The role of imatinib mesylate (Glivec) for treatment of patients with malignant endocrine tumors positive for c-kit or PDGF-R

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Abstract

Imatinib mesylate (IM), a small molecule that is a selective inhibitor of the ABL, platelet derived growth factor receptor (PDGFR-R) and stem cell ligand receptor (c-kit) tyrosine kinases (TK). IM was also found to inhibit the TK activity of BCR/ABL fusion protein produced in chronic myelogenous leukemia, with marked clinical activity against the disease. Since both PDGF-R and c-kit both having a putative role in tumorigenesis, we investigated the efficacy and safety of the use of IM in patients with endocrine tumors unresponsive to conventional therapies that expressed c-kit and/or PDGF-R (within the framework of a comprehensive phase II multi-center study of IM in patients with solid tumors). IM was initiated at a dose of 400 mg/day, with possible dose escalation within 1 week to 600 mg/day and an option to raise the dose to 800 mg/day in the event of progression and in the absence of safety concerns for a period of up to 12 months. Between September 2002 and July 2003, 15 adult patients with disseminated endocrine tumors were recruited as follows: medullary thyroid carcinoma (MTC, $n = 6$); adrenocortical carcinoma (ACC, $n = 4$); malignant pheochromocytoma (pheo, $n = 2$); carcinoid (non-secreting, $n = 2$), neuroendocrine tumor (NET, $n = 1$). No objective responses were observed. MTC – disease progression in 4 patients, and treatment discontinuation in 2 patients due to adverse events; ACC – disease progression in 3 patients, and treatment discontinuation in 1 patient due to severe psychiatric adverse event; Pheo – disease progression in 2 patients; Carcinoid – stable disease in 1 patient (6.5 months), and disease progression in 1 patient; NET – disease progression in 1 patient. IM does not appear to be useful for treatment of malignant endocrine tumors, also causing significant toxicity in this patient population.

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Introduction

Imatinib mesylate (IM), is a small molecule selective inhibitor of the c-ABL, platelet derived growth

factor receptor (PDGFR-R) and stem cell ligand receptor (c-kit) tyrosine kinases (TK) (Mol *et al.* 2004). IM was also found to inhibit the TK activity of BCR/Abl fusion protein produced in

chronic myelogenous leukemia (CML). Subsequently, in clinical trials IM was found to be highly effective in patients with CML, featuring unprecedented hematological, cytogenetic and molecular responses; IM has become the treatment of choice for such patients (Druker 2003). Both c-kit and PDGFR have been shown to play important roles in oncogenesis in a broad spectrum of hematological and solid tumors (Fletcher 2004). Moreover, occasional patients with solid tumors expressing c-kit and/or PDGFR have also shown responses to IM. This is particularly striking in patients with c-kit positive gastrointestinal stromal tumors (GIST) for which IM has become standard therapy in inoperable cases (Connolly *et al.* 2003, Eisenberg & von Mehren 2003). IM has also proved to be useful in the cutaneous malignant tumor dermatofibrosarcoma protuberans, in those cases associated with a translocation between chromosomes 17 and 22 that places the platelet-derived growth factor-B under the control of the collagen 1A1 promoter (McArthur *et al.* 2005). These observations prompted us to design a multi-center national study for patients with solid tumors, other than GIST, expressing either c-kit and/or PDGFR to evaluate the clinical response to IM. In this paper, we report the results of IM in patients with cancers of the endocrine system, within the framework of the more comprehensive national study.

Patients and methods

Patients and eligibility criteria

This was a non-randomized, open label, Phase II, dose escalating study performed at the Hadassah-Hebrew University Medical Center (Jerusalem, Israel) within the framework of a investigator initiated, comprehensive multi-center study assessing the effect of glivec in patients with a variety of solid tumors. The Local Research Ethics Committee at each of the participating institutions and the Israeli Ministry of Health approved the study, all patients gave written, informed consent. All of the patients entered into this study had unresectable and/or metastatic endocrine cancers, pathologically verified, and therefore incurable with any conventional multimodality approach. All patients had immunohistochemical documentation of *c-kit* and/or PDGFR expression in the primary tumor or metastases by a central laboratory (Oncotest, Netanya, Israel). Eligible patients were those

with a life expectancy of at least 3 months; age >18 years; ECOG performance status 0–3; no chemotherapy, immunotherapy, or radiotherapy within 4 weeks of entering the study; at least one measurable site of disease; adequate organ function (absolute neutrophil count $>1.5 \times 10^9/l$, platelets $>100 \times 10^9/l$), total serum bilirubin $< \times 1.5$ the upper limit of normal, serum alanine aminotransferase and aspartate aminotransferase $< \times 2.5$ upper limit of normal or $< \times 5$ the upper limit of normal if hepatic metastases were present and serum creatinine $< \times 1.5$ of the upper limit of normal. Patients with cerebral metastases or pregnant women were excluded.

Treatment administration

Pretreatment evaluation included a complete history and clinical examination, full blood count, biochemical profile, coagulation profile and pregnancy test for women of childbearing age. CT or MRI studies to evaluate sites of disease were performed up to 4 weeks before starting chemotherapy. Serum calcitonin and CEA levels were also ascertained prior to therapy in patients with medullary thyroid carcinoma (MTC) and urinary catecholamines in patients with malignant pheochromocytoma (Pheo). IM was supplied to the study investigators by Novartis as 100 mg capsules packaged in polyethylene bottles. Patients received IM orally 400 mg/day for an exposure period of up to 12 months, providing that the patient was considered to benefit from the treatment and the absence of safety concerns. In the event of lack of response, the dosage could be increased to 600 mg/day with the option to increase dosage to 400 mg twice daily. Patients were instructed to take the medication with breakfast in the sitting position together with a large glass of water to prevent local irritation and to refrain from caffeine or grapefruit containing foods that affect drug absorption.

Evaluation of toxicity and dose escalation

Drug toxicity was graded using National Cancer Institute Common Toxicity Criteria version 2.0. Toxicity assessment, full physical examination, full blood count, and a biochemical profile were performed weekly during the first month of the study, bi-weekly during the second month and subsequently on a monthly basis for the duration of the study (one year). The algorithms for dose modifications in the event of hematological or

Table 1 Patient characteristics

Patient no.	Gender	Age	Tumor type	Tumor sites	Disease status	PDGF-R	c-kit
1	M	18	MTC (MEN2b)	Neck, lungs, liver	SD	+	+
2	F	62	MTC	Liver	SD	+	+
3	M	71	MTC	Neck, lungs, mediastinum	PD	+	+
4	F	32	MTC	Neck, bone	PD	+	–
5	M	52	MTC	Neck, lung, bone	PD	+	+
6	F	28	MTC	Neck, lungs	PD	–	+
7	F	44	ACC	Lungs, liver, adrenal bed	PD	n.d.	+
8	F	34	ACC	Lungs, liver, adrenal bed	PD	+	+
9	F	49	ACC	Lungs, liver, adrenal bed	PD	+	–
10	M	63	ACC	Lungs, liver, mediastinum	PD	+	+
11	F	56	carcinoid	Liver, retroperitoneum	PD	+	+
12	M	55	carcinoid	Lung, pericard, pleura	SD		
13	F	18	islet cell	Pancreas, liver	PD	–	+
14	M	58	pheochromocytoma	Lungs, liver, retroperitoneum	PD	+	–
15	M	25	pheochromocytoma	Retroperitoneum	PD	+	+

PDGFR-R, platelet derived growth factor receptor; SD, stable disease; PD, progressive disease; n.d., not detected.

non-hematological toxicity are available from the authors upon request.

Disease evaluation and response assessment

Tumor assessments consisted of radiological evaluations (computed tomography scan of disease sites); determination of serum calcitonin and CEA levels in MTC patients; urinary catecholamine determinations in pheochromocytoma patients and clinical assessments. These tests were performed before starting treatment and after three months of therapy. Patients who received treatment for at least three months were evaluable for response. In addition, patients who developed rapid tumor progression or died of progressive disease before the three-month period were considered evaluable for response. Responses to treatment were defined using the WHO criteria.

Results

Fifteen patients with endocrine cancers were recruited into the study. Patient characteristics at baseline are summarized in Table 1. Tumor types (number of patients in parenthesis): MTC (6), ACC (4), carcinoid tumors (2), Pheo (2) and pancreatic neuroendocrine tumor (1). All but three patients had radiological evidence of progressive disease. Two patients had received at least one previous chemotherapy regimen for advanced disease, two patients received experimental treatment with thalidomide and one MTC patient received experimental radio-immunotherapy with ¹³¹I-anti-CEA antibodies. All patients were started on the initial dose of 400 mg IM, four patients reached a dosage of 600 mg/day and six patients 800 mg/day. Treatment duration for each disease is detailed in Table 2. In five patients the drug was

Table 2 Results of treatment

	<i>n</i>	Treatment duration (months)		Complete remission	Partial remission	Stable disease	Progressive disease
		mean ± S.D.	range				
Tumor type							
MTC	6	3.4 ± 2.5	1–6	0	0	2	4
ACC	4	4.9 ± 3	1–7.5	0	0	0	4
carcinoid	2	6	6	0	0	1	1
pheochromocytoma	2	4 ± 0.7	4–5	0	0	0	2
NET	1	3	3	0	0	0	1

Table 3 Toxicity (adverse effects) of imatinib mesylate

	No. (%)
NCI CTC(v 2.0) grading	
Grade 3–4	
Bleeding tendency	3 (20)
Suicide attempt	1 (7)
Grade 1–2	
Fatigue	11 (73)
Anorexia	8 (53)
Nausea	6 (40)
Bleeding tendency	4 (26)

discontinued prior to the initial 3 months evaluation point due to major side effects (Table 3). None of the patients showed an objective anatomical tumor response. One MTC patient displayed an apparent acceleration of tumor growth under IM and developed superior vena cava syndrome. In three patients who had slow growing disease at study entry, the disease remained stable. In the remainder of the patients disease progression was unrelenting despite IM treatment. In the two pheochromocytoma patients, urinary catecholamines levels

were determined prior to and after therapy and were not affected by IM treatment (data not shown). In the patients with MTC pre and post treatment levels of serum calcitonin and carcinoembryonic antigen (CEA) were determined (Fig. 1): in 1 out of 5 patients, a marked decrease in calcitonin level was noted, however in the same patient the CEA level increased. In the remainder of the patients either no change or a slight increase in calcitonin and CEA levels was noted. We noted an unexpected frequency of side effects in our patients (Table 3): nausea, anorexia, fatigue and diarrhea were common and did not lead to withdrawal from the study; tendency to bleed was noted in: five patients with MTC (one of which developed disseminated intravascular coagulation that subsided with drug withdrawal); one patient with ACC and one pheochromocytoma patient. One patient with ACC attempted suicide leading to drug discontinuation. All 4 patients who had grade 3–4 adverse effects (Table 3) were withdrawn from the study.

Discussion

In this study, we examined the effect of IM on progression of disease in a group of patients with metastatic endocrine cancers, within the framework of a comprehensive multi-center study on patients with c-kit/PDGF-R positive solid tumors. Due to the small number of patients in the group as a whole and within each category, and the relatively short duration of treatment due to adverse effects, it is clear that statistically significant conclusions cannot be drawn from this study. However, in view of the rarity of the tumors examined, and the lack of any prior information regarding the effect of IM in these diseases, we believe it is important to report the results of this study.

The largest sub-group of patients treated with IM had MTC. This thyroid neuroendocrine cancer is frequently associated with mutations causing constitutive activation of the *ret* proto-oncogene tyrosine kinase both in premalignant lesions (C-cell hyperplasia) and frank MTC. IM has recently been shown to inhibit *ret* proto-oncogene tyrosine kinase activity in an MTC cell line *in vitro* (Cohen *et al.* 2002, Skinner *et al.* 2003), together with a decrease of either cell replication (Cohen *et al.* 2002) or viability (Skinner *et al.* 2003). Moreover, in the related neuroendocrine tumor neuroblastoma (NBL), IM has recently been shown to inhibit the growth of tumor cells *in vitro* and *in vivo*,

Figure 1 The effect of IM on pre and post-treatment serum levels of calcitonin and carcinoembryonic antigen (CEA) in five patients with MTC

associated with suppression of PDGF-R and *c-kit* phosphorylation (Beppu *et al.* 2004). Thus, pre-clinical evidence suggested a possible beneficial role for IM in MTC patients. In this clinical trial, we did not observe any beneficial effect in any of the MTC patients, in fact there was a significant occurrence of side effects. One patient had rapid tumor growth leading to superior vena cava syndrome, suggesting acceleration of his disease under therapy. The putative anti-cancer effect of inhibition of PDGF-R activity is thought to be due to an anti-angiogenic effect, thus depriving the tumor of its oxygen supply (Adams *et al.* 2002). However, it has recently been shown that tumor oxygen deprivation can be a double-edged sword, since hypoxia induced signaling via the *c-Met* in tumor cells can result in a more aggressive tumor phenotype (Bottaro & Liotta 2003). Since *c-Met* is expressed in some MTC tumors (Papotti *et al.* 2000), it is quite possible that the potential anti-tumor effect of IM in MTC is offset by hypoxia-enhanced aggressiveness of the tumor phenotype. A possible solution to this problem is to treat with a *c-Met* inhibitor in addition to IM.

Pheochromocytoma and NBL are closely related tumors of adrenomedullary origin, both secreting catecholamines. In fact, some malignant pheochromocytomas have a histological appearance similar to NBL, as was apparent in one of the two pheochromocytoma patients enrolled in this study. Expression of *c-kit* has been shown in both normal and neoplastic adrenomedullary tissue (Matsuda *et al.* 1993). *c-kit* has been shown to be a survival factor in NBL (Timeus *et al.* 1997, 2001) and could play a similar role in pheochromocytoma. IM therefore would appear to be of potential therapeutic value in these patients. We did not see a beneficial effect of IM on tumor progression in the two pheochromocytoma patients. However, a ^{123}I -metaiodobenzylguanidine (^{123}I -MIBG) scan that was negative in one patient prior to IM therapy became positive subsequent to treatment, allowing effective treatment of this patient with high-dose ^{131}I -MIBG; in the other patient a pretreatment somatostatin receptor scintigraphy (Octreoscan) became positive subsequent to therapy. These observations are of potential clinical utility and warrant further investigation.

ACC is a rare endocrine tumor originating from the adrenal cortex. This tumor has a dismal prognosis with less than 30% of patients surviving for five years (Wajchenberg *et al.* 2000). The potential roles of *c-kit* and/or PDGF-R in ACC evolution are unknown. However, some patients show *c-kit*

expression in the tumor (Gross DJ, unpublished observations). In view of the dismal prognosis, patients with either *c-kit* or PDGF-R expression were considered candidates for IM. We did not, however, observe any beneficial effect of IM in the four ACC patients treated with IM.

Carcinoid tumors originate from the enterochromaffin cells in the gut or bronchi. Most tumors (~75%) are of midgut origin and are located in the distal ileum. Approximately 40–70% of cases present with multicentric disease. In these cases the five-year survival is approximately 38% (Modlin *et al.* 2003). Carcinoids have been shown to express the PDGF system to a high degree. PDGF-R was found to be expressed on tumor cells and stroma in 70% of tissues examined (Funa *et al.* 1990). These findings suggest that PDGF may be involved in the autocrine stimulation of tumor cells and stimulation of stromal cell growth through paracrine and possibly autocrine mechanisms. Thus, IM-induced inhibition of PDGFR function could be of benefit in these patients. In a preliminary report, IM was found to be of benefit in patients with carcinoid tumor (Oberg 2003), however in a study of 31 patients, 21 of which were concurrently treated with octreotide, only a marginal benefit was observed (Carr *et al.* 2004). In the two carcinoid patients and an additional patient with a pancreatic neuroendocrine tumor in this study, we did not observe any beneficial effect of IM.

In summary, in this pilot study of IM in patients with endocrine malignancies, we did not discern a beneficial effect on the course of the disease. Our findings are in keeping with recent reports on the effect of IM in patients with small cell lung carcinoma, a cancer with a related neuroendocrine phenotype (Gambacorti-Passerini *et al.* 2004, Dy *et al.* 2005, Krug *et al.* 2005). The lack of efficacy in our study might have been due, in part, to the high frequency of adverse effects that required early cessation of therapy in many of the patients, which could reflect our inclusion of patients with advanced disease, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–3, while most phase II studies are restricted to PS 0–2. Further studies on the effect of IM in our patient group may be warranted in conjunction with other therapeutic modalities, such as *c-MET* inhibition.

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