Cancer Chemother Pharmacol (2004) 53: 433–438
DOI 10.1007/s00280-003-0756-z

ORIGINAL ARTICLE

**Zariana Nikolova · Bin Peng · Martine Hubert
Michael Seiberling · Urs Keller · Yu-Yun Ho
Horst Schran · Renaud Capdeville**

Bioequivalence, safety, and tolerability of imatinib tablets compared with capsules

Received: 18 August 2003 / Accepted: 19 November 2003 / Published online: 23 January 2004

Abstract *Purpose*: Imatinib (Glivec) has been established as a highly effective therapy for chronic myeloid leukemia and gastrointestinal tumors. The recommended daily dosage of 400–600 mg requires simultaneous intake of up to six of the current 100-mg capsules. Due to the need to swallow multiple capsules per dose, there is a potential negative impact on treatment adherence; therefore, a new imatinib 400-mg film-coated tablet has been developed. To improve dosing flexibility, particularly with regard to the pediatric population and the management of adverse events, a scored 100-mg film-coated tablet has also been introduced. *Experimental design*: A group of 33 healthy subjects were randomly assigned to one of six treatment sequences, in which they received imatinib as 4×100-mg capsules (reference), 4×100-mg scored tablets (test), and 1×400-mg tablet (test). Blood sampling was performed for up to 96 h after dosing, followed by a 10-day washout period prior to the next sequence. After the third dosing, subjects were monitored to assess delayed drug-related adverse events. Pharmacokinetic parameters were assessed using concentration-time curves for plasma imatinib and its metabolite CGP74588. *Results*: Median T_{max} was 2.5 h for capsules and tablets. Mean $AUC_{(0–inf)}$ values were 27094, 26081 and 25464 ng·h/ml for 4×100-mg capsules, 4×100-mg tablets, and 1×400-mg tablets, respectively. C_{max} values were 1748, 1638 and 1606 ng/ml, and $t_{1/2}$ values were 15.8, 15.9 and 15.7 h. The test/reference ratios for $AUC_{(0–inf)}$, $AUC_{(0–96\ h)}$, and C_{max} were 0.98, 0.98 and 0.95 for 4×100-mg tablets versus 4×100-mg capsules, and 0.95, 0.95 and 0.92 for 1×400-mg tablet versus 4×100-mg capsules. The 95% confidence intervals were fully contained within the interval (0.80, 1.25). Eight mild and one moderate adverse event considered to be drug related were reported. These events showed no clustering by type of dosage form and were of little to no clinical significance. *Conclusions*: Film-coated 100-mg (scored) and 400-mg tablet dose forms of imatinib are bioequivalent to the commercial 100-mg hard-gelatin capsule, and are as safe and well tolerated.

Keywords Imatinib · Safety · Treatment optimization · Oral anticancer agents · Imatinib pharmacokinetics

Z. Nikolova (✉) · R. Capdeville
Novartis Oncology, Basel, Switzerland
E-mail: zariana.nikolova@pharma.novartis.com
Tel.: +41-61-6961792
Fax: +41-61-6961822

B. Peng · Y.-Y. Ho · H. Schran
Novartis Oncology, East Hanover, NJ, USA

M. Hubert
Novartis Oncology, Rueil Malmaison, France

M. Seiberling · U. Keller
Swiss Pharma Contract, Allschwil, Switzerland

Z. Nikolova
Oncology Business Unit, Novartis Pharma AG,
WKL-490.2.03, Lichtstrasse 35,
4056 Basel, Switzerland

Introduction

Imatinib (Glivec), a phenylaminopyrimidine derivative, is a tyrosine kinase inhibitor that targets BCR-ABL, platelet-derived growth factor receptors (PDGF-Rs), and c-KIT receptors for stem cell factor (SCF) [1]. Constitutive activation of these tyrosine kinases is crucial to the pathogenesis of certain tumors and myeloproliferative disorders [1]. Imatinib is currently considered the "gold standard" pharmacotherapy for chronic myelogenous leukemia (CML) at all stages (400 or 600 mg/day for advanced stages) [2]. Imatinib is also approved at doses of 400 or 600 mg/day for malignant unresectable or metastatic gastrointestinal stromal tumor (GIST).

Optimization of imatinib drug dosage is an important variable that affects treatment outcome. To ensure that the majority of patients achieve drug levels at or above the therapeutic threshold (300 mg/day), a dose of

400 mg/day was selected for use in phase II clinical studies [3, 4]; doses higher than 400 mg/day may yield improved responses [4]. Approximately 70% of patients are currently initially prescribed 400 mg/day. Given that imatinib was introduced to the market as a 100-mg hard-gelatin capsule, concerns regarding treatment adherence were raised because of the need to swallow a high number of capsules over a long period of time to achieve therapeutic dosages. Adherence to prescribed regimens is an increasingly important issue in oncology since exposure to less than required doses could lead to disease recurrence [5]. In GIST and some other solid tumor indications, ongoing studies have shown that a dose of 800 mg/day (given twice a day) is superior to a dose of 400 mg/day, but has a greater likelihood of nonadherence [6].

Two new dose forms of imatinib, film-coated 400-mg and 100-mg scored tablets, were approved by the US Food and Drug Administration (FDA) in April 2003; approval was expected in Europe by the end of 2003. Since the tablets are also much smaller than the capsules, patients now have the convenience of a once-daily, single, easy-to-swallow tablet of imatinib. The divisibility of the scored 100-mg tablet permits 50-mg incremental dose adjustments of imatinib for pediatric use (recommended dose of 260–340 mg/m^2 per day) or for patients who need higher than the recommended starting doses of 400 or 600 mg/day. In capsule form, imatinib is highly soluble in water and low-pH aqueous solutions (data on file, Novartis). The new tablets are also highly soluble and dissolve rapidly in aqueous buffer solutions over a pH range of 1–6.8. The dissolution profiles of the 100- and 400-mg tablets are similar to those of the 100-mg capsules, as demonstrated by the release of more than 85% of the labeled amount of the drug within 15 min (data on file, Novartis).

Pharmacokinetic studies on the capsule form have indicated that imatinib is rapidly absorbed after oral administration, with C_{max} achieved within 2–4 h [7]. Mean absolute bioavailability is 98%, and the elimination half-life of imatinib and its major metabolite (CGP74588) are approximately 18 and 40 h, respectively. The pharmacokinetics of imatinib are similar in CML and GIST patients [7]. In this study, the bioequivalence, clinical tolerability, and safety of the two new dose forms were compared with those of the existing 100-mg capsule.

Materials and methods

Subjects

A group of 33 healthy male and female volunteers between 18 and 65 years of age were enrolled. These subjects underwent a medical screening that included medical history, vital signs, and physical and laboratory examinations. Genotyping of the cytochrome P450 (CYP) isoenzyme CYP2D6 was done because imatinib has been identified in vitro as a competitive inhibitor of CYP2D6 [7]. Testing was also done for HIV, hepatitis B and C, pregnancy, and alcohol or drug abuse within a period of 21 days prior to the beginning of the study. Subjects with a history of smoking or drug use or those who were using any medication for a 14-day period prior to dosing were eliminated from the study. The three subjects who discontinued the study prematurely were replaced.

Study design and analysis

This was a single-center, open-label, randomized, crossover study in which subjects satisfying the inclusion criteria took either a single dose of 400 mg imatinib as four 100-mg hard-gelatin capsules, as a single 400-mg film-coated tablet, or as four 100-mg film-coated tablets in six different sequences. Subjects were randomly allocated to one of these six sequences, and a total of at least 10 days of washout elapsed between administrations of drug. For each subject there was a screening period from day −21 through day −2. There were three treatment periods, each consisting of a baseline evaluation, the drug administration, and a 96-h post-dose pharmacokinetic sampling and observation phase. After the three treatments and the washouts, there was a study completion evaluation, followed by a 4-week safety phase (Table 1). Subjects reported to the study site 12–14 h prior to each round of dosing, underwent baseline evaluation and administration of the relevant formulation of imatinib, and were followed for a period of 96 h. The study drug was administered following an overnight fast of at least 10 h, and subjects continued to fast for at least 4 h after dosing. Subjects were discharged after the 24-h pharmacokinetic sampling. All later samples were collected on an ambulatory basis.

Blood sampling

To determine the plasma concentration of imatinib and its primary metabolite N-desmethyl CGP74588, 5.5 ml of whole blood was drawn from each of the subjects. The time-points at which blood was collected in each case were before dosing and 0.5, 1, 1.5, 2, 2.5, 4, 6, 8, 12, 24, 36, 48, 72, and 96 h after dosing. These samples were stored at −18°C for subsequent evaluation.

Evaluation of plasma imatinib and CGP74588

The plasma concentrations of imatinib and N-desmethyl CGP74588 were determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method using deuterium-labeled imatinib as an internal standard [8]. The limit of quantification of this method was found to be 4 ng/ml for both imatinib and CGP74588. Sample preparation for this analysis was done by solid-phase extraction.

Pharmacokinetic analysis

Pharmacokinetic parameters were determined using noncompartmental method(s) using WinNonlin Pro 3.2 (Pharsight Corporation, Mountain View, Calif.). The pharmacokinetic parameters determined included C_{max} and t_{max} , which are the maximum concentration observed after dosing and the time at which C_{max} occurred, respectively. In addition, areas under the concentration curves (AUC) were also calculated from time zero to t_{max}, 24 h, 96 h or infinity, as indicated. $AUC_{(0–24\ h)}$ and $AUC_{(0–96\ h)}$ were calculated by the linear/log trapezoid method and $AUC_{(0–inf)}$ was calculated as $AUC_{(0–t)} + C_t/\lambda_t$ where C_t is the concentration at time t, the last measuring sampling time-point, and λ_t is the terminal elimination constant. The elimination half-life ($t_{1/2}$) was determined as $0.693/\lambda_z$.

Assay performance

Within-study assay validation was performed by analysis of calibration and QC samples together with the study samples. The limit of quantitation was 4 ng/ml for STI571 and CGP74588. The values for between-run bias of the calibration samples (4 to 5000 ng/ml)

Table 1 Study design (*D* day, *PK* pharmacokinetic)

Pretreatment period	Treatment period 1		Washout	Treatment period 2		Washout	Treatment period 3		Posttreatment period
Screening evaluations	Baseline evaluation	Dosing and PK sampling		Baseline evaluation	Dosing and PK sampling		Baseline evaluation	Dosing and PK sampling	End-of-study evaluations + safety period
D −21 to −2	D −1	D 1 to 5	D 6 to 13	D 14 (= D −1)	D 15 to 19	D 20 to 27	D 28 (= D −1)	D 29 to 33	D 33 to 61

ranged from −7.8% to 4.5% for STI571 and from −9.4% to 6.0% for CGP74588, and for precision (CV%) ranged from 3.1% to 6.7% for STI571 and from 4.0% to 6.7% for CGP74588. The values for bias and precision at the limit of quantitation were 2.8% and 6.7% for STI571 and 3.5% and 4.8% for CGP74588. The values for between-run bias of the QC samples were 3.6%, −0.5% and 5.2% for STI571, and 3.6%, 1.0% and 11.3% for CGP74588 for the concentrations 11.2, 203 and 4060 ng/ml, respectively. The values for between-run precision (CV%) were 10.5%, 5.2% and 4.9% for STI571 and 12.8%, 9.0% and 7.8% for CGP74588.

Statistical methods

The analyses for $AUC_{(0-inf)}$, $AUC_{(0-96\ h)}$, and C_{max} were regression fits using a linear model for the log-transformed pharmacokinetic parameters. The regression model included sequence of treatment, subjects within each sequence, period, and treatment. The 90% confidence limits for the difference between least squares means on the log-scale were calculated using Dunnett's test [9]. The antilogarithm gives the 90% simultaneous confidence limits for the ratio of the two least squares means on the untransformed scale.

According to current FDA guidelines, the bioequivalence criterion for the three dose forms could be considered met if the 90% confidence interval around the ratio of pharmacokinetic parameters, AUC, and C_{max} was entirely contained in the interval (0.8, 1.25) [10]. Dunnett's method was used to calculate 90% confidence limits to ascertain that the overall type I error for comparisons of both test dose forms versus the reference was equal to 10%. This approach was needed to test whether each of the two strengths of the tablets was bioequivalent to the marketed 100-mg capsule.

Results

Subject disposition

The protocol design required the enrolment of 33 subjects, and 30 completed the study. Three subjects discontinued the study due to (1) a positive hepatitis C test, (2) an inability to adhere to the study schedule for personal reasons, and (3) recurrent vomiting after drug administration in periods 1 and 2, resulting in the possibility of inadequate drug absorption and thus unrepresentative pharmacokinetic values. These subjects were

Table 2 Baseline characteristics

All subjects (n)	33
Age (years)	
Mean ± SD	38.3 ± 11.83
Range	19–60
Median	39.0
Height (cm)	
Mean ± SD	176.6 ± 8.24
Range	161–194
Median	177.0
Weight (kg)	
Mean ± SD	75.52 ± 10.77
Range	57.6–101.7
Median	76.60
Sex	
Male	27 (81.8%)
Female	6 (18.2%)
Race	
Caucasian	33 (100%)

subsequently replaced. The background and demographic characteristics of the 33 individuals who entered the study are summarized in Table 2.

Pharmacokinetic analysis

Figures 1 and 2 represent the mean plasma concentration-time profile of imatinib and CGP74588 following oral administration of imatinib either as capsules (4×100 mg) or tablets (4×100 mg or 1×400 mg). These data were used to determine the comparative pharmacokinetic parameters of imatinib (Table 3) and CGP74588 (Table 4) following administration of the three dose forms. Absorption of imatinib was rapid and unaffected by dose form. Maximum absorption (C_{max}) was found to be comparable between dose forms and was achieved in approximately 2.5 h for capsules and tablets. Comparable values were also obtained for the AUC measurements of imatinib at different time-points for all three dose forms. The coefficient of variation for C_{max} and AUCs showed considerable intersubject variability.

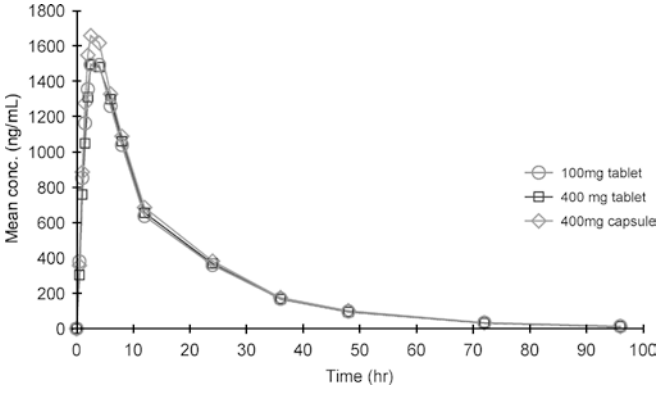

Fig. 1 Mean plasma concentrations of imatinib

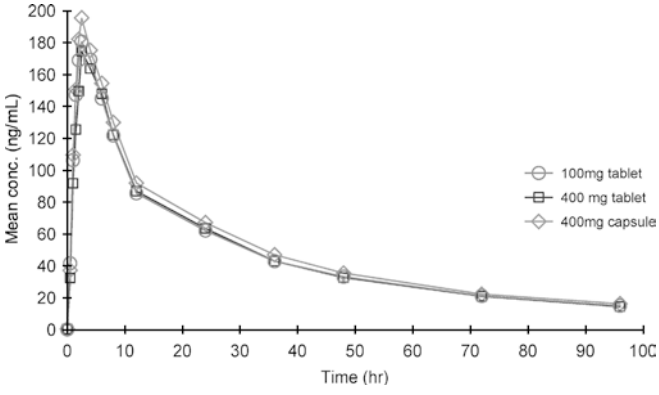

Fig. 2 Mean plasma concentrations of imatinib metabolite CGP74588

The mean plasma concentration-time profile of CGP74588 (Fig. 2) demonstrated similar kinetics for both the appearance of imatinib in plasma after oral administration and breakdown resulting in the metabolite CGP74588. The AUC of CGP74588 in plasma was found to be about 20% of that of the parent compound for both capsule and tablet dose forms, and the $t_{1/2}$ of CGP74588 was double that of the parent compound. The pharmacokinetic values (C_{max}, t_{max}, and AUC) for CGP74588 were similar for both the test and reference dose forms of imatinib.

The test/reference ratios for $AUC_{(0–inf)}$, $AUC_{(0–96\ h)}$, and C_{max} were 0.98, 0.98 and 0.95 for 4×100-mg tablets versus 4×100-mg capsules, and 0.95, 0.95 and 0.92 for 1×400-mg tablet versus 4×100-mg capsules (Table 5). Dunnett's adjusted confidence limits for each of these parameters were in the interval (0.80, 1.25), as were unadjusted confidence limits. The test/reference ratios of pharmacokinetic parameters obtained indicated the bioequivalence of the three different dose forms of imatinib tested.

Table 4 Metabolite (CGP74588) pharmacokinetic parameters following oral administration of 400-mg imatinib capsules or tablets. Values are means ± SD, except T_{max} median (range)

Parameter	Capsule	Tablet	
	4×100 mg	4×100 mg	1×400 mg
T_{max} (h)	2.51.0–6.0	2.51.0–8.0	2.51.5–6.0
C_{max}(ng/ml)	206 ± 80	204 ± 89	186 ± 72
$t_{1/2}$(h)	37.4 ± 7.0	39.9 ± 10.1	40.9 ± 10.2
$AUC_{(0–2.5\ h)}$ (ng·h/ml)	289 ± 121	283 ± 130	240 ± 96
$AUC_{(0–24\ h)}$ (ng·h/ml)	2563 ± 1138	2457 ± 947	2378 ± 895
$AUC_{(0–96\ h)}$ (ng·h/ml)	4865 ± 2206	4656 ± 1840	4505 ± 1785
$AUC_{(0–inf)}$ (ng·h/ml)	5771 ± 2714	5581 ± 2320	5352 ± 2113

Table 3 Imatinib pharmacokinetic parameters following oral administration of 400-mg imatinib capsules or tablets. Values are means ± SD, except T_{max} median (range)

Parameter	Capsule	Tablet	
	4×100 mg	4×100 mg	1×400 mg
T_{max} (h)	2.5 (2.0–6.0)	2.5 (1.5–6.0)	2.5 (1.5–6.0)
C_{max} (ng/ml)	1748 ± 702	1638 ± 604	1606 ± 647
$t_{1/2}$ (h)	15.8 ± 2.9	15.9 ± 3.1	15.7 ± 2.8
$AUC_{(0–2.5\ h)}$ (ng·h/ml)	2,448 ± 1,198	2,294 ± 1,076	2,029 ± 957
$AUC_{(0–24\ h)}$ (ng·h/ml)	19,959 ± 8,794	19,019 ± 7,684	18,658 ± 8,016
$AUC_{(0–96\ h)}$ (ng·h/ml)	26,749 ± 12,623	25,724 ± 11,450	25,150 ± 11,611
$AUC_{(0–inf)}$ (ng·h/ml)	27,094 ± 12,933	26,081 ± 11,757	25,464 ± 11,846
V_z/F (l)	383 ± 133	387 ± 114	404 ± 144
CL/F (l/h)	17.1 ± 5.8	17.3 ± 5.1	18.0 ± 5.7

Table 5 Statistical comparisons of the ratios (test/reference) of the geometric means of pharmacokinetic parameters

Parameter	Treatment	Geometric mean	Ratio of geometric means	90% Dunnett adjusted CI for ratio
$AUC_{(0-inf)}$	4×100-mg capsules	24,962.3	Reference	
	4×100-mg tablets	24,365.4	0.98	(0.91, 1.04)
	1×400-mg tablet	23,608.0	0.95	(0.89, 1.01)
$AUC_{(0-96\ h)}$ (ng·h/ml)	4×100-mg capsules	24,676.3	Reference	
	4×100-mg tablets	24,063.7	0.98	(0.91, 1.04)
	1×400-mg tablet	23,334.4	0.95	(0.89, 1.01)
C_{max}(ng/ml)	4×100-mg capsules	1,632.5	Reference	
	4×100-mg tablets	1,552.4	0.95	(0.88, 1.03)
	1×400-mg tablet	1,502.0	0.92	(0.85, 0.99)

Safety and tolerability

During the study 32 adverse events were reported in 16 of the 33 subjects; few subjects experienced more than one adverse event. Of the 32 adverse events, 23 were thought to be unrelated to imatinib and were either mild (n = 14) or moderate (n = 9) in severity, and 9, experienced by four subjects, were suspected to be imatinib-related. Of these, 8 were considered mild (including nausea, vomiting and headache) and 1 was considered moderate (nausea). These adverse events resolved within 1.5–5 h without comedication. The frequency and intensity of adverse events was comparable across all formulations of imatinib.

Clinical laboratory evaluations (biochemistry, hematology and urinalysis), electrocardiographic assessment, and monitoring for vital signs revealed no abnormalities that could be clinically significant or related to the use of imatinib.

Discussion

The current study demonstrated comparable bioavailability of imatinib 4×100-mg capsules with 4×100-mg tablets and 1×400-mg tablet. The pharmacokinetic values (C_{max}, t_{max}, and AUC) for CGP74588 were also found to be nearly identical for both the test and reference dose forms of imatinib. The similar pharmacokinetic property of the metabolite further supports the bioequivalence of the tablet product.

Previous laboratory tests have indicated that the tablet forms of imatinib can dissolve as easily and over the same pH range (1.0–6.8) as the capsule (data on file, Novartis). This study indicated rapid absorption of the 400-mg tablet (median t_{max} 2.5 h) after oral administration that was comparable with that of the capsule. Taken together, these results demonstrate that imatinib is as highly soluble and as rapidly absorbed in tablet form as in capsule form.

The coefficient for variation for C_{max} and AUCs showed considerable intersubject variability. Although the cause of this was not clear, it may be attributed to intersubject differences in plasma proteins binding to the parent compound or to variations in CYP3A4, the major CYP isoenzyme involved in the microsomal metabolism of imatinib. Variability in CYP3A activity between individuals is large [11], and may in part have contributed to the large intersubject variability.

In this study, adverse effects of imatinib administration were closely monitored and found to have a similar distribution among the three dose forms. None of these effects showed clinical significance. Overall, 32 adverse events were reported in 16 out of 33 subjects, and only 9 were considered to be related to administration of imatinib. These drug-related adverse events, seen in only four subjects, were either mild or moderate in severity and included low-grade headache, nausea, and vomiting. The types of adverse events observed in this study are consistent with those reported in other studies [12, 13]. The data presented in this study clearly demonstrate the safety and tolerability of the new 100- and 400-mg formulations of imatinib.

The advantages of the 400-mg tablets include (1) convenience for patients who, in most cases, will need to take only one tablet per day (instead of four 100-mg capsules), and (2) the potential to sustain adherence over the long run. The scored 100-mg tablet offers dosing flexibility for the pediatric patient population, for which the recommended dose is 260–340 mg/m^2 per day.

In conclusion, the bioavailability, safety, and tolerability of the scored 100- and 400-mg film-coated tablet forms of imatinib are comparable to those of the 100-mg hard-gelatin capsule. The tablets can be safely prescribed to replace the capsules in the treatment of CML and GIST.

Acknowledgements We wish to thank members of the nursing and research staff who participated in this study. The support of Petra Brinkmann, Ann E. Bolton, Agnes Brunner, and Roland Waite at Novartis is gratefully acknowledged. All experimental procedures performed in this study were in accordance with current Swiss law.

References

1. Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ, Lydon NB (2000) Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-Kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 295:139

2. Peggs K, Mackinnon S (2003) Imatinib mesylate—the new gold standard for treatment of chronic myeloid leukemia. N Engl J Med 348:1048
3. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantargian H, Capdeville R, Ohno-Jones O, Sawyers CL (2001) Efficacy and safety of a specific inhibitor of the Bcr-Abl tyrosine kinase in chronic myeloid leukemia. New Engl J Med 344:1031
4. Deininger MWN, O'Brien SG, Ford JM, Druker BJ (2003) Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol 21:1637
5. Partridge AH, Avorn J, Wang PS, Winer EP (2002) Adherence to therapy with oral antineoplastic agents. J Natl Cancer Inst 94:652
6. Verweij J (2003) Early efficacy comparison of two doses of imatinib for the treatment of advanced gastro-intestinal stromal tumors (GIST): interim results of a randomized phase III trial from the EORTC-STBGS, ISG and AGITG (abstract 3272). Proc Am Soc Clin Oncol 22:814
7. Novartis Pharma (2001) Glivec^{TM} (imatinib mesylate) (prescribing information). Novartis Pharma, Basel, Switzerland
8. Bakhtiar R, Lohne J, Ramos L, Khemani L, Hayes M, Tse F (2002) High-throughput quantification of the anti-leukemia drug STI571 (Gleevec) and its main metabolite (CGP 74588) in human plasma using liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 768:325
9. Dunnett CW (1955) A multiple comparison procedure for comparing several treatments with a control. JASA 50:1096
10. US Department of Health and Human Services (2003) Guidance for industry. Statistical approaches to establishing bioequivalence. Food and Drug Administration, Office of Training and Communications, Rockville, MD. http://www.fda.gov/cder/guidance/3616fnl.htm
11. Wilkinson GR (1996) Cytochrome P4503A (CYP3A) metabolism: prediction of in vivo activity in humans. J Pharmacokinet Biopharm 24:475
12. Demetri GD, von Mehren M, Blanke CD, van den Abeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corles C, Fletcher CD, Joensuu H (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347:472
13. O'Brien SGO, Guilhot F, Larson R, Gathmann I, Baccarani M, Cervantes F, Cornelisson JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ (2003) Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic phase chronic myeloid leukemia. N Engl J Med 348:994