Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

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Summary

Background **Imatinib is approved worldwide for use in gastrointestinal stromal tumours (GIST). We aimed to assess dose dependency of response and progression-free survival with imatinib for metastatic GIST.**

Methods **946 patients were randomly allocated imatinib 400 mg either once or twice a day. Those assigned the once a day regimen who had progression were offered the option of crossover. The primary endpoint was progression-free survival. Analysis was by intention to treat.**

Findings **At median follow-up of 760 days (IQR 644–859), 263 (56%) of 473 patients allocated imatinib once a day had progressed compared with 235 (50%) of 473 who were assigned treatment twice a day (estimated hazard ratio 0·82 [95% CI 0·69–0·98]; p=0·026). Side-effects arose in 465/470 (99%) patients allocated the once daily regimen compared with 468/472 (99%) assigned treatment twice a day. By comparison with the group treated once a day, more dose reductions (77 [16%] *vs* 282 [60%]) and treatment interruptions (189 [40%] *vs* 302 [64%]) were recorded in patients allocated the twice daily regimen, but treatment in both arms was fairly well tolerated. 52 (5%) patients achieved a complete response, 442 (47%) a partial response, and 300 (32%) stable disease, with no difference between groups. Median time to best response was 107 days (IQR 58–172).**

Interpretation **If response induction is the only aim of treatment, a daily dose of 400 mg of imatinib is sufficient; however, a dose of 400 mg twice a day achieves significantly longer progression-free survival.**

Introduction

Gastrointestinal stromal tumours (GIST) are a subgroup of soft-tissue sarcomas with an estimated prevalence of 15–20 per 1 000 000.[1,2] These tumours are thought to arise from Cajal cells in intestinal walls, which are important for intestinal motor function.[3,4] GIST were previously classified as leiomyoma, leioblastoma, or leiomyosarcoma. They are insensitive to conventional chemotherapy[5] and are generally characterised by a gain-of-function mutation of the KIT receptor[6] and, occasionally, of the platelet-derived growth factor receptor α.

The clinical activity of imatinib—a small-molecule tyrosine-kinase inhibitor active against BCR-ABL, KIT, and platelet-derived growth factor—has been confirmed in GIST, both in an EORTC (European Organisation for Research and Treatment of Cancer) phase I study,[7] in which the highest feasible dose of imatinib was identified as 400 mg twice a day, and in phase II studies with doses of 400–800 mg daily.[8,9] Imatinib is approved worldwide for use in GIST, with a usual recommended dose of 400 mg daily. However, we still do not know whether the highest feasible daily dose yields a higher initial response rate or a better progression-free survival than the recommended dose. For this reason, we did a randomised trial to compare imatinib 400 mg once a day with 400 mg twice daily.

Patients and methods

Patients

Between February, 2001, and February, 2002, we recruited patients from 56 hospitals in 13 countries from Europe, Australia, New Zealand, and Singapore into our study. Eligibility criteria included histologically proven advanced or metastatic GIST characterised by c-KIT expression (assessed by DAKO immunohistochemical assay). Patients were not required to have measurable disease, and we did not need histological re-confirmation of malignant disease. Previous chemotherapy was accepted but should have been discontinued for more than 4 weeks. Other eligibility criteria included: age 18 years or older; WHO performance status less than 4; absolute neutrophil count greater than $1{\cdot}5\times10^9$/L; platelet count greater than 100×10^9/L; serum creatinine up to 1·5 times the upper limit of normal (average 180 μmol/L); and total bilirubin less than 1·5 times the upper limit of normal (average 30 μmol/L). The study protocol was approved by institutional review boards according to applicable laws in all participating countries. All patients gave written informed consent.

Procedures

Within 14 days before we started treatment, we did a physical examination and complete blood count, including differential, platelets, and serum chemistry (bilirubin, creatinine, aspartate transaminase, alanine

transaminase, alkaline phosphatase, lactate dehydrogenase, and albumin), and obtained chest radiographs and computed tomography (CT) or MRI scans of involved disease sites. In the first 2 months we repeated the physical examination, haematology, and chemistry tests every week, every month between months 3 and 6, and every 3 months thereafter. We obtained CT scans after 2, 4, and 6 months and every 3 months thereafter, until progression of disease.

To assess treatment response we used standard RECIST criteria.[10] We had to confirm complete and partial responses at the next planned disease evaluation. Duration of complete response was calculated from the date of registration to the date of documented progression. We graded toxic effects with National Cancer Institute common toxicity criteria, version 2.0.

Patients were randomised centrally at the EORTC data centre, via the internet or phone, to receive 400 mg imatinib orally either once a day or twice daily (800 mg daily dose), directly after a meal. A minimisation technique was used, with stratification by hospital, measurability of disease, and performance status. Treatment allocation was not masked. No prophylactic comedication was given. All patients were scheduled to continue treatment until disease progression happened or unacceptable toxic effects arose (toxic effects of grade 3 or 4, which could not be resolved by co-medication or dose reduction).

If the amount of neutrophils fell to less than $1{\cdot}0\times10^9$/L, or platelets to less than 50×10^9/L, we withheld treatment until the patient recovered back to the above levels (grade 2) and then restarted the drug at the initial daily dose. If the toxic effect recurred, we again withheld imatinib until recovery to grade 2 and restarted the drug at a reduced dose of either 300 mg once a day for patients allocated 400 mg daily or 300 mg twice a day for those assigned 400 mg twice daily. If recurrence of grade 3–4 haematological toxic effects happened, the dose was further reduced to 200 mg once or twice a day. No dose reductions were made for anaemia, and we allowed use of epoetin alfa.

If we recorded non-haematological toxic effects of grade 2 or more we withheld treatment until the patient recovered to at least grade 1 and then restarted the drug at the initial daily dose. If the toxic effect recurred, imatinib was again withheld until recovery to at least grade 1 and we restarted treatment at a reduced dose of 300 mg daily for patients allocated 400 mg once a day and 300 mg twice a day for those assigned 400 mg twice daily. In case of recurrence of such non-haematological toxic effects, we reduced the daily dose further to 200 mg once or twice a day. We allowed prophylactic antiemetics after occurrence of nausea or vomiting.

If a patient did not tolerate a daily dose of 200 mg, we took that individual off study. After dose reduction, we did not allow re-escalation. However, in case of disease progression in a patient allocated 400 mg daily we allowed crossover to 400 mg twice daily, irrespective of the dose they were taking at the moment of progression. Crossover to a dose lower than 400 mg twice daily was not allowed.

Statistical analysis

We designed the study to assess whether the higher imatinib dose (400 mg twice daily) would result in at least 10% improvement of progression-free survival compared with the recommended dose (400 mg once daily), which corresponded to a hazard ratio of up to 0·737 by the proportional-hazards method. To detect a difference between regimens, a total of 344 events needed to be recorded (α=0·05, β=0·2). We had to recruit at least 600 patients.

The primary endpoint of the study was progression-free survival. Secondary endpoints were overall survival, response to treatment, and toxic effects. We measured progression-free survival from the date of randomisation to the date of documented progression or death (whatever the cause). Patients who were alive and progression free at last follow-up were censored. Those who had started another anticancer treatment without evidence of progression were followed up until progression or death. We measured overall survival from the date of randomisation to the date of death (whatever the cause). Patients alive at the time of analysis were censored at date of last follow-up. Overall and progression-free survival were estimated by the Kaplan-Meier method. We compared the two treatment groups with a two-sided logrank test. Analysis was by intention to treat.

We used competing risk methods[11] to estimate cumulative incidence of dose reductions (*vs* treatment discontinuation or crossover without previous dose

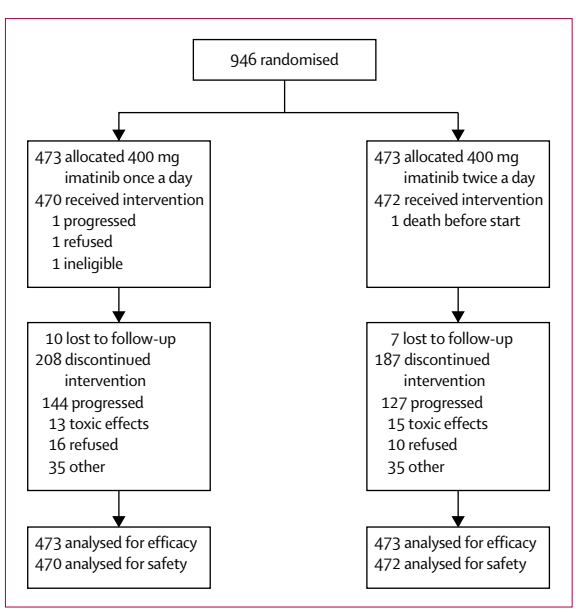

Figure 1: **Trial profile**

	400 mg once a day (n=473)	400 mg twice a day (n=473)
Demographics		
Age (years)	59 (49–67)	60 (49–68)
Men	283 (60%)	290 (61%)
WHO performance score		
0	217 (46%)	219 (46%)
1	191 (40%)	192 (41%)
2	48 (10%)	44 (9%)
3	17 (4%)	18 (4%)
Primary site of disease		
Gastrointestinal	403 (85%)	390 (82%)
Gastric	159 (34%)	157 (33%)
Small bowel	124 (26%)	114 (24%)
Duodenal	53 (11%)	36 (8%)
Omental	20 (4%)	27 (6%)
Rectal	21 (5%)	23 (5%)
Colon	11 (2%)	12 (3%)
Other abdominal	58 (12%)	71 (15%)
Retroperitoneal	12 (2%)	12 (3%)
Time since primary diagnosis		
<12 months	247 (52%)	246 (52%)
12–24 months	83 (18%)	74 (16%)
>24 months	143 (30%)	153 (32%)
Site of active disease		
Primary tumour	149 (32%)	167 (35%)
Liver	331 (70%)	344 (73%)
Lung	41 (9%)	39 (8%)
Ascites	25 (6%)	35 (8%)
Pleura	13 (3%)	12 (3%)
Bone	7 (1%)	12 (3%)
Skin	7 (1%)	4 (1%)
Previous treatment		
Surgery	410 (87%)	392 (83%)
Radiotherapy	26 (6%)	37 (8%)
Chemotherapy	156 (33%)	155 (33%)

Data are median (IQR) or number of patients (%).

Table 1: **Baseline characteristics**

	400 mg once a day (n=470)	400 mg twice a day (n=472)
Treatment interruption*	189 (40%)	302 (64%)
Reason for interruption		
Haematological toxic effects	28 (6%)	32 (7%)
Non-haematological toxic effects	107 (23%)	203 (43%)
Both	7 (1%)	17 (4%)
Unrelated to treatment	38 (8%)	42 (9%)
Not reported	9 (2%)	8 (2%)
Dose reduction*	77 (16%)	282 (60%)
Reason for dose reduction		
Haematological toxic effects	11 (2%)	17 (4%)
Non-haematological toxic effects	49 (10%)	196 (42%)
Both	2 (1%)	8 (2%)
Unrelated to treatment	7 (1%)	27 (6%)
Not reported	8 (2%)	34 (7%)

*$p<0.0001$ by χ^2 test.

Table 2: **Treatment interruptions and dose reductions in patients who started protocol treatment**

reduction), responses (*vs* disease progression without response), and progressions (*vs* death in the absence of progression). For comparisons, we used the Gray test,[12] and to compare frequency and grade of side-effects between treatment groups we used the Cochran-Armitage trend test. The Hommel step-up procedure for repetitive testing[13] was applied: calculated p values were adjusted accordingly and compared with the nominal p value—ie, p=0·05. To avoid repeated testing, comparisons between treatment groups were only done for toxic events of grade 3 or 4 that occurred in at least 2·5% of patients.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 946 patients were randomly allocated treatment; 473 were assigned imatinib 400 mg once daily and 473 the twice daily regimen (figure 1). 18 patients (2%) were ineligible for the study: six had another type of cancer, four had concomitant diseases excluded by protocol, and eight were ineligible for miscellaneous reasons. According to the intention-to-treat policy, these patients were included in the analysis. At the time of analysis (May, 2004) per-protocol treatment had been completed in 412 patients.

Table 1 shows patients' characteristics. Fewer than 4% (n=32) of randomised patients had non-measurable (but still visible) disease. 311 (33%) had previously had chemotherapy. Treatment deviations from protocol were

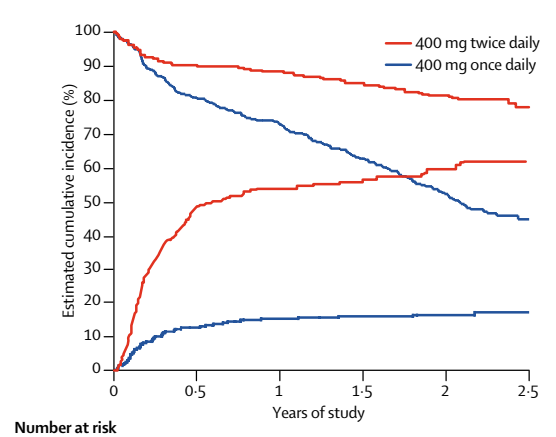

Figure 2: **Estimated cumulative incidence of dose reduction and treatment discontinuation or crossover**

Cumulative incidence of dose reduction is significantly higher in the twice daily arm than in the once daily arm (p<0·0001, Gray test). The two lower lines show the estimated cumulative incidence of dose reduction and the upper two lines (starting at 100%) show estimated cumulative incidence of treatment discontinuation or crossover without dose reduction.

	400 mg once a day (n=470)				400 mg twice a day (n=472)			
Grade	1	2	3	4	1	2	3	4
Any side-effect	98	215	123	29	41	190	201	36
Anaemia	257	128	26	7	195	187	55	24
Leucopenia	128	59	13	-	138	77	10	2
Granulocytopenia	96	63	20	13	89	81	22	11
Thrombocytopenia	18	3	5	2	19	6	2	4
Oedema	236	86	13	1	200	169	41	2
Fatigue	201	90	28	-	177	146	50	1
Fever	39	13	4	-	60	15	6	-
Pruritus	55	17	4	-	70	36	7	-
Rash	80	34	11	-	121	74	24	1
Anorexia	76	37	8	1	119	63	8	-
Constipation	52	18	4	1	61	19	7	-
Diarrhoea	160	58	7	1	170	73	25	-
Nausea	170	47	12	-	170	101	15	-
Vomiting	86	25	12	1	107	60	13	-
Bleeding	34	4	12	1	64	3	30	8
Infection	34	34	12	1	41	36	21	1
Dizziness	44	7	1	-	50	9	2	-
Arthralgia	50	11	-	-	56	15	4	-
Headache	59	15	1	-	54	8	4	-
Myalgia	87	27	1	-	91	35	5	-
Pleuritic pain	159	60	19	2	143	83	33	1
Cough	52	8	1	-	53	13	1	-
Dyspnoea	-	39	14	1	-	62	16	5
Renal or genitourinary	43	16	2	1	48	22	10	3

Data are number of patients who started per-protocol treatment.

Table 3: **Side-effects by grade of toxic effect**

reported in 155 patients (16%), most of which were attributable to inappropriate dose reductions in patients allocated imatinib twice daily, leading to underdosing compared with protocol intentions in 111 of the 155 patients (11%), of whom 21 (4%) were assigned once daily treatment and 90 (19%) were allocated treatment twice a day.

Of 942 patients who started treatment, dose reductions were reported in 359 (38%) and treatment interruptions in 491 (52%; table 2). Most treatment discontinuations (271; 66%) were due to disease progression and 28 (7%) were attributable to toxic effects. Compared with patients allocated treatment once a day, those assigned twice daily imatinib were significantly more likely to have a treatment interruption or dose reduction (table 2). The daily dose

	Calculated p value	Adjusted p value*
Oedema	<0·0001	<0·0001
Anaemia	<0·0001	<0·0001
Rash	<0·0001	<0·0001
Fatigue	<0·0001	<0·0001
Nausea	<0·0001	<0·0001
Bleeding	<0·0001	<0·0001
Diarrhoea	0·0005	0·0026
Dyspnoea	0·009	0·036
Pleuritic pain	0·018	0·053
Infection	0·12	0·24
Granulocytopenia	0·42	0·42

Only events reported with a grade 3 or 4 toxic effect in more than 2·5% of patients are included in this analysis. *Adjusted for repetitive testing (Hommel step-up procedure).

Table 4: **Comparison of toxic effects between treatment groups**

	400 mg once a day (n=473)	400 mg twice a day (n=473)
Complete response	24 (5%)	28 (6%)
Partial response	213 (45%)	229 (48%)
No change	150 (32%)	150 (32%)
Progression	61 (13%)	42 (9%)
Not assessable	25 (5%)	24 (5%)

Table 5: **Best overall response to treatment (intention-to-treat analysis)**

of imatinib had to be reduced to 300 mg or less in 74 (16%) patients allocated once daily treatment (after a median of 64 days [IQR 40–172]) and in 41 (9%) assigned the twice daily regimen (121 days [62–187]). Further dose reduction to 200 mg was needed in 34 (7%) allocated treatment once a day (after a median of 99 days [42–189]) and in 21 (4%) assigned the twice daily regimen (72 days [48–142]). Reasons for dose interruption, treatment reduction, or both were balanced between treatment groups, and in about a third of cases were attributable to non-haematological toxic effects. Figure 2 presents the cumulative incidence of dose reduction and treatment discontinuation or crossover (competing risk).

Side-effects were frequent but mostly mild and arose in 468/472 (99%) in the twice daily arm and 465/470 in the once daily arm. Table 3 lists side-effects arising in more than 10% of patients. The most usually reported haematological events were anaemia (879, 93%) and granulocytopenia (395, 42%). Haemoglobin count fell by a median of 8% of its initial value in patients allocated 400 mg once a day and 13% in those assigned 400 mg twice daily, and then stabilised. The most typical non-haematological side-effects were oedema (748, 80%), fatigue (693, 74%), nausea (515, 55%), pleuritic pain (500, 53%), diarrhoea (494, 52%), and rash (345, 37%). Analysis of toxic effects over time showed that they were mostly recorded during the first 8 weeks of treatment (data not shown).[9]

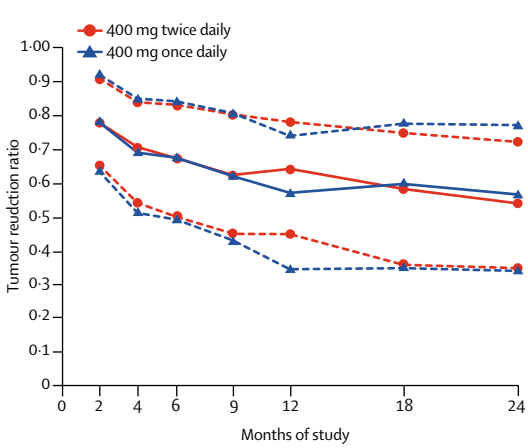

Figure 3: **Time to best response on treatment**
The graph shows the total tumour load measured at subsequent timepoints, divided by the initial tumour load (ie, the tumour reduction ratio). Solid lines indicate the median value and dotted lines the IQR.

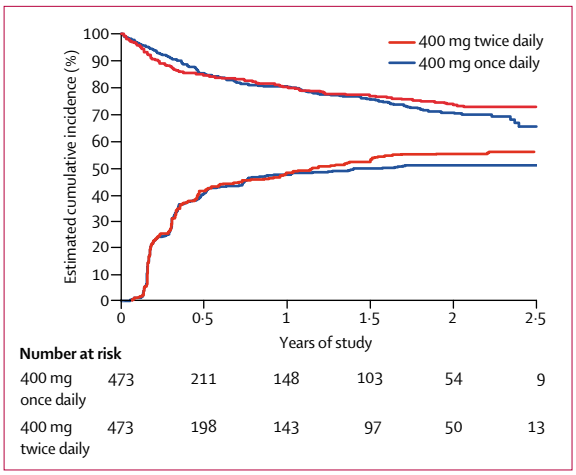

Figure 4: **Estimated cumulative incidence of response and treatment discontinuation**
The two lower lines show the estimated cumulative incidence of response and the upper two lines (starting at 100%) show estimated cumulative incidence of treatment discontinuation without response.

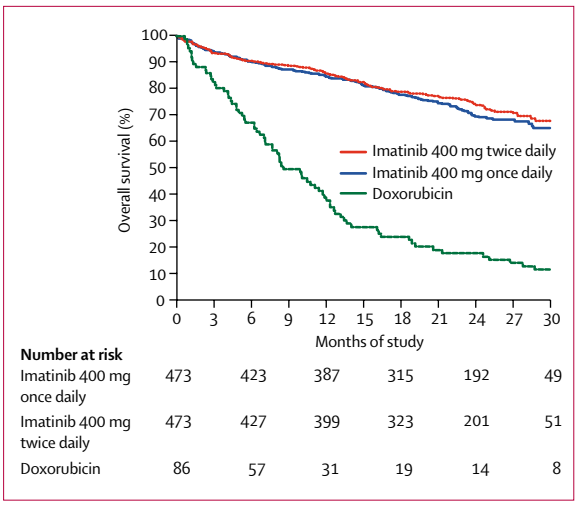

Figure 6: **Overall survival for total study population**
Data are compared with historical (GIST) controls from the EORTC database. Dox=doxorubicin-based regimen

Since many patients had more than one side-effect, table 3 also shows the worst grade of toxic effect recorded. Only nine (1%) patients did not have any toxic effects, and 389 (41%) had at least one grade 3–4 event (152 [32%] on once daily treatment and 237 [50%] on the twice daily regimen; p<0·0001). Table 4 shows differences in toxic effects between treatment groups (adjusted according to the Hommel step-up procedure); oedema, anaemia, rash, lethargy, nausea, bleeding, diarrhoea, and dyspnoea were recorded more usually in patients allocated imatinib twice a day than in those assigned once daily treatment.

Serious adverse events were reported for 174 (37%) patients allocated treatment once a day and for 180 (38%) assigned the twice daily regimen. Imatinib was the most probable cause of death in five (0·5%) patients (two in the once daily group, three on the twice daily regimen), and for 13 (1%) the drug could not be completely ruled out as the cause. Hepatic toxic events (three patients) and bleeding (two patients) were linked to five deaths.

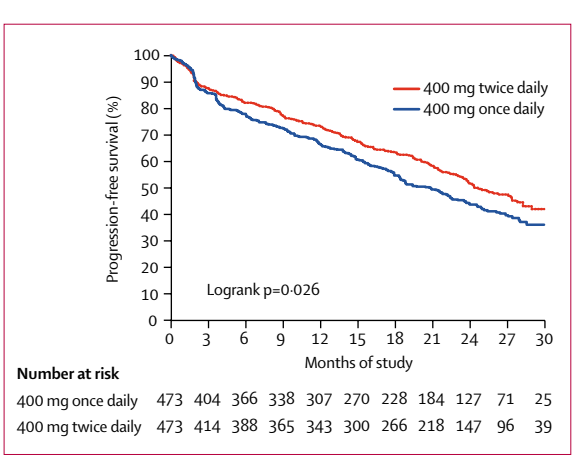

Figure 5: **Progression-free survival**

In the intention-to-treat analysis, treatment responses were noted equally with both regimens (table 5). 52 patients (5%) achieved a complete response. Median time to onset of complete response was 210 days (IQR 114–373), and time to best response in all responding patients was 107 days (IQR 58–172). Figure 3 shows the distribution of the tumour reduction ratio. Most responses happened in the first 9 months of treatment, but occasional best responses were reported after as long as 2 years of treatment. Figure 4 shows the cumulative incidence of response and treatment discontinuation or crossover (without documented response), which has been regarded as a competing risk (patients who crossed over to treatment twice a day remained in the analysis of response).

Median follow-up at the time of the present analysis was 760 days (IQR 644–859); 927 (98%) patients had been followed up for 1 year and 549 (58%) for 2 years (Kaplan-Meier estimates). 273 deaths and 498 treatment failures (progressions or deaths) had been reported; 215 (79%) reported deaths were due to progression, nine (3%) to toxic effects, and in five (2%) we could not distinguish between progression and toxic effects.

Figure 5 shows progression-free survival by treatment group. 263 (56%) patients allocated imatinib once a day had progression compared with 235 (50%) who were assigned treatment twice a day (estimated hazard ratio 0·82 [95% CI 0·69–0·98]; p=0·026). Results were not substantially different if patients with a poor performance status (grade 2 or 3) were excluded. At the time of the present analysis, progression-free survival did not differ between complete and partial responders. Progression-free survival is a composite primary endpoint because it includes two types of failure: disease

progression and death by any other cause. The competing-risk analysis showed that, after 2 years in those treated once a day, the 56% of failures consisted of 53% progressions and 3% deaths, and in those treated twice a day, the 48% of failures consisted of 44% progressions and 4% deaths.

Overall survival (Kaplan-Meier) estimates are 85% at 1 year and 69% at 2 years in patients treated once a day, and 86% at 1 year and 74% at 2 years in those allocated treatment twice a day (figure 6).

Discussion

Our study has shown similar response induction rates for imatinib 400 mg given once or twice a day but significantly better progression-free survival for the twice daily regimen.

Previously, GIST—if not resectable or if metastatic—were judged to be untreatable. Clinical trials of imatinib for treatment of GIST led to early registration in 2002, with a recommended initial dose of 400 mg daily.[7–9] However, the formal phase I study in solid tumours[7] identified a highest feasible dose of 400 mg twice a day, which is double the current label dose. In that phase I study, the time to progression was very long for patients treated at total daily doses of 600 mg or greater. Therefore, a randomised comparison of the recommended dose of 400 mg daily and the highest feasible dose of 400 mg twice a day was judged to be of importance. Two studies with similar design were undertaken, one in the USA[14] and this present trial, both comparing the same two daily doses. The major difference was that the primary endpoint of the study done in the USA was overall survival whereas for the study we report here it was progression-free survival.

The most typically reported haematological events in our study were anaemia and granulocytopenia and non-haematological side-effects were oedema, fatigue, nausea, pleuritic pain, diarrhoea, and rash. Side-effects were most usually reported, and of greater severity, with the twice daily dose. Although only 1% of patients did not have any toxic effect, and despite the fact that 41% had at least one grade 3–4 event during their total time on treatment, about two-thirds of patients did not need a dose reduction. Recurrence of grade 3–4 side-effects was a reason for a reduction in dose, which generally happened in the twice daily arm. However, almost all events of this grade resolved without sequelae. In fact, most side-effects happened early in the course of treatment, similar to our observations in the previous phase II study.[9] This reduced frequency and intensity of side-effects contrasts with usual experience with conventional cytotoxic drugs. A possible explanation could be enhanced drug clearance over time,[15] which leads to a reduction in exposure. In 16% of patients, dose reductions were not done according to protocol, mostly because the recorded side-effects were not severe enough to justify a dose reduction as specified. Yet, when sensitivity analyses were undertaken, excluding all patients with unjustified dose reductions, the results were not different from those of the intention-to-treat analysis.

The cause of death in five patients was attributable to imatinib. Nevertheless, in general, treatment was judged to be fairly well tolerated, certainly when taking into account the prolonged time of treatment. In view of the number of side-effects encountered and their occasionally severe and unpredictable nature, we recommend that imatinib should be used in GIST with extreme caution.

Despite the increased need for dose reduction in the group allocated imatinib 400 mg twice a day, these patients still received a higher dose of treatment throughout the treatment period compared with individuals assigned the once daily regimen.

Our data confirm that imatinib is a very active drug for treatment of GIST and show striking similarity with previously reported response rates.[7–9] 11% of patients did not benefit from imatinib at all, similar to previously reported experience.[7–9] Although the overall response rate is in the same range as previously reported,[7–9] our observation of complete remission is a different finding. Yet, the proportion of complete remissions is equally distributed between study arms. In general, no difference was noted in response induction rates between regimens, which means that for patients in whom achievement of response is the major aim of treatment, as is the case for neoadjuvant use of the drug with the aim to downsize a tumour before surgery, the 400 mg daily dose is adequate. Because studies on neoadjuvant use are currently being designed, they should focus on this dose and a length of treatment of 4 months, which is the median time to best response reported here. Because some responses happened even later than 4 months, we could consider extension of neoadjuvant use of imatinib in study protocols to 6 months. Similar response data have been reported in the other phase III study,[14] and in essence, the observations are the same as ours.

Our protocol did allow reductions to a dose as low as 200 mg daily if needed because of toxic effects. We could only make these reductions after extensive efforts to keep the original dose with other supportive measures. Yet, less than a fifth of patients in the two treatment arms were treated with a daily dose of 300 mg or less. To our knowledge, no published data lend support to clinical activity at these doses. However, progression-free survival in patients treated at 300 mg in our study did not seem to differ from that seen for patients at higher doses. Patients who needed dose reduction to 200 mg seemed to have a worse progression-free survival compared with all other doses, ie, 300–800 mg (494 days *vs* 729 days). We should stress that this comparison is probably affected by selection bias, and therefore has to be interpreted with caution.

RECIST criteria might not be optimum for response assessment in GIST because of the cystic change of lesions when responding. This cystic change can lead to underassessment of objective activity; however, it will not affect assessment of progression-free survival. Therefore, the most important observation from our present study is that initial treatment at 400 mg twice a day induces a significantly longer progression-free survival compared with treatment once a day. The benefit in terms of median progression-free survival is an extra 5 months. In view of this benefit, the dose of 400 mg twice a day might be the preferred dose in instances when duration of effect is crucial, such as in metastatic disease with symptoms.

The randomised phase II study comparing a dose of 400 mg daily with 600 mg daily[8] did not report progression-free survival data by treatment arm because the study was not designed or powered to detect such a difference. We cannot exclude that the doses used in that study were not enough different to detect a benefit. More important is the other phase III study, that has been presented in abstract format at the 2004 American Society of Clinical Oncology conference.[14] The progression-free survival curves in that study are similar to ours, albeit they are non-significant, which is probably attributable to the fact that it was a smaller study than ours.

Interruption of imatinib treatment at the time of best response can be detrimental.[16] We recommend continuation of treatment even in patients achieving complete remission, as was actually done in our study. However, how will this observation affect the design of adjuvant studies with imatinib?

Our study was designed and powered to detect a possible difference in progression-free survival. Moreover, the crossover design we used could affect overall survival because crossover to the 400 mg twice a day dose would yield many responses or prolonged stable disease. Early indications suggest this outcome is indeed the case,[14,17] although it is too early to assess if crossover has affected overall survival. Therefore, analysis of overall survival is premature. 344 deaths would be required to provide 80% power to detect a difference similar to the one we needed for progression-free survival (hazard ratio 0·737). However, if the true difference in survival is only half of this value (0·86), 1380 deaths would be needed to reach this power and the size of our study would not be sufficient.

We compared survival data of our study (including all patients) with those from the EORTC database on patients who received doxorubicin-based chemotherapy for GIST as first-line treatment. Even in view of the limitations to this approach, the difference in overall survival (figure 6) is so striking that to attribute this finding to chance is difficult. This information is important for health-care agencies that still seem to doubt the relevance of imatinib for the treatment of advanced or metastatic GIST. Withholding this treatment is difficult to justify ethically.

In conclusion, if the aim of treatment is response induction, a daily dose of 400 mg given for 4–6 months seems to be sufficient. However, in patients with widespread metastatic disease, the prolonged progression-free survival achieved with 400 mg twice daily might lead one to favour this regimen. Whether a similar outcome could be achieved with fewer side-effects by making use of the reduction in drug clearance over time—eg, with a starting dose of 400 mg daily followed by stepwise dose escalation to 400 mg twice a day—is still a matter for further clinical investigations.

Contributors

J Verweij and M Van Glabbeke wrote the report. All authors have contributed to the study by treating a least 5% of patients, by analysing data, or by reviewing the pathology of tumours, and all have approved the content of the paper.

Conflict of interest statement

JV, JYB, AvO, and PH have received honoraria from Novartis for consultancy. PC has received honoraria from Novartis for lectures, written contributions, and participation in advisory boards, has received travel reimbursement for meetings, and research or educational grants for his institution. JZ has received honoraria for lectures from Novartis and a study grant for the Australasian Gastrointestinal Trials Group. PR has received a study grant and honoraria for lectures from Novartis. MVG has received a study grant for EORTC from Novartis. RB has received from Novartis travel reimbursement for meetings and research or educational grants for her institution. IJ has received honoraria for consultancy and participation in symposia from Novartis. ALC and RI declare that they have no conflict of interest.

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