 0 to 2 (Eastern Cooperative Oncology Group), adequate end organ function (total bilirubin <1.5 × upper limit of normal [ULN], serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase <2.5 × ULN, creatinine <1.5 × ULN, absolute neutrophil count >1.5 × 10^9/L, platelets >100 × 10^9/L, and leukocytes >3 × 10^9/L), and life expectancy more than 3 months. Written informed consent was obtained.

Patients were treated with imatinib (supplied by Novartis, Basle) 600 mg by mouth once a day. The dosage was increased to 800 mg/d (400 mg twice daily) if there was evidence of objective progression. The maximum duration of treatment was 12 months. Beyond this period, treatment was to be continued at the discretion of the investigator. In case of toxicity, dose adjustments were made according to previously reported guidelines.[8] If treatment was interrupted for ≥14 days, then therapy was discontinued. Tumor response was evaluated according to WHO response criteria. Patients with nonmeasurable (but evaluable) disease were evaluated only in terms of time to progression (TTP) and overall survival. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Before implementing this study, all necessary approvals were obtained from the Institutional Review Board/Independent Ethics Committee.

Expression and Mutation Analysis

Histologic samples were used for IHC to test expression of c-KIT. Expression was assessed as described previously[9] and was based on conventional hematoxylin and eosin stains and indirect immunoperoxidase stains for CD117 (polyclonal, 1/250; DAKO, Glostrap, Denmark). The CD117 immunostaining was performed without antigen retrieval, and the presence of mast cells served as an internal control. IHC results were reported as positive/negative.

Sequencing ot the hot spots tor mutations was performed for *c-KIT* and *PDGFRA* genes. Tumor DNA was isolated from formalin-fixed paraffin-embedded material. DNA was isolated as described earlier.[10] Exon 9, 11, 13, and 17 of the *c-KIT* gene and exon 12 and 18 of the *PDGFRA* gene were amplified by polymerase chain reaction (PCR) using the primers listed in Table 1. The PCR products were purified (Qiaquick PCR purification KIT, Qiagen, The Netherlands) and screened for mutations by bidirectional sequence analysis, using the forward and reverse PCR primers.

Statistical Considerations

The primary end point of this study was to assess response rate, and secondary end points were assessment of safety, TTP, and overall survival. The Simon optimal design was used. The accrual goal for the first stage of the trial was 14 patients.

RESULTS

Between June 2005 and August 2006, seven patients with progressive disease and a median age of 67 years (range 36–76) were enrolled from one institution. Three patients who were either elderly or refused chemotherapy received imatinib as first-line therapy. Accrual was stopped after no responses were seen in these patients, and the results of mutation analysis did not confirm presence of mutations in our study and in other series. Survival data has been updated in April 2009. Patient characteristics and treatment outcome are summarized in Table 2.

Toxicity

Five patients did not report side effects, or they reported only grade 1 nausea or edema. One patient had grade 4 vomiting, which required interruption of treatment twice until progression (no. 1). Another patient (no. 2) developed grade 3 depression, associated with grade 2 asthenia and requested interruption of treatment when no response was documented at first computed tomography evaluation.

Responses and Survival

All five patients with TC had rapid disease progression and have died; the two patients with WHO B3 thymomas had stable disease and are still alive. One of these patients subsequently received carboplatin-etoposide, which induced a minor response, followed by radical resection of the tumor. Seventeen months after surgery, the patient had a locoregional recurrence that was irradiated; the patient is still alive with disease more than 38 months from initiation of imatinib. The other patient stayed on imatinib for two cycles and on progression received pemetrexed and then radiation therapy; he is still alive with disease after more than 35 months from start of imatinib. Median TTP was 2 months and median survival was 4 months for all patients. Patients with B3 thymoma survived significantly longer than patients with TC ($p = 0.037$).

Immunohistochemistry and Mutation Analysis

Tumor samples could be retrieved from only four patients for molecular analysis. IHC revealed some positivity in one case of B3 thymoma, but was negative in the other patient

with B3 thymoma and in two TC (Table 3). Mutation analysis failed in one of the four cases tested. No mutations could be detected in any of the exons of *c-KIT* or *PDGFRA* in the other three cases.

DISCUSSION

In this prospective study, no responses were seen with imatinib therapy in two patients with WHO B3 thymoma and five patients with TC and progressive disease at study entry. No mutations were detected in *c-KIT* and *PDGFRA* genes in three cases where they could be assessed.

The *KIT* gene belongs to the family of class III receptor tyrosine kinases, which also includes the platelet derived growth factor receptors alpha and beta (*PDGFRA* and *PDGFRB*). Overexpression of KIT is seen in a variety of human tumors. However, apart from GISTs, activating mutations of the KIT and *PDGFRA* genes are uncommon in the majority of human solid tumors.[11]

A large proportion of TCs (but not thymomas) show immunohistochemical expression of KIT. Strobel et al.[12] have described a case of epidermoid carcinoma of the thymus with strong expression of KIT, an activating mutation in exon 11 of the *KIT* gene (V560del) and a response to imatinib that lasted 6 months.

Pan et al.[5] found lmmunohistochemical expression of KIT in 19 of 22 cases (86%) of TC but no expression in 110 thymomas or 16 non-neoplastic thymus glands. They also found no *c-KIT* mutations in exons 9, 11, 13, and 17 of the *KIT* gene in 21 of 22 cases of TC by direct DNA sequencing.

Tsuchida et al analyzed KIT expression in 20 cases of thymoma and 17 cases of TC. KIT expression by IHC was seen in 11 cases of TC (all squamous cell carcinomas) and 0 thymomas. No mutations of *c-KIT* exons 9, 11, 13, and 17 were found in nine cases of TC that were tested.[13]

Yoh et al.[14] analyzed 24 cases of thymoma and 17 cases of TC and found KIT protein expression by IHC in 88% of TC and 0% of thymomas. In 22 cases of thymoma and 11 cases of TC analyzed for mutations of exons 9, 11,13, and 17 of the *KIT* gene, only one case of TC harbored a missense mutation in exon 11 (L576P).

The presence of mutations in the *c-KIT* gene determines response to imatinib therapy. In GIST, response rates in patients who harbor mutations in exon 11, exon 9, and those who lack detectable mutations are more than 80, 48, and 0, respectively.[7] A phase II study of imatinib at a dose of 400 mg twice daily in 21 patients with metastatic melanoma showed one partial response in a patient with a tumor that displayed a three base pair deletion in exon 15.[15]

Results of another small study of imatinib in patients with TC were reported by Salter et al. [16] Eleven patient s with advanced, unresectable, previously treated TC that was positive by IHC for c-KIT (nine cases) or PDGFR (two cases) were treated with imatinib at a dose of

600 mg by mouth daily on a 21-day cycle. No objective responses were observed. Tumor samples were not analyzed for the presence of mutations in the *KIT* gene.

A recent report (W. Pao, personal communication) identified two *KIT* mutations in six resected TC analyzed, one of which is a novel mutation. The potential use of more sensitive methods for mutation analysis may be of interest, and it is conceivable that a small percentage of TCs may harbor *KIT* mutations.

In summary, imatinib does not seem to have activity in TCs. The rarity of *KIT* mutations in this disease may be the reason for this negative result. Selection of patients with TC harboring *KIT* mutations may be of interest for further studies.

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TABLE 1.

Primers Used for the Sequencing of c-KIT and PDGFRA Genes

Gene	Exon	Forward Primer	Reverse Primer	Product Size
c-KIT	9	AGTGCATTCAAGCACAATGG	TGGTAGACAGAGCCTAAACATCC	151
c-KIT	11	CTCCAGAGTGCTCTAATGACTGA	TGTTATGTGTACCCAAAAAGGTG	248
c-KIT	13	CATCAGTTTGCCAGTTGTGC	CAGCTTGGACACGGCTTTAC	182
c-KIT	17	TGGTTTTCTTTTCTCCTCCAA	TGCAGGACTGTCAAGCAGAG	185
PDGFRA	12	CCAGTTACCTGTCCTGGTCAT	GGAGGTTACCCCATGGAACT	183
PDGFRA	18	TTCCTTTTCCATGCAGTGTG	GACCAGTGAGGGAAGTGAGG	165

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TABLE 2.

Patient Characteristics and Outcome

Patient No	Gender	Age, yr	Previous Therapy	Stage	Histology	PS	Response	Toxicity	TTP (m)	Following Therapy	Survival (m)
1	M	36	VIP (NC)	IVB liver bone	Thymus carcinoma	2	NE/PD	Vomiting grade 4	1	None	2
2	M	67	Debulking; RT; metastasectomy; carboplatingemcitabine (NC)	IVA pleura	B3	1	NC	Asthenia grade 2, rash grade 1, depression grade 3	8	Pemetrexed (NC); RT	35 +
3	M	47	VIP (PR)	Locoregional relapse (IVA)	B2/3	1	NC	None	9+[a]	Carboplatin-etoposide (MR); radical resection	38 +
4	M	76	No	IVB lung	Thymus carcinoma	1	PD	Nausea grade 1	2	Carboplatin-etoposide (PR); RT	22
5	M	36	CAP	IVB bone	Thymus carcinoma	2	PD	Nausea grade 1, edema grade 1	2	None	4
6	M	71	No	IVB pericardium bone	Thymus carcinoma	2	PD	Nausea grade 1	1	None	1
7	F	69	No	IVB lung, neck	Thymus squamous carcinoma	2	PD	None	0.5	Carboplatin-etoposide (PD)	2

[a]TTP censored; patient underwent further chemotherapy followed by resection, in absence of progression on imatinib.

NC, no change; PR, partial response; PD, progressive disease; RT, radiotherapy; VIP, etoposide, ifosfamide, cisplatin; CAP, cyclophosphamide, doxorubicin, cisplatin; TTP, time to progression; MR, minor response.

TABLE 3.

Results of c-Kit Immunohistochemistry and Mutation Analysis of *c-KIT* and *PDGFRA* Genes

Patient No	Histology	Kit Immunohistochemistry	Kit Mutations	PDGFRA Mutations
1	Thymus carcinoma	ND	ND	ND
2	B3	15% cells positive	None	None
3	B2/3	Negative	Failed	Failed
4	Thymus carcinoma	ND	ND	ND
5	Thymus carcinoma	ND	ND	ND
6	Thymus carcinoma	Negative	None	None
7	Thymus squamous carcinoma	Negative	None	None

ND, not done.