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ORIGINAL REPORT

Initial and Late Resistance to Imatinib in Advanced Gastrointestinal Stromal Tumors Are Predicted by Different Prognostic Factors: A European Organisation for Research and Treatment of Cancer–Italian Sarcoma Group–Australasian Gastrointestinal Trials Group Study

Martine Van Glabbeke, Jaap Verweij, Paolo G. Casali, Axel Le Cesne, Peter Hohenberger, Isabelle Ray-Coquard, Marcus Schlemmer, Allan T. van Oosterom, David Goldstein, Raf Sciot, Pancras C.W. Hogendoorn, Michelle Brown, Rossella Bertulli, and Ian R. Judson

From the European Organisation for Research and Treatment of Cancer Data Center, Brussels; University Hospital Gasthuisberg, Leuven, Belgium; Erasmus University Medical Center, Rotterdam; Leiden University Medical Center, Leiden, the Netherlands; Istituto Tumori, Milano, Italy; Institut Gustave Roussy, Villejuif; Centre Leon Berard, Lyon, France; Charite Campus Buch, Robert Roessle Hospital, Berlin; Klinikum Grosshadern; Gesellschaft für Strahlenforschung–National Research Center for Environmental and Health, Munich, Germany; Prince of Wales Hospital, Randwick, Australia; and Royal Marsden Hospital, London, United Kingdom.

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Address reprint requests to Martine Van Glabbeke, MD, European Organisation for Research and Treatment of Cancer Data Center, Av. E. Mounier, 83, bte 8, B1200 Brussels, Belgium; e-mail: mvg@eortc.be.

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ABSTRACT

Purpose

The aim of this study was to identify factors predicting initial and late resistance of GI stromal tumor (GIST) patients to imatinib and to document the dose-response relationship in the prognostic subgroups. This study is based on the European Organisation for Research and Treatment of Cancer–Italian Sarcoma Group–Australasian Gastrointestinal Trials Group randomized trial comparing two doses of imatinib in advanced disease.

Patients and Methods

Initial resistance was defined as progression within 3 months of randomization, and late resistance was defined as progression beyond 3 months. Investigated cofactors include imatinib dose, age, sex, performance status, original disease site, site and size of lesions at trial entry, and baseline hematologic and biologic parameters.

Results

Initial resistance was recorded for 116 (12%) of 934 assessable patients and was independently predicted by the presence of lung and absence of liver metastases, low hemoglobin level, and high granulocyte count. Among 818 patients who were alive and progression free at 3 months, 347 subsequent progressions were recorded, and late resistance was independently predicted by high baseline granulocyte count, primary tumor outside of the stomach, large tumor size, and low initial imatinib dose. The impact of initial dose on late resistance was mainly significant in patients with a high baseline granulocyte count ($> 5.10^9$/L) and in patients with tumors of GI origin outside of the stomach and small intestine.

Conclusion

Our study identifies patients for whom initial and/or long-term treatment needs to be improved and patients who require a high initial dose. Correlation of these results with immunohistochemistry and molecular parameters may further help to understand the biologic mechanisms of resistance.

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INTRODUCTION

Soft tissue sarcomas represent 1% of adult malignancies and are a heterogeneous group of neoplasms whose only common denominator is their derivation from mesenchymal tissue. GI stromal tumors (GIST) are a subset of soft tissue sarcomas that were classified relatively recently. Their local treatment essentially consists of surgery. After the stage of resection, these tumors have proven to be insensitive to chemotherapy and radiotherapy.[1]

Imatinib is a small-molecule tyrosine kinase inhibitor that is active against *BCR-ABL, KIT*, and *PDGFR. KIT* is expressed in the vast majority of GISTs and is frequently mutated, leading to constitutive activation in these tumors. A European Organisation for Research and Treatment of Cancer (EORTC) phase I study[2] identified the highest feasible dose of imatinib to be 400 mg bid and indicated extensive activity of imatinib in GIST. Phase II studies showed activity at all doses tested (400 to 800 mg).[3,4] Two large, randomized, phase III studies comparing doses of 400 mg once a day to 400 mg bid have confirmed the activity of imatinib in terms of progression-free survival and overall survival.[5,6] One of these studies has also documented a small but significant benefit with the high-dose regimen (400 mg bid) in terms of progression-free survival.[5] Finally, a randomized trial from the French Sarcoma Group has demonstrated that imatinib therapy should be continued indefinitely, even after complete response.[7]

Response of GIST to imatinib does not always result in an immediate decrease of the size of the lesions but, rather, in an initial inhibition of growth. Objective response (according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria[8]) has been reported in approximately half of the patients, but time to onset varies largely among patients, and some responses have been first documented more than 1 year after start of therapy.[5] Therefore, response to imatinib is frequently defined as absence of progression at the time of the first formal disease evaluation (2 to 3 months after starting therapy), whereas progression at this time point is considered as initial or primary resistance. In patients who have experienced an initial stabilization, further progressions (or relapses) are considered late or secondary resistance. These two distinct mechanisms of drug resistance are reflected in progression-free survival curves by a rapid drop off at the time of first evaluation (initial resistance), followed by a slower continued decrease with a small hazard rate (late resistance). Analysis of genomic and biologic profiles has suggested that heterogeneous biologic mechanisms may be responsible for drug resistance; some of the mechanisms may already be present and active at baseline, and others may be activated later or result from acquisition of new mutations.[9,10]

The current article reports on an analysis of the clinical and biologic factors affecting initial and late resistance to imatinib, based on the data of the randomized trial jointly conducted by the EORTC, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group. This article also explores whether the recently reported advantage of high-dose imatinib[5] is homogeneous among prognostic subgroups.

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologically proven advanced and/or metastatic unresectable GIST characterized by c-KIT expression as assessed by polyclonal CD117 antibodies (Dako Cytomation, Glostrup, Denmark) were eligible for this trial. Any prior chemotherapy was accepted if discontinued for more than 4 weeks. Patients with measurable or nonmeasurable disease that was documented by conventional scan imaging or physical examination were eligible. Other eligibility criteria are described elsewhere.[5] Each participating institution obtained the approval of the competent ethical review board, and all patients gave written informed consent.

Prestudy and Follow-Up Investigations

Within 14 days before treatment, a physical examination was performed, CBC count and serum chemistry were assessed, and relevant computed tomography scans were performed for tumor assessment. Computed tomography scans were repeated after 2, 4, and 6 months and every 3 months thereafter until progression of disease. The RECIST[8] method was used for evaluation of response and for documentation of progression.

After completion of recruitment, paraffin-embedded tumor blocks were collected for a central pathology review and obtained for approximately half of the patients. Results of this review will be analyzed in the subgroup of patients for whom material is available and published separately.

Treatment and Dose Modifications

Patients were randomly assigned to receive either 400 mg administered orally once daily or 400 mg bid. All patients were scheduled to continue treatment until disease progression or unacceptable toxicity. Dose modifications requested in case of toxicity are described in detail elsewhere.[5] In case of disease progression in a patient randomly assigned to the 400 mg once daily dose, a cross over to the 400 mg bid dose was allowed, regardless of the dose the patient was taking at the moment of progression.

Statistical Analysis

Initial resistance was defined as objective disease progression (according to RECIST[8]) within 3 months of randomization. The cutoff point was selected to include progressions documented at the first disease evaluation (after 2 months) but exclude progressions documented at the second disease evaluation (after 4 months). This end point was analyzed as a binary variable. Patients who either died in the absence of progression or who were lost to follow-up within 3 months of randomization were excluded from the analysis.

Late resistance was analyzed as a time to event variable (time to objective progression) with a 3-month landmark period. Patients who experienced progression, died, or were lost to follow-up within 3 months of random assignment were excluded from this analysis. Patients who died in the absence of progression after 3 months were censored at the date of death.

Cofactors investigated in the analysis included the initial daily dose of imatinib (randomized), age, sex, performance status at trial inclusion, primary site of disease (abdominal, stomach, small bowel, other GI, or other site), time since first GIST diagnosis, prior treatments for GIST (surgery, radiotherapy, and chemotherapy), site (primary tumor, liver metastases, or lung metastases) and size of lesions (diameter of the largest lesion) at the time of trial inclusion, and baseline hematologic and biologic parameters (WBCs, granulocytes, platelets, hemoglobin, creatinine, bilirubin, and albumin). Continuous variables were not recoded for building the prognostic models, but prognostic variables had to be recoded for drawing time to progression curves; in such cases, values close to quartiles were chosen as category cutoff points.

Both univariate and multivariate analyses used logistic regression (initial resistance) and Cox regression (late resistance) models. Factors found to be significant in the univariate analysis at the $P = .05$ level were subsequently included in a step-down multivariate model. Correlation between cofactors was measured by the Spearman rank correlation coefficient.

Integrating results of the pathology review in this analysis would not have been possible without losing substantial power, but the analyses have been repeated on the subgroup of patients for whom the GIST histology had been externally confirmed as sensitivity analyses. The impact of significant prognostic factors is detailed in overall time to progression curves, which were estimated by the Kaplan-Meier method. All randomly assigned patients are included in those curves. The prognostic value of the randomly allocated initial imatinib dose has been subsequently explored in prognostic subgroups using the Wald test adjusted for repetitive testing.

RESULTS

A total of 946 patients were included in the trial. At the time of this analysis, the median follow-up was 25 months (1- and 2-year follow-up rates, 98% and 58%, respectively). Comparisons of efficacy and toxicity parameters between therapeutic arms have been published elsewhere.[5]

Demographic Data

Cofactors and their distribution are listed in Table 1. There was no major imbalance between the randomized arms.

Initial Resistance

Among the 946 randomly assigned patients, 11 died within 3 months without evidence of progression (six patients from the 400 mg once daily arm and five from the 400 mg bid arm) because of toxicity (n = 2), infection (n = 3), hemorrhage (n = 3), severe diarrhea and vomiting (n = 1), and cardiac disease (n = 2). One ineligible patient (non-GIST, 400 mg once daily arm) was lost to follow-up. These 12 patients were excluded from the analysis. Among the 934 remaining patients, 116 (12%) experienced progression within 3 months (initially resistant).

The following prognostic factors of initial resistance were identified by univariate analysis (in order of significance): presence of lung metastases, low baseline hemoglobin level, high baseline granulocyte and platelet count, poor performance status, low baseline albumin level, absence of liver metastases, and short interval since the initial diagnosis of the disease (Table 2). None of the other cofactors showed any significant correlation with initial resistance.

In the multivariate model, presence of lung metastases, low baseline hemoglobin level, and absence of liver metastases were highly significant adverse prognostic factors, and high baseline granulocyte count showed borderline significance (Table 2). Highly significant ($P < .005$) correlation coefficients (Spearman) were observed between baseline hemoglobin level and albumin level ($r = 0.51$), performance status ($r = -0.32$), platelet count ($r = -0.26$), granulocyte count ($r = -0.092$), and time since GIST diagnosis ($r = 0.097$), and between time since GIST diagnosis and liver metastases ($r = 0.24$). The logistic regression model was applied to 456 assessable patients with an independently confirmed GIST diagnosis. In this sensitivity analysis, only baseline hemoglobin level and granulocyte count retained a significant prognostic value.

Late Resistance

The late resistance analysis is based on the 818 patients who where progression free and alive at 3 months (404 patients from the 400 mg once daily arm and 414 patients from the 400 mg bid arm). A total of 347 progressions were subsequently recorded. Patients who died without evidence of progression because of toxicity (n = 3), drug- and disease-unrelated events (n = 14), and unknown causes (n = 7) were censored at the date of death (10 patients from the 400 mg once daily arm and 14 patients from the 400 mg bid arm).

The following prognostic factors of late resistance were identified in the univariate analysis (in order of significance): high baseline granulocyte count, tumor size (largest diameter of the largest lesion), high baseline WBC count, poor performance status, nongastric primary tumor, small bowel primary tumor, low baseline albumin, prior chemotherapy, and random assignment to 400 mg once daily (Table 3). None of the other cofactors showed any significant correlation with late resistance.

In the multivariate analysis, only four factors remained as significant independent factors of adverse prognosis: tumor size, high baseline granulocyte count, nongastric primary tumor, and random assignment to imatinib 400 mg once daily (Table 3). Highly significant ($P < .0001$) correlation coefficients (Spearman) were observed between baseline granulocyte count and WBC count ($r = 0.90$), tumor size ($r = 0.33$), performance status ($r = 0.26$), and albumin level ($r = -0.24$), and between tumor size and albumin level ($r = -0.34$) and performance status ($r = 0.32$). The final Cox regression model was also applied to the subgroup of 421 patients assessable for late resistance and with independent confirmation of the GIST diagnosis. The results of this sensitivity analysis were similar to the results observed for the whole cohort (with lower significance levels).

Impact of the Most Significant Cofactors

Liver and lung lesions. Initial resistance was documented in 96 (11%) of 857 patients without lung lesions, 10 (20%) of 50 patients with both lung and liver lesions, and 11 (41%) of 27 patients with lung but no liver lesions; in patients with externally confirmed GIST diagnosis, these progression rates were 8% (34 of 426 patients), 7% (two of 27 patients), and 0% (zero of 11 patients), respectively.

Baseline hemoglobin level. Figure 1 illustrates the increased initial resistance to imatinib in patients with a low

Table 1. Distribution of the Cofactors

Factor	All Patients		Randomized Arm (No.)	
	No.	%	400 mg Once Daily	400 mg bid
Age, years				
Median, years	59			
Range, years	18-91			
< 40 years	72	7.6	38	34
40-50 years	176	18.6	87	89
50-60 years	228	24.1	122	106
60-70 years	282	29.8	138	144
> 70 years	188	19.9	88	100
Sex				
Male	573	61.3	283	290
Female	373	38.7	190	183
WHO performance score				
0	436	46.1	217	219
1	383	40.5	191	192
2	92	9.7	48	44
3	35	3.7	17	18
Primary site of disease				
GI	793	84	403	390
Gastric	316	33.4	159	157
Small bowel	238	25.2	124	114
Abdominal	129	13.6	58	71
Other site	19	2.0	11	8
Unknown	5	0.5	1	4
Time since primary diagnosis				
Median, days	338			
Range, days	6-10,092			
< 12 months	493	52.11	247	246
12-24 months	157	16.60	83	74
> 24 months	296	31.29	143	153
Site of active disease				
Primary tumor	316	33.40	149	167
Liver	672	71.0	329	343
Lung	80	8.5	41	39
Diameter of largest lesion				
Median, mm	78			
Range, mm	< 20-800			
< 40 mm	203	21.5	104	99
40-80 mm	295	31.2	150	145
80-120 mm	225	23.8	108	117
> 120 mm	218	23.0	109	109
Unknown	5	0.5	2	3
Prior therapy				
Surgery	802	84.8	410	392
Radiotherapy	63	6.7	26	37
Chemotherapy	311	32.9	156	155
Baseline hemoglobin				
Median, mmol/L	7.9			
Range, mmol/L	4.7-15.6			
< 7 mmol/L	245	25.9	124	121
7-8 mmol/L	245	25.9	127	118
8-8.8 mmol/L	236	24.9	104	132
> 8.8 mmol/L	220	23.3	118	102
Baseline granulocytes				
Median, 10^9/L	4.8			
Range, 10^9/L	1.5-30.6			
< 4 × 10^9/L	318	33.6	172	146
4-5 × 10^9/L	196	20.7	99	97
5-6.5 × 10^9/L	195	20.6	94	101
> 6.5 × 10^9/L	237	25.1	108	129

(continued on following page)

Table 1. Distribution of the Cofactors (continued)

Factor	All Patients		Randomized Arm (No.)	
	No.	%	400 mg Once Daily	400 mg bid
Baseline platelets, 10^9/L				
Median	297			
Range	28-1,245			
Baseline creatinine, μmol/L				
Median	79.6			
Range	35-795.6			
Baseline bilirubin, μmol/L				
Median	10			
Range	1.7-138.8			
Baseline albumin (g/L)				
Median, g/L	39.2			
Range, g/L	4.1-70.0			
$<$ 35 g/L	189	20.0	99	90
35-39 g/L	181	19.1	86	95
39-43 g/L	222	23.5	108	114
$>$ 43 g/L	155	16.4	79	76
Unknown	199	21.0	101	98

baseline hemoglobin level ($<$ 7 mmol/L or 11.27 mg/100 mL). After the first 3 months, the curves remained parallel, which is reflected in the lack of prognostic significance of this factor for late resistance.

Baseline granulocyte count. As shown in Figure 2, baseline granulocyte count slightly affected the initial drug resistance but largely affected the late resistance, which is substantially increased in patients with a baseline count greater than 5×10^9/L.

Tumor size. Figure 3 illustrates the impact of tumor size on late resistance, which was mainly observed after 1 year of imatinib therapy and with an increasing failure rate in patients with large lesions ($>$ 12 cm).

Site of primary disease. Figure 4 shows the time to progression for tumors according to the site of primary disease. Patients with a disease of gastric origin have a better prognosis than patients with disease originating in the small bowel. In other subgroups, the limited sample size does not allow any formal comparison.

Competing risk. The aim of this study was to identify factors that could predict resistance to imatinib, and therefore, progression and time to progression have been chosen as primary end points. The competing risk of death in the absence of progression was ignored in the principal analyses (those patients were censored). However, in the same data set, a cumulative incidence analysis demonstrated a limited contribution ($<$ 10%) of intercurrent deaths on progression-free survival.[5] We also performed a sensitivity analysis, considering all deaths as events, and obtained similar results.

Subgroup analysis. The impact of the randomly allocated initial dose on time to progression was evaluated in the following subgroups: patients with a baseline granulocyte count greater or less than 5×10^9/L; patients with tumors smaller or larger than 12 cm; and patients with tumors of stomach origin, small bowel origin, or other GI origin (the number of events was too small in other subgroups). Table 4 lists the estimates of the hazard ratios, their 95% CIs, and the results of the Wald test for all subgroups.

Table 2. Prognostic Factors for Initial Resistance

Factor	Univariate Analysis		Multivariate Model	
	Odds Ratio	*P*	Odds Ratio	*P*
Lung metastases	0.323	$<$ .0001	0.332	.0001
Baseline hemoglobin	1.421	$<$ .0001	1.380	.0004
Baseline granulocytes	0.926	.0049	0.935	.0208
Baseline platelets, /100	0.845	.0082	—	—
Performance status	0.734	.0079	—	—
Baseline albumin	1.040	.0186	—	—
Liver metastases	1.611	.0212	1.816	.0055
Time since GI stromal tumor diagnosis	1.297	.0488	—	—

Table 3. Prognostic Factors for Late Resistance

Factor	Univariate Analysis		Multivariate Model	
	Hazard Ratio	*P*	Hazard Ratio	*P*
Baseline granulocytes	1.064	< .0001	1.051	.0009
Diameter of the largest lesion	1.033	.0001	1.023	.0095
Baseline WBCs	1.051	.0001	—	—
Performance status	1.241	.0014	—	—
Gastric primary tumor	0.712	.0042	0.731	.0088
Bowel primary tumor	1.385	.0053	—	—
Baseline albumin	0.976	.0095	—	—
Prior chemotherapy	1.298	.0184	—	—
Dose of imatinib	0.779	.0202	0.754	.0093

The advantage of the high initial dose of imatinib (in terms of time to progression) was statistically significant in the following two subgroups (overall $P < .05$, nominal $P < .007$): patients with a high ($> 5 \times 10^9$/L) baseline granulocyte count (Fig 5) and patients with tumors of GI origin outside of stomach or small bowel (Fig 6). However, time to progression was not affected by the initial dose in patients with tumors of small bowel origin.

DISCUSSION

This prognostic factor analysis is based on the largest available series of patients with advanced or metastatic GIST who were consistently treated with imatinib, observed, and documented. The large sample size provides the appropriate power to identify with high confidence those factors that have an independent prognostic value.

Information on all cofactors investigated in this study is usually available for individual patients in any clinical practice. Therefore, our results do provide immediate prognostic information for any patient diagnosed with advanced GIST and treated with imatinib. The results may guide decisions on individual treatment with imatinib and help to identify patients who require an initial high dose or who may not benefit from imatinib and for whom a different treatment approach may be considered.

The obtained prognostic models have not been validated. We could have built the prognostic models on a randomly selected subset of the data (a training sample) and validated the results on the remaining data (validation sample), but this would have reduced the power of the analyses. Because other large similar data series will become available, we elected to build the model on the whole study cohort, assuming that external validation will be carried out by independent groups and will provide more reliable results than internal validation.

We have demonstrated that initial and late resistance to imatinib are predicted by different clinical and biologic factors. This is analogous to the existence of different competing mechanisms of resistance as identified on the basis of the analysis of genomic and molecular profiles.[9,10] Analysis of *KIT*

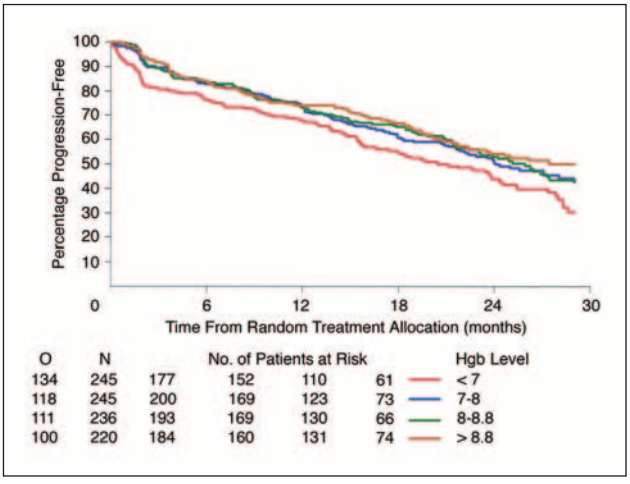

Fig 1. Time to progression as a function of the baseline hemoglobin level (mmol/L). Hgb, hemoglobin. O, observed failures; N, number of cases.

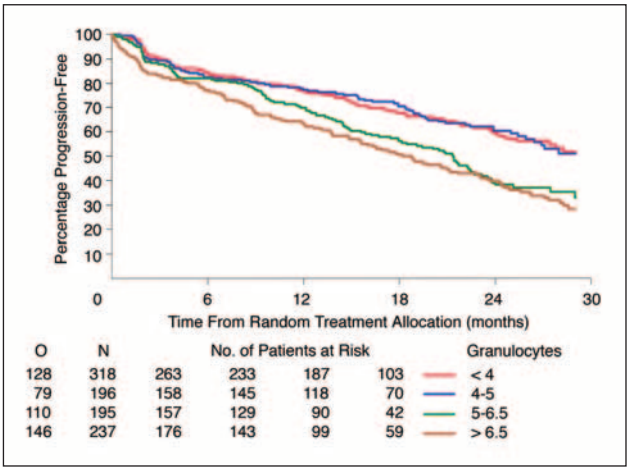

Fig 2. Time to progression as a function of the baseline granulocyte count (10^9/L). O, observed failures; N, number of cases.

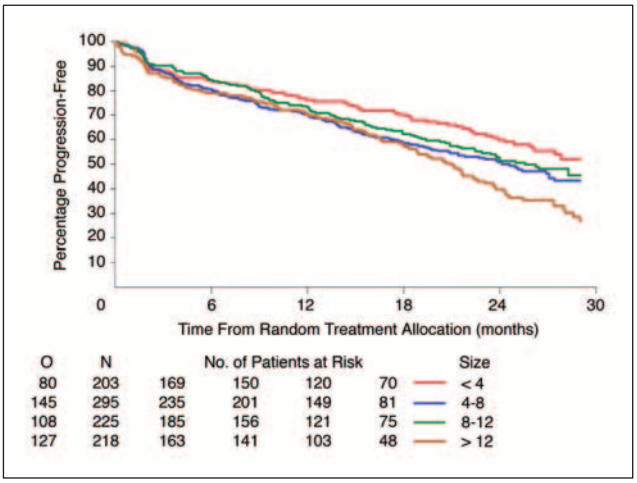

Fig 3. Time to progression as a function of the largest diameter of the largest lesion (cm). O, observed failures; N, number of cases.

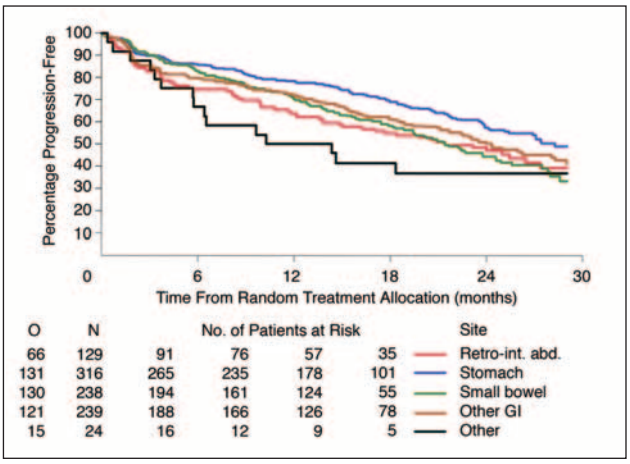

Fig 4. Time to progression as a function of the original tumor site. O, observed failures; N, number of cases; Retro-int.abd., retro- or intra-abdominal.

and/or *PDGF* mutations will probably provide additional prognostic information, as already suggested.[11] However, nonbiomolecular mechanisms may also play a different role in the initial and late resistance setting.

In the whole cohort of patients, initial resistance was predicted by the following four independent factors: baseline hemoglobin level, baseline granulocyte count, presence of lung metastases, and absence of liver metastases. The two last factors probably characterize a small proportion of misdiagnosed non-GIST patients. Sarcomas other than GIST have been proven to be unresponsive to imatinib.[4] Inclusion of a small proportion of non-GIST patients can largely affect the prognostic model for initial resistance because it is based on a 12% progression rate. This hypothesis is reinforced by the fact that those factors lose their significance when the analysis is restricted to the subgroup of patients with an external confirmation of the GIST diagnosis. Disease presentation with lung and/or without liver metastases should be an indication for external review of the pathologic diagnosis, but these factors probably do not affect resistance to imatinib in true GIST patients.

Hemoglobin level has also been reported to be a prognostic factor in patients treated with imatinib for chronic myeloid leukemia.[12,13] In a previous EORTC study, low hemoglobin has been found to be correlated with pharmacokinetic parameters including small distribution volume, short half-life, low clearance (in L/h), and high area under the curve,[14,15] and a first hypothesis is that hemoglobin level could affect the drug transport and delivery, resulting in insufficient intratumoral drug levels to inhibit disease proliferation in some patients with low hemoglobin. Indeed, small distribution volume (ie, high concentration) associated with short half-life may suggest that the drug remains in the blood instead of being distributed to organs (and to the tumor), which is in contrast to a high concentration associated with prolonged half-life that results from drug accumulation in the whole body (blood and tumor).

The role of hemoglobin in drug transport is further suggested by the fact that significant amounts of imatinib could be quantified in the erythrocyte sediments of patients treated with the drug.[16] Erythrocyte loading was dose dependent in both volunteer and patient blood, and partition ratios of erythrocytes versus plasma ranged between 0.01

Table 4. Subgroup Analysis

Subgroup	No. of Patients		Hazard Ratio		Wald Test
	Total	Experienced Treatment Failure	Estimate	CI	*P*
All patients	946	463	0.801	0.667 to 0.961	.017
Baseline granulocytes $< 5 \times 10^9$/L	514	207	0.874	0.665 to 1.15	.3368
Baseline granulocytes $< 5 \times 10^9$/L	432	256	0.678	0.530 to 0.867	.0020
Largest diameter < 120 mm	728	336	0.793	0.640 to 0.982	.0337
Largest diameter > 120 mm	218	127	0.796	0.560 to 1.131	.2025
Stomach origin	316	131	0.836	0.593 to 1.179	.3077
Small bowel origin	238	130	1.025	0.726 to 1.446	.8886
Other GI origin	239	121	0.576	0.400 to 0.828	.0029

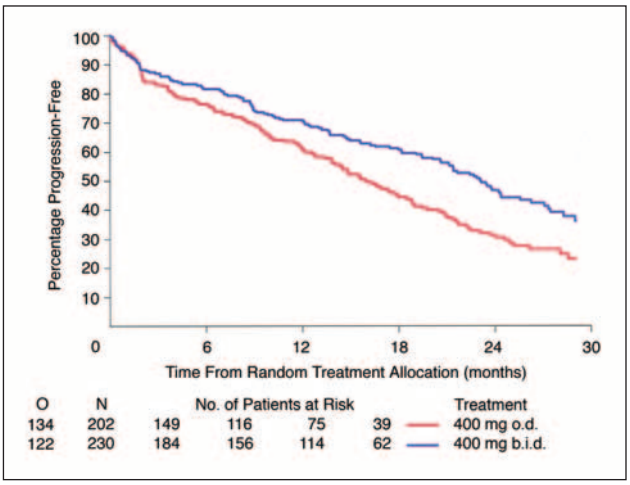

Fig 5. Time to progression by treatment arm in patients with a high baseline granulocyte count ($> 5 \times 10^9$/L). O, observed failures; N, number of cases; od, once daily.

and 0.5. However, when patients have been treated with imatinib over prolonged periods of time, partition ratios can increase beyond 3 (Prenen et al, personal communication, April 2004). Various anticancer agents are capable of inducing changes in their own partition ratios[17]; the implications for imatinib are subject of further investigations.

Another hypothesis is that low hemoglobin reflects a more aggressive type of disease or a more advanced stage that is associated with mucosal ulceration and tumor bleeding and is less responsive to imatinib. Any other hypotheses suggesting that one of the molecular mechanisms of drug resistance either affects or is affected by hemoglobin levels could also explain this finding.

The same kind of hypotheses can be made for granulocyte counts, which apparently affect both initial and late drug resistance. A high granulocyte count may reflect an inflammatory reaction induced by an aggressive type of tumor that tends to progress earlier. Molecular classification of patients with low hemoglobin levels and high granulocyte counts may help in understanding those findings.

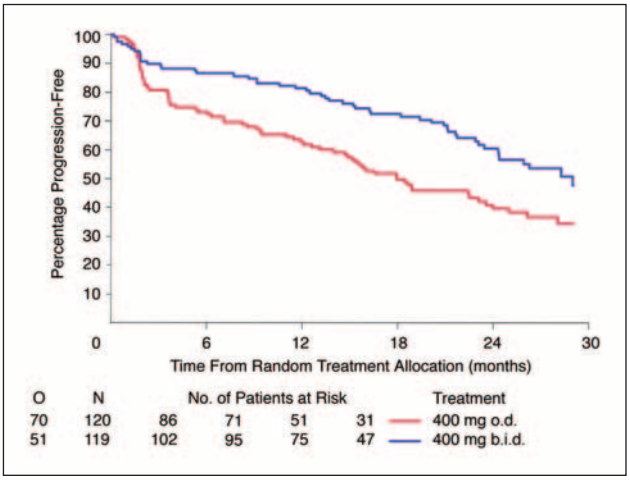

Fig 6. Time to progression by treatment arm in patients with tumors of GI origin other than stomach or small bowel. O, observed failures; N, number of cases; od, once daily.

Late resistance to imatinib is independently predicted by the size of the lesions present at treatment start. Tumor size has also been reported as a prognostic factor for primary disease by several groups and, therefore, has been included in the definition of risk groups for GIST established by a consensus meeting.[18] In our study, tumor size did not affect initial resistance to the drug (as demonstrated both by the univariate and the multivariate analyses), suggesting that patients with an advanced stage of disease are initially responsive to imatinib (as opposed to what is observed with conventional chemotherapy in solid tumors). However, tumor size has a significant impact on late resistance, which seems to increase with time, suggesting correlation with a delayed mechanism of drug resistance. Patients with large lesions are probably more exposed to the risk of secondary mutations because of a higher likelihood of emergence of new clones, which explains the increasing risk of late resistance.

According to our data, tumors of gastric origin tend to progress later than tumors of small bowel origin. This has also been reported for primary disease, and it has been suggested that the proportion of benign (as opposed to malignant) GISTs is higher in the stomach than in the small bowel[19] and that the mitotic index is highly site dependent.[20] Our model demonstrates that, in advanced disease, site of origin adds independent prognostic information to baseline granulocyte count and tumor size, but it still needs to be investigated whether this prognostic information is also independent of mitotic index.

Despite the inclusion of 20% of patients older than the age of 70 years, age did not show any prognostic value for either initial or late resistance to imatinib, even in the univariate analysis. The same observation has been reported for chronic myeloid leukemia, with the conclusion that the adverse prognosis of elderly patients is generally related to the treatment rather than the intrinsic biology of the disease.[21] This statement is probably also true for GIST.

Finally, the subgroup analysis suggests that delayed resistance to imatinib in patients allocated to the high-dose regimen is mainly observed in patients with a high baseline granulocyte count ($> 5 \times 10^9$/L) and in patients with a GI tumor origin outside of the stomach and the small bowel; our data do not suggest such an advantage in patients with tumors of small bowel origin. However, cross over from 400 mg once daily to 400 mg bid after progression has been shown to induce further disease stabilization in some patients,[22] and only survival data will be able to demonstrate whether increasing the initial dose of imatinib results in a clinical benefit for all patients or subgroups of patients with advanced GIST.

Our results may be used to identify patients for whom initial and long-term treatment should be improved. In particular, imatinib resistance can be delayed by increasing the initial dose in patients with high granulocyte counts and in patients with tumors of GI origin outside of the stomach and small bowel. These results may also be helpful in the investigation or confirmation of the different biologic mechanisms of drug resistance. Correlation of identified prognostic factors with immunohistochemical and molecular parameters could improve the knowledge of this disease.

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Appendix

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Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Martine Van Glabbeke						Novartis (A)		
Jaap Verweij			Novartis (A)			Novartis (B)		
Paolo G. Casali			Novartis Pharma (A)		Novartis Pharma (B)			
Peter Hohenberger						Novartis (B)		
Isabelle Ray-Coquard			Roche (A)					
Allan T. van Oosterom			Novartis; Pfizer (A); Pharmamar; Roche (A); Aventis; Lilly; BMS (A)			Novartis; Roche (B); Shering Plough (B); Amgen (B)		
David Goldstein			Novartis (A)		Novartis (A)		Novartis	Novartis (A)
Ian R. Judson			Novartis (A)		Novartis (A)		Novartis	Novartis (A)
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