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Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg

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Abstract

In the EORTC-ISG-AGITG trial 946 patients with advanced gastro-intestinal stromal tumours (GIST) were randomised to receive 400 or 800 mg of imatinib daily. An increase in progression free survival (PFS) was demonstrated for patients randomised to the high-dose arm. Patients randomised to low-dose could cross-over to high-dose upon progression. We evaluated the feasibility, safety and efficacy of this policy. Of the 241 patients available for follow-up, 133 patients (55%) crossed over to high-dose imatinib according to the protocol. Of these patients, 92% had not had a prior dose reduction. The cumulative incidence of subsequent dose reductions after cross-over was 17% after six months with 51% discontinuing therapy without requiring a dose reduction. The extent of anaemia and fatigue increased significantly after cross-over, whilst neutropenia was less severe than during low-dose treatment. Objective responses after cross-over included three patients (2%) with a partial response and 36 (27%) with stable disease. The median PFS after cross-over was 81 days, although 18.1% of patients were still alive and progression free one year after cross-over. We conclude that a cross-over to high-dose imatinib is feasible and safe in GIST patients who progress on low-dose therapy.

Keywords: Imatinib; GIST; Dose effects; Progression

1. Introduction

Gastrointestinal stromal tumours (GIST), usually defined as c-KIT-positive mesenchymal neoplasias, mostly

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arise in the stomach and small bowel. Tumours generally present with activating KIT mutations, a fundamental step in the development of disease [1]. Although surgical resection is the standard of care for primary GIST, roughly one half of patients with localised GIST relapse after adequate surgery [2]. For metastatic GIST imatinib mesylate, a small molecule tyrosine kinase inhibitor active against BCR-ABL, KIT and PDGFR, is the standard of care.

Although the recommended dose of imatinib in GIST is 400 mg daily, a phase I study [3] identified the highest feasible dose of imatinib as 800 mg per day and two studies [4,5] have used doses ranging from 400 to 800 mg daily. Two very similar, large phase III studies [6,7], comparing the registered and the highest feasible doses of imatinib in patients with metastatic GIST have been conducted. In the recently reported EORTC-ISG-AGITG international, intergroup study [6], the response rate was the same with either dosage but progression-free survival (PFS) was significantly better in patients treated with 800 mg compared with 400 mg daily. In a preliminary analysis of the US/Intergroup study [7], 400 mg daily was also found to be equivalent to 800 mg daily with respect to response rate, and while the curves for PFS, and overall survival (OS) at 12 months also diverged, this did not reach statistical significance.

In both of these trials, patients initially randomised to receive 400 mg of imatinib daily could cross-over to 800 mg daily upon disease progression. The objective of this analysis is to report the results seen with the higher dose of imatinib with respect to the feasibility, safety and efficacy of this policy in patients in the EORTC-ISG-AGITG study who crossed over according to the study protocol.

2. Patients and methods

2.1. Study design

Details of the trial design and method have been published previously [6]. Briefly, the EORTC-ISG-AGITG trial was a randomised, phase III study designed to compare the impact of high-dose (800 mg daily) imatinib or standard dose (400 mg daily) imatinib on the primary outcome of PFS. After written informed consent had been obtained, patients with histologically proven, advanced and/or metastatic GIST characterised by c-KIT expression were randomised to receive either 400 mg of imatinib administered orally once daily, or 400 mg twice daily continuously. All patients were scheduled to continue treatment until disease progression or unacceptable toxicity. Local ethics board approval was obtained in all participating institutions.

Physical examination, haematology and chemistry profiles were recorded weekly in the first two months, monthly between months three and six, and three-monthly thereafter. Computed tomographic (CT) scans were performed after two, four and six months and three monthly thereafter until disease progression. Tumour responses were judged using standard RECIST criteria [8]. Complete and partial responses were confirmed at the next planned visit for disease evaluation. The duration of complete response was calculated from the date of registration to the date of documented progression. National Cancer Institute Common Toxicity Criteria version 2.0 were used to grade toxicity.

In cases of disease progression in patients randomised to the 400 mg daily dose, a cross-over to the 800 mg daily dose was allowed regardless of the dose of imatinib the patient was taking at the time of progression. However, an escalation to a dose lower than 800 mg daily was not allowed. Patients who continued to progress despite a cross-over to 800 mg daily were removed from the trial, discontinuing further study drug.

The objective of the present analysis is to evaluate the feasibility of crossing over to the higher dose of imatinib at the time of progression, as well as the outcome of patients who did cross-over. Feasibility was estimated by evaluating the fraction of patients on low-dose imatinib with progression who crossed over to high-dose imatinib. Outcome end-points included the cumulative incidence of subsequent dose reductions (with treatment discontinuation as a competing risk); intra-patient comparisons of toxicities observed at low-dose *versus* high-dose imatinib as well as objective response rate and progression free survival after cross-over.

2.2. Statistical methods

Competing risk methods [9] were used to estimate the cumulative incidence of dose reductions; treatment discontinuation without prior dose reduction was considered as a competing risk. Intra-patient comparisons of toxicities observed at low-dose and high-dose were performed using a McNemar paired test.

Objective response after cross-over was evaluated using the RECIST criteria. The measurements performed at the time of cross-over were taken as baseline reference for this purpose. PFS was measured from the date of cross-over to the date of documented progression or death (whatever the cause) and estimated by the Kaplan–Meier method.

The Growth Modulation Index (GMI) was employed as a measure of the activity of second-line treatment. The GMI was defined for each patient as the ratio between time to progression observed after cross-over (with a daily dose of 800 mg) and the time to progression observed before cross-over (with an initial daily dose of 400 mg). A relative increase of at least 33% in the time to second progression (TTP2) as compared to the time to first tumour progression (TTP1) has been

suggested to indicate the activity of the agent being tested [10,11].

3. Results

3.1. Patient characteristics following progression on low-dose imatinib

At the time of the analysis (April 2004), 247 of the 473 patients randomised to the low-dose arm had progressive disease (PD). The median follow-up from randomisation was 25 months with a maximum follow-up of 35 months. Of the 241 patients with follow-up information, 133 (55%) crossed over to high-dose imatinib (800 mg daily) according to the study protocol. Seventy-four patients (31%) continued treatment with imatinib but not according to the study protocol. Of these, there were 43 cases (18%) where the dose was not increased to 800 mg; 22 patients (9%) continued treatment at the 400 mg dose level for at least two months and only subsequently was the dose increased to 800 mg, and in nine patients (4%), the dose had already been increased to 800 mg before the documentation of disease progression. In 34 patients (14%), imatinib was stopped upon disease progression.

Of those 241 patients, 38 (16%) required a dose reduction before progressing. However, the proportion of patients who crossed-over according to the protocol was lower (29%) in the group requiring dose reductions on the 400 mg dose compared to the 60% of patients with no prior dose reductions who subsequently crossed over (Table 1). Looked at another way, of the patients who crossed over to the higher daily dose according to the protocol, over 92% had not required a dose reduction prior to the documentation of PD at the lower starting dose of imatinib. By comparison, in those patients crossing over to high-dose imatinib but not according to study protocol, 70% did not require a dose reduction.

The remaining analyses in this report are based on the 133 patients who crossed over to high-dose imatinib according to the protocol recommendations within two months of documented progression. Baseline characteristics for these patients are presented in Table 2. Of these 133 patients, discontinuation of imatinib has since been documented in 97 patients. At the time of analysis, the median time on treatment after cross-over was 112 days (95% confidence interval: 83–154 days). According to an actuarial analysis (Kaplan–Meier), 23% of the patients (standard error: 4%) were estimated to still be on imatinib treatment one year after cross-over (Fig. 1). Disease progression was the cause of discontinuation in 88.4% of patients.

The cumulative incidence of dose reductions after cross-over is displayed in Fig. 2. The occurrence of dose reductions and the proportion of discontinuations without dose reduction are presented as competing risks. Six months after cross-over, 17% of patients required a dose

Table 2
Patient characteristics – 133 patients who crossed over according to protocol

	Median	Range
Age (years):	59	20–85
	N	%
Gender		
Male	87	65
Female	46	36
PS at study entry		
0	63	47
1	49	37
2	12	9
3	9	7
Primary site of disease		
Gastro-intestinal	109	82
Gastric	34	26
Small bowel	35	26
Duodenum	20	15
Other GI	20	15
Other abdominal	20	15
Retroperitoneal	4	3
Time since primary diagnosis		
<12 months	70	53
12–24 months	29	22
>24 months	34	26
Site of active disease at study entry		
Primary tumour	50	38
Liver	96	72
Lung	16	12
Ascites	12	9
Pleura	4	3
Bone	3	2
Skin	3	2
Prior therapy		
Surgery	116	87
Radiotherapy	6	5
Chemotherapy	51	38

PS, performance status.

Table 1
Impact of dose reduction before cross-over

	Dose reduction before progression		Total
	No	Yes	
Cross-over to 800 mg acc. to protocol	122 (60%)	11 (29%)	133 (55%)
Continued imatinib not acc. to protocol	51 (25%)	23 (61%)	74 (31%)
Stopped imatinib	30 (15%)	4 (11%)	34 (14%)
Total documented progressions	203	38	241

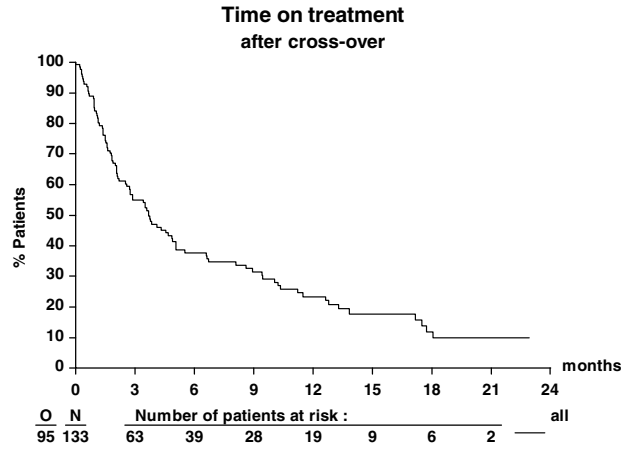

Fig. 1. Time on treatment after cross-over. Median time on study after cross-over was 112 days (95% CI: 83–154 days). O, number of patients stopping treatment after cross-over; N, number of patients with cross-over; Number of patients at risk, number of patients still in follow-up.

reduction and 51% of patients had discontinued protocol therapy (without dose reduction). In comparison, amongst patients initially treated at 800 mg daily, 49% required at least one dose reduction within the first six months.

3.2. Toxicity

Toxicity after cross-over was compared to the same toxicity observed in the same patient before cross-over (Table 3). Anaemia and fatigue were significantly more likely to be worse after cross-over ($P = 0.015$ and $P = 0.00001$ respectively). Haemoglobin count decreased by a median of 10% within the first eight weeks after cross-over, and then remained stable. This is consistent with what was observed after initial treatment with imatinib [6]. Neutropenia was slightly less acute after cross-over ($P = 0.002$). All other toxicities were no more likely to have increased *versus* decreased in severity after cross-over.

3.3. Response to therapy

Objective responses observed after cross-over are summarised in Table 4. At the time of this analysis three partial responses have been observed and 36 patients have displayed further disease stabilisation. This represents 2.3% and 27.1% of the whole cohort respectively. For the 39 patients who demonstrated either stable disease or an objective response, the median duration of documented stabilisation (from the date of cross-over to the last documentation of stable disease) was 153 days (range 37–574 days).

PFS is shown in Fig. 3. The median PFS (Kaplan–Meier estimates) after cross-over is 81 days. Sixty-seven patients (53.3%) progressed or died within three months

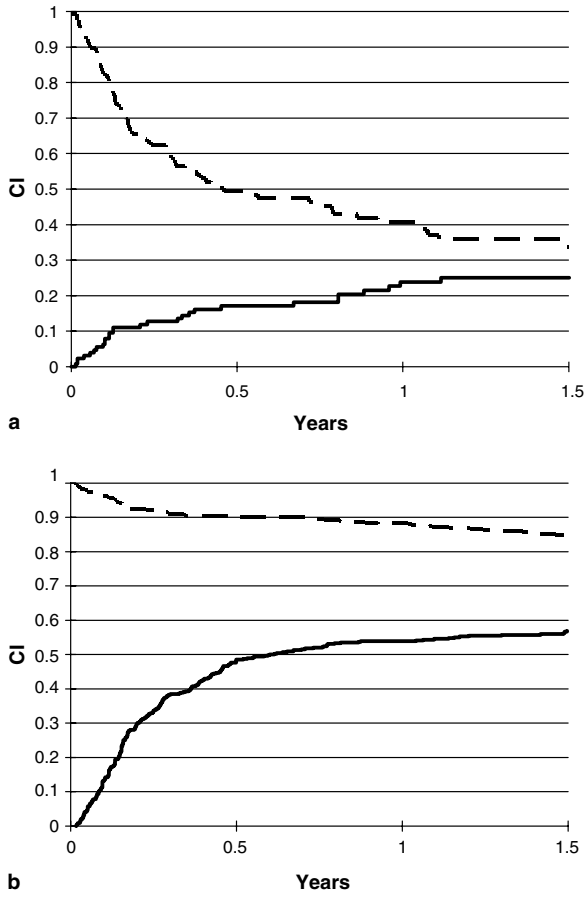

Fig. 2. Cumulative incidence of dose reductions and discontinuations. Dose reductions and the proportion of discontinuations without dose reduction are presented as competing risks. (a) The cumulative proportion of patients who needed a dose reduction after cross-over to a daily dose of 800 mg (lower curve). The cumulative proportion of patients who discontinued therapy before dose reduction is represented on the same graph (upper curve) from top to bottom. (b) The cumulative incidence of dose reduction (lower curve) and discontinued therapy (upper curve) from the start of protocol therapy for patients randomised to the high-dose arm. CI = cumulative incidence.

while 18.1% were still alive and progression free after one year. A competing risk analysis (considering progression and death without progression as competing risks) shows that the estimated one-year failure rate in 81.9% of patients consists of 77.5% progression and 4.4% deaths without progression. TTP1 of the same patients has been reported on the same graph (dotted line). It should be underlined that the TTP1 and first PFS are identical in this cohort of patients who crossed over at the TTP1, and therefore were all still alive by definition.

At the time of analysis, a total of 110 patients were assessable using the GMI. Although these results are still premature (the total duration of TTP2 is not yet evaluated for all patients) 27 patients have demonstrated an increase of at least 33% in TTP2 compared to TTP1. Amongst the three partial responders, two had a GMI greater than 1.33 and one was not assessable as yet. Amongst the 36

Table 3
Toxicity after *versus* before cross-over – patients with 60 days follow-up

	No toxicity	Same level	More severe before cross-over	More severe after cross-over	New grade 3–4
Oedema	25	41	25	33	7
Skin rash	79	3	23	19	2
Fatigue	22	34	21	47	10[a]
Dyspnoea	94	8	8	14	1
Infection	104	2	9	9	1
Nausea	42	18	38	26	3
Leucopenia	65	15	25	16	0
Neutropenia	72	6	30	13	0[b]
Thrombocytopenia	114	1	4	2	0
Anaemia	2	53	15	51	17[c]

[a] $P = 0.00001$.
[b] $P = 0.002$.
[c] $P = 0.015$.

Table 4
Response to treatment after cross-over (RECIST criteria)

	N	%
Partial response	3	2.3
Stable disease	36	27.1
Progression	79	59.4
Not evaluable	1	1.1
Too early	14	–
Total	133	

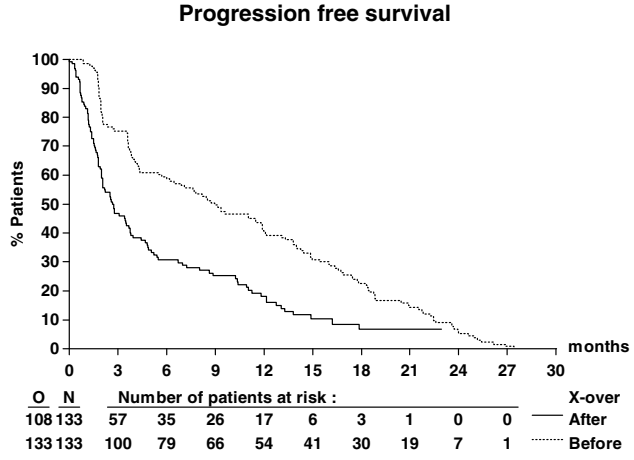

Fig. 3. Progression free survival (PFS) after cross-over (solid line) and time to first progression of the same patients (dotted line), in patients who crossed over to high-dose imatinib according to protocol. Median PFS after cross-over is 81 days. O, number of patients stopping treatment after cross-over; N, number of patient with cross-over; Number of patients at risk, number of patients still follow-up.

patients with disease stabilisation, 13 had a GMI greater than 1.33 although 11 were not yet assessable.

4. Discussion

Our study has demonstrated that in a proportion of patients with advanced GIST with disease progression on the 400 mg daily dose of imatinib, a dose increase to 800 mg daily leads to further therapeutic activity. However, this practice led to a significant increase in anaemia and fatigue although less neutropenia was documented after cross-over. The severity of other toxicities was similar to those occurring prior to cross-over despite a doubling of the dose. Overall, toxicity after dose doubling remained easily manageable and dose-reductions were rarely necessary.

Prior to the year 2000, there was no effective systemic therapy for patients with unresectable or metastatic GIST. Indeed, attempts to treat this disease with conventional cytotoxic chemotherapy have been widely accepted as futile [12,13]. Given the previously poor outlook in patients with this disease, the initial results of treatment with imatinib in GIST were particularly impressive [3–5]. However, despite a daily dose of 400 mg being registered for treatment of GIST, the optimal dose of imatinib for this disease remains unknown. We recently reported prolonged PFS in patients randomised to a dose of 800 mg daily compared to the control group, randomised to 400 mg daily [6]. Early results of a US phase III trial [7] showed the same trend, although the result was not statistically significant, possibly because this slightly smaller study was not designed or statistically powered to demonstrate a difference in PFS.

Importantly, the presence of a clinically relevant dose response had not been ruled out by the early clinical experience with this agent and it is possible that higher doses of imatinib in patients developing imatinib resistance after response to an initial dose of 400 mg daily (defined as "secondary resistance") would again yield relevant responses or absence of progression. Alternatively, higher doses of imatinib could prove not to be, or be only minimally more effective but potentially more toxic. It was, therefore, logical to specifically analyse the effectiveness of the higher dose of imatinib in those patients with progression whilst on low-dose therapy.

At the time of the current analysis, 247 patients randomised to the low-dose arm had progressed. Despite the study design recommending that patients progressing on the standard dose cross-over to the 800 mg daily dose, only 55% of these patients crossed over to the high-dose arm. As dose reductions had been observed in a substantial proportion of the patients, we investigated whether the proportion of patients who crossed over was different in patients who had needed a dose reduction before progression. As shown in Table 1, the total proportion of patients who remained on imatinib therapy was not substantially different [(34/38) 89% *versus* (173/203) 85%], but the proportion of patients who crossed over according to the protocol was lower in the group requiring a prior dose reduction (29% *versus* 60%). This suggests that toxicity resulting in previous dose reductions was the main reason that patients did not cross-over according to protocol with 38% of patients experiencing at least one Grade 3 or 4 toxicity [6]. Indeed, 43 patients in the low-dose arm continued imatinib, albeit at a dose of less than 800 mg daily. As the current analysis is based on the 133 patients crossing over to the high-dose arm according to the protocol, it is unclear whether a dose increase to less than 800 mg daily can be effectively employed in routine clinical practice.

In the cohort of 133 patients, the median time on treatment after cross-over was 112 days (four months), although 23% of patients were still on treatment 12 months after cross-over. Disease progression rather than toxicity was the cause of discontinuation in 88.4% of patients. Compared to patients treated with an initial daily dose of 800 mg, cross-over from low-dose to high-dose appeared to be well tolerated. It has been shown that there is a trend towards increased imatinib clearance with time, which may in part explain the apparently better tolerance of the drug after initial exposure to a lower dose [14]. Six months after cross-over, only 17% of patients had required a dose reduction. However, the number of patients discontinuing treatment without dose reductions (due to PD) was substantially greater in the cross-over group compared to those patients initially treated with 800 mg daily.

After cross-over, a significant increase in anaemia and fatigue was documented but the severity of other toxicities was similar despite a doubling of the imatinib dose. Data on dose reductions and toxicities should however, be interpreted with care as patients were a selected group (only 8% of patients with a prior dose reduction were able to cross-over), and the duration of therapy was shorter. In contrast, neutropenia was more likely to improve than to get worse after cross-over. This observation is in keeping with previous trials in which the majority of side effects occurred early during the course of treatment [4,6], and again may be explained by the increase in drug clearance over time [14]. Taken together these changes suggest that the increase in the severity of anaemia and fatigue were due to disease progression as well as potentially drug toxicity.

Following cross-over, the non-progression rate (PR + SD) to the higher dose of imatinib was 29.4%. The median PFS was only 81 days (11.5 weeks), although 18.1% of the patients were still alive and progression free one year after cross-over. These results are mirrored by the US phase III trial [7] presented in abstract format at the American Society of Clinical Oncology meeting in 2004. The response rate and PFS in patients that crossed over in that trial were reported as 36% and four months respectively. The GMI comparing TTP after cross-over (TTP2) to TTP before cross-over (TTP1), was greater than 1.33 in 27/110 patients. This suggests that second-line therapy with higher dose imatinib is active [11]. Based on these three criteria (response rate, clinically relevant percentage of patients still on treatment and progression-free at one year and a GMI of 25%), we conclude that a dose increase of imatinib following progression on the standard dose of imatinib of 400 mg daily, *i.e.*, after the development of secondary resistance, may lead to further therapeutic activity in a significant proportion of patients. At this point, it is unclear whether the population of patients who might benefit from this approach can be selected based on pre-treatment phenotypic or genotypic characteristics, although these analyses are underway.

It should be noted that this analysis has several limitations and should be considered as descriptive only. It can be used however, to generate hypotheses regarding the role of the dose of imatinib for the treatment of secondary resistance in patients with advanced GIST. The median follow-up is still relatively short given the impact of imatinib in advanced GIST (median follow-up (actuarial) estimate after cross-over is 403 days), only 55% of patients crossed over to the higher dose of imatinib according to protocol and finally the statistical power of the current analysis is compromised because the number of patients and events available for assessment is still relatively small. Nevertheless, as indicated in Fig. 3 and Table 4, benefits were seen in PFS and response rate respectively following cross-over to high-dose imatinib.

In conclusion, imatinib is the first biological agent that has been demonstrated to be of benefit in patients with GIST. These data suggest that patients progressing on an initial daily dose of 400 mg may benefit from a higher dose of imatinib before considering other modalities of therapy.

Conflict of interest statement

Professor John Zalcberg, Jean-Yves Blay and Professor Ian Judson have received travel support from Novartis as well as honoraria for speaking engagements and as members of various Novartis Advisory Boards.

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