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Imatinib mesylate (STI-571 Glivec®, Gleevec™) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target: Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study

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Abstract

The aim of this study was to assess the antitumour response and time to progression (TTP) of patients treated with imatinib mesylate (Glivec®, Gleevec™, formerly STI-571) who had advanced and/or metastatic gastrointestinal stroma tumours (GIST) or other soft tissue sarcomas (STS). Patients with measurable lesions and adequate organ function were entered. They were treated with imatinib mesylate at the dose of 400 mg twice daily (bid). All tumours were subject to a stringent pathological review by an expert panel. Immunohistochemical expression of KIT expression was evaluated. A total of 51 patients (27 GIST, 24 other STS), median age 53 years, median World Health Organization (WHO) performance score 1, were entered. 71% of the patients had received prior chemotherapy. The most frequent side-effects were anaemia (92%), periorbital oedema (84%), skin rash (69%), fatigue (76%), nausea (57%), granulocytopenia (47%) and diarrhoea (47%). Most of these side-effects were mild to moderate and no patient was taken off study due to side-effects. Skin rash and periorbital oedema frequently seem to be self limiting, despite continued treatment. In GIST patients, the current response rates (RRs) are 4% complete remission (CR), 67% partial remission (PR), 18% stable disease (SD) and 11% progression (PD). 73% of GIST patients are free from progression at 1 year. In the other STS group, there were no objective responses. The median time to progression in this subgroup was only 58 days. Imatinib mesylate is well tolerated at a dose of 400 mg bid. This dose is active in patients with KIT-positive GIST, but patients with other STS subtypes unselected for a molecular target are unlikely to benefit.

Keywords: Gastrointestinal stroma tumours; Sarcoma; Imatinib mesylate

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1. Introduction

Soft-tissue sarcomas (STS) represent 1% of all adult malignancies and are a heterogeneous group of neoplasms whose only common denominator is their derivation from mesenchymal tissue. Surgery to obtain wide margins is usually the first-line of treatment for STS. In the case of lesions of the extremities, the standard of radical, or limb-sparing surgery leaving wide-margins plus radiotherapy has dramatically improved the local control of the disease [1–4]. Radiation therapy as a single primary modality is only used in patients with lesions that are not amenable to surgery because of their tumour size, or the relationship of their tumour to vital anatomical structures [5]. Nevertheless, despite improved rates of local control, many patients still die from metastatic disease.

Chemotherapy is currently used for the treatment of advanced and/or metastatic STS, but only a few cytotoxic drugs have demonstrated activity in this disease. Doxorubicin is the most active single agent, with an associated response rate of approximately 20–25% [6]. Ifosfamide and dacarbazine have also demonstrated activity [6,7]. Although some studies suggested that combination chemotherapy has higher response rates than single-agent doxorubicin therapy [8,9], the largest such study performed by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group and accruing more than 700 patients, showed that there was significantly more myelosuppression with the combinations of doxorubicin and ifosfamide and of cyclophosphamide, vincristine, doxorubicin and dacarbazine, but the response rates were not significantly different [10]. In all of the studies, there was no benefit in terms of survival for patients receiving combination chemotherapy. Therefore, conventional-dose single-agent chemotherapy can still be considered standard treatment for metastatic STS. Gastrointestinal Stroma Tumours (GIST) are a relatively recently described STS subtype, that were previously included with other sarcoma subtypes. GIST have a specific natural history [11] and a high rate of resistance to standard conventional chemotherapy agents (EORTC, data on file).

Imatinib mesylate (Glivec, Gleevec, STI-571) is a small molecule tyrosine kinase inhibitor designed to target c-ABL and BCR-ABL, but is also able to target KIT and the platelet-derived growth factor receptor (PDGFR). KIT is extensively expressed in GIST [11], and *KIT* proto-oncogene is often mutated resulting in activation of the kinase. PDGFR is widely expressed in mesenchymal tissues and the majority of other STS subtypes. A previous EORTC phase I study [12] identified the highest feasible dose of imatinib mesylate to be 400 mg twice daily (bid) in solid tumours, and this dose had extensive activity in GIST. A randomised phase II study exploring lower doses also confirmed activity in GIST [13].

To assess the activity of imatinib mesylate in GIST at the highest feasible dose of 400 mg bid, and to explore potential activity in other subtypes of STS, we performed a phase II study in these patient groups.

2. Patients and methods

2.1. Eligibility criteria

Eligibility criteria included histologically-proven advanced and/or metastatic GIST characterised by KIT expression, or any other subtype of STS, not necessarily selected by KIT expression, graded according to the Trojani system and incurable by surgery or radiotherapy, excluding malignant mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma and embryonal rhabdomyosarcoma.

The immunohistochemical expression of KIT was assessed by standard immunohistochemistry without antigen retrieval using antibodies obtained from DAKO (Dakopatts, Glostrup, Denmark). Mast cells served as an internal positive control in tumour-negative cases; in other STS cases staining in parallel was performed on a GIST with a known expression as an external positive control.

Patients had to have at least one measurable target lesion with a minimum size of at least one diameter $\geqslant 2$ cm, or $\geqslant 1$ cm if measured on spiral computed tomography (CT) scan, with evidence of progression within 6 weeks prior to study entry: No more than one line of previous combination chemotherapy or two single-agent regimens were allowed. The chemotherapy should have been discontinued for more than 4 weeks; for GIST, patients who had not been previously treated were also eligible: Patients had to have had no previous radiation therapy to the sole index lesion used to assess response and be aged greater than 15 years with a World Health Organization (WHO) performance status <2; an absolute neutrophil count more than 1.5×10^9/l; platelet count more than 100×10^9/l; serum creatinine $\leqslant 120$ micromol/l or calculated creatinine clearance (Cockcroft method) >1.1 ml/s; total bilirubin $\leqslant 30$ micromol/l; no co-medication with warfarin was allowed. All patients gave their written informed consent. Histology was centrally reviewed and the expression of KIT was assessed by immunohistochemistry at one of the reference centres.

2.2. Prestudy and follow-up investigations

Before the first and all subsequent treatment courses, a physical examination was performed. Electro-

cardiography and chest radiography were performed at baseline and repeated every 8 weeks.

Before the study and every 4 weeks thereafter, total bilirubin. alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, sodium, potassium, calcium, glucose, creatinine, and albumin levels were measured. White Blood Cells (WBC), neutrophil, and platelet counts and haemoglobin levels were performed weekly. Tumour assessments were performed every 8 weeks until month 6, and every 3 months thereafter until the end of treatment. Standard Response Evaluation Criteria in Solid Tumours (RECIST) criteria [14] were used for evaluating response and all responses were subject to independent review. The duration of partial response or no change was calculated from the date of registration to the date of documented progression, and the duration of complete response noted to the documented time of progression. Time to progression (TTP) was calculated from the date of registration to progression or last contact. Duration of survival was calculated from the date of registration to the date of death.

Toxicity was graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

2.3. Treatment and dose modifications

Imatinib mesylate (Novartis, Basle, Switzerland) was supplied as 100 mg yellow hard gelatine capsules packaged in polystyrene bottles, and administered orally at a dose of 400 mg bid, continuously. Imatinib mesylate was to be taken directly after a meal. There was no prophylactic co-medication. All patients were scheduled to continue treatment until disease progression, or unacceptable toxicity.

If the neutrophil count became less than 1.0×10^9/l or the platelet count was less than 50×10^9/l, treatment was withheld until recovery to grade 1 and then restarted at a daily total dose of 600 mg. If similar toxicity recurred, a further dose reduction to 400 mg daily was permitted. For any grade $\geqslant 2$ non-haematological toxicity, the drug was to be withheld until recovery to grade 1. It could than be resumed at the same daily dose. If grade $\geqslant 2$ non-haematological toxicity recurred, imatinib mesylate was again withheld and upon recovery the dose was reduced to 600 mg daily, or (if necessary) further reduced to 400 mg daily.

2.4. Statistical analysis

The study was designed as a two strata phase II study evaluating response, using a Fleming one-stage design testing procedure, with P_0 taken as 10%, P_1 as 30%, α as 0.1 and β as 0.1. Under these hypotheses, 24 evaluable patients per stratum were required.

3. Results

3.1. Patient characteristics

A total of 51 patients (27 GIST, 24 other STS) were entered onto the study by 13 centres over a 2-month period. Patients' characteristics and pathological diagnosis following external review are listed in Table 1. Diagnostic criteria used are detailed elsewhere [15]. All GIST were shown to express membranous KIT. In the other STS group, none of the tumours was KIT-positive.

2 patients in the other STS group were formally ineligible, because they had not received any prior chemotherapy. All analyses were performed on an intent-to-treat basis.

The median time on treatment was 13+ months for the GIST patients and 2 months for the other STS patients.

3.2. Toxicity

No patient discontinued therapy because of toxicity. The side-effects are listed in Table 2. The most frequent side-effects were anaemia (92%), oedema (particularly periorbital oedema) (84%), skin rash (69%), fatigue (76%), nausea (57%), granulocytopenia and diarrhoea (47%). Most of these side-effects were mild to moderate and tended to occur in the first 8 weeks of treatment. Although the numbers are small, the decrease of side-effects did not seem to be related to dose reductions (data not shown). Periorbital oedema showed as puffy

Table 1
Patients' characteristics

No. of patients entered	51
Gender	
Male/female	67%/33%
Age (years)	
Median (range)	53 (21–75)
WHO performance score	
Median (range)	1 (0–1)
Prior treatment	
Surgery	88%
Radiotherapy	24%
Chemotherapy	71%
Histology	
GIST	27
Liposarcoma	6
Leimyosarcoma	4
Fibrosarcoma	3
Synovial sarcoma	3
Unclassified	3
Miscellaneous	5

WHO, World Health Organization; GIST, Gastrointestinal Stromal Tumours.

Table 2
Side-effects (worst per patient; %)

Side-effect	Grade (NCI-CTC)				
	0	1	2	3	4
Granulocytopenia	53	31	10	4	2
Anaemia	8	49	31	10	2
Oedema	16	49	35	–	–
Fatigue	24	29	35	12	–
Chills	80	20	–	–	–
Rash	31	43	12	14	–
Anorexia	61	19	14	6	–
Diarrhoea	53	27	16	4	–
Nausea	43	35	18	4	–
Vomiting	57	33	4	6	–
Bleeding	92	2	–	4	2

NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

eyes and mainly involved the skin above the eye. Skin toxicity existed mainly of erythema that sometimes became crusty. Just like the periorbital oedema, it was most frequently self-limiting in most patients experiencing these side-effects, despite continued treatment. Oedema, skin rashes and nausea decreased in severity over time (Fig. 1).

3.3. Response

All responses reported were subject to peer review and responses were classified according to the RECIST criteria. In an intent-to-treat analysis, in the GIST patients the current response rates are 4% complete remission (CR) ($n=1$), 67% partial remission (PR) ($n=18$), 19%

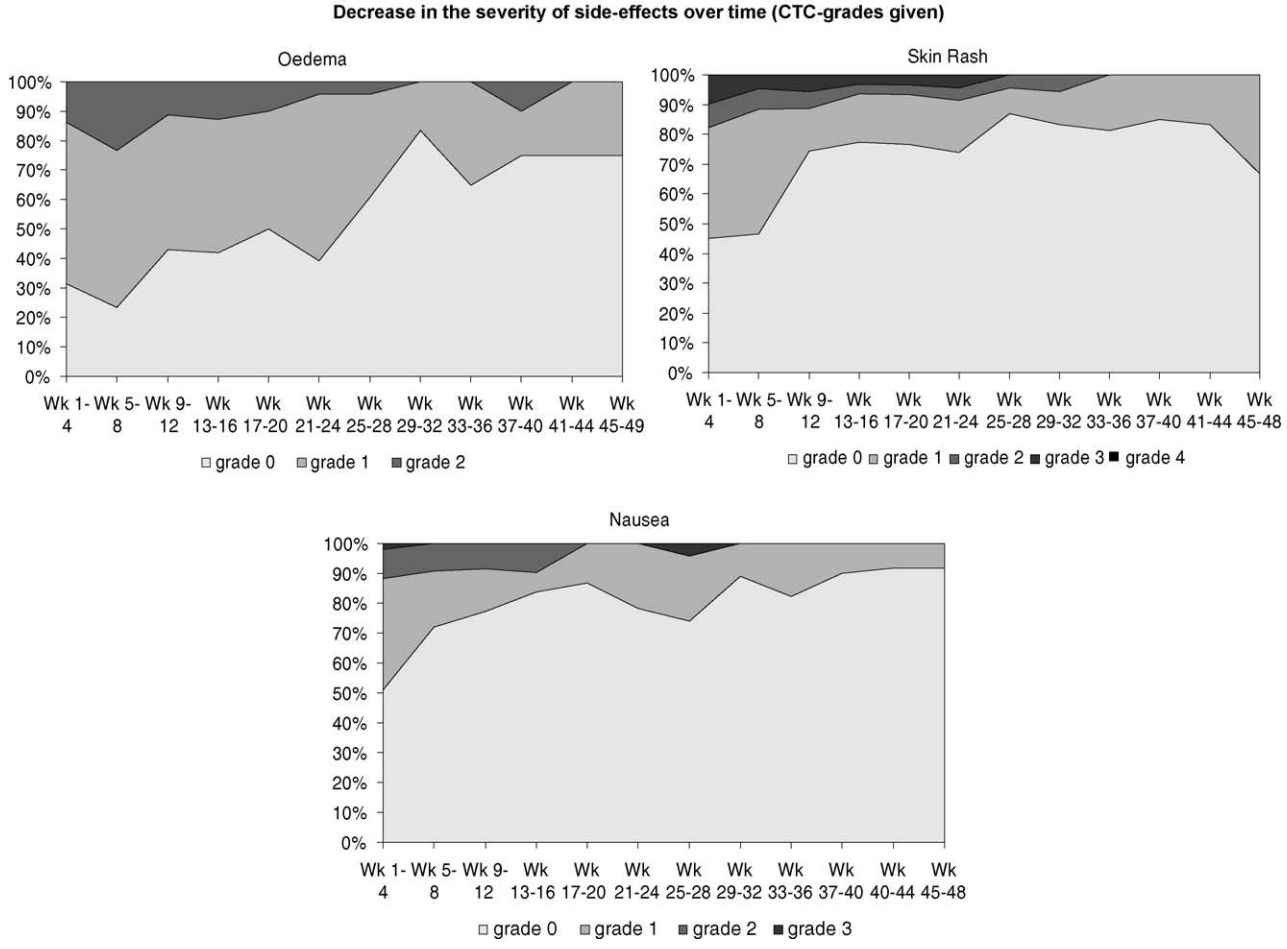

Fig. 1. Decrease in the severity of side-effects over time: (a) Oedema; (b) skin rash; (c) nausea. CTC, Common Toxicity Criteria; Wk, week.

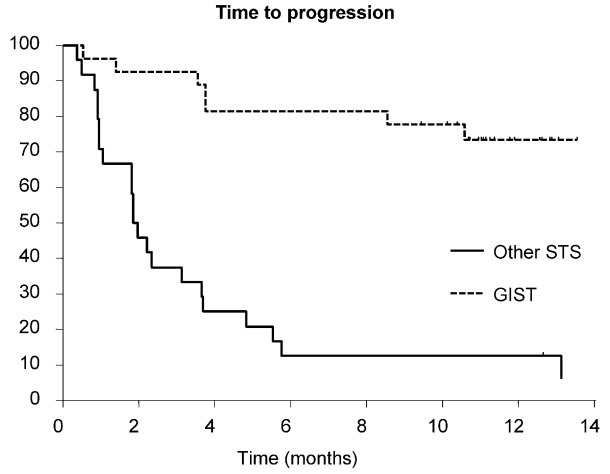

Fig. 2. Time to progression, by histology: GIST versus other soft-tissue sarcomas (STS).

stable disease (SD) ($n=5$) and 11% progression (PD) ($n=3$). While some patients responded early after the start of treatment, in others this response took a long time to occur. The median time to onset of response was 113 days. Responses and stable diseases seem to be long-lasting, with 73% of GIST patients free from progression at 1 year (Fig. 2).

In the other STS group, there were no objective responses or regressions, and only 29% of patients experienced a stable disease with an estimated duration of 176 days. The median time to progression in this group of patients was 58 days (Fig. 2).

4. Discussion

The treatment of metastatic STS continues to be difficult because of a paucity of active agents. The only two agents with proven activity are doxorubicin and ifosfamide [6–10], and these lack activity in the subset of GISTs for which there is currently no standard medical treatment (EORTC, data on file).

Imatinib mesylate is a protein-tyrosine kinase inhibitor which potently inhibits the ABL tyrosine kinase (TK) *in vitro* and *in vivo*. The drug was found to be highly active in clinical studies in chronic myeloid leukaemia (CML) expressing the fusion protein BCR-ABL [16].

In addition, imatinib mesylate is a potent inhibitor of the receptor tyrosine kinases for PDGF and stem cell factor (SCF), and inhibits PDGF- and SCF-mediated biochemical events [17]. The tyrosine kinases are a family of phospho-transferase enzymes that include many growth factor receptors and are frequently products of proto-oncogenes. Furthermore, PDGF has been suggested to be a major mitogen for connective tissue cells. In almost all sub-types of STS, overexpression of PDGF has been reported, while KIT overexpression although not strictly specific, is highly suggestive of a diagnosis of GIST for sarcomas arising in the digestive tract or abdomen [11,15]. After oral administration, imatinib mesylate is rapidly absorbed with a dose-proportional exposure up to 1000 mg/day, albeit with large interindividual variations, and the terminal half-life ($t_{1/2}$) is 10–23 h, resulting in 2–3-fold accumulation of drug at steady state.

A previous EORTC phase I study [12] identified the highest feasible dose of imatinib mesylate in solid tumors to be 400 mg bid. Importantly, the objective response rate in GIST patients was as high as 69% and only 11% of the patients progressed, while 89% of symptomatic patients experienced total relief from symptoms, or major symptom improvement. A randomised phase II study, exploring lower doses, confirmed activity in GIST [13].

To assess the activity of imatinib mesylate in GIST at the highest feasible dose of 400 mg bid, and to explore potential activity in other subtypes of STS, we performed a phase II study in these two groups.

In 27 GIST patients, we confirmed activity that is similar to that observed in our phase I study [12]. Interestingly, this activity seems to be higher than that reported in the United States (US) study [13]. Whether the difference is related to a difference in the applied dose, or simply to patient selection bias, remains to be elucidated. Recently two parallel phase III studies have been performed, one co-ordinated by the South West Oncology Group (SWOG), the other co-ordinated by the EORTC. Both studies compared a daily dose of 400 mg to one of 800 mg. Given the interpatient variation in pharmacokinetics, it is more likely that these large studies will be able to detect a dose–response relationship if there is one, than the above mentioned study [12], that was not designed or intended for this purpose. The SWOG study accrued 746 patients, the EORTC-Italian Sarcoma Group (ISG)-Australasian Gastro-Internal Tumor Group (AGITG) study 946 patients, both accrued patients in less than one year. Despite this rapid accrual and the recent study closure, it will be several years before the question of a possible dose–response relationship can be answered, especially with respect to response duration.

There is evidence that patients with different mutations of the KIT receptor respond differently to treatment. In the (randomised) phase II study, comparing 400 with 600 mg/day, Blanke and colleagues [18] reported a 70% response rate (RR) in patients with a mutation of exon 11 (the majority of patients), but in patients with wild-type KIT or mutations in exon 9, this rate was less than 20%. In 24 patients with KIT-negative STS other than GIST in this study, there were no objective responses and only one long-lasting SD was observed in a patient with a previously clearly progressive liposarcoma. This is in total contrast to the findings in GIST, and in line with the data for inactive agents as previously studied by EORTC [19]. The other STS tumours were not selected for PDGFR expression, since

based on previous reports this was assumed to be a common feature. The lack of clinical activity in this group may be due to a less important role for PDGF in tumour growth, particularly in STS, or may be related to the reduced sensitivity of PDGFR to imatinib mesylate, leading to the need for a higher dose for inhibition. Our results at the very least suggest that patients with STS that lack KIT expression should not be offered imatinib mesylate treatment outside of specific study protocols. It is likely that such patients should only be considered for imatinib mesylate treatment within study protocols if there is evidence of KIT expression and perhaps only in the presence of an exon 11 mutation of KIT, given the relative insensitivity of tumours with wild-type receptors or other activating mutations.

The toxicity of imatinib mesylate given at a dose of 800 mg daily was manageable. Skin rash and periorbital oedema seem to be self-limiting despite continued treatment in most patients experiencing these side-effects. Bleeding at tumour sites, a feature known to be related to GIST, also occurred, but was not common and was never considered to be a severe event. Whether the occurrence of haemorrhage soon after the initiation of treatment was disease- or drug-related or both is unclear. Further studies should help to elucidate this. The profile of side-effects confirms the impression reported in the extended part of the published phase I study [12], that the drug at this dose is generally safe. This profile may reflect the presence of the drug target KIT on normal cells outside the digestive tract such as mast cells, melanocytes, basal cells of the epidermis and salivary gland epithelium.

In conclusion, imatinib mesylate is well tolerated at a dose of 400 mg bid. This dose is highly active in patients with c-KIT-positive GIST, but patients with other STS subtypes unselected for a molecular target are unlikely to benefit. Further studies in GIST are currently exploring the possibility of a dose–effect relationship.

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