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Predicting toxicities for patients with advanced gastrointestinal stromal tumours treated with imatinib: A study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC–ISG–AGITG)

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ABSTRACT

The aim of this study was to identify prognostic factors for toxicity to treatment with imatinib. The study was based on 942 patients with gastrointestinal stromal tumours (GIST) randomised to receive imatinib at different doses. The correlation between toxicities occurring with a Common Toxicity Criteria (CTC) grade 2 or more (non-haematological) or grade 3 or 4 (haematological) and imatinib dose, age, sex, performance status, original disease site, site and size of lesions at trial entry, baseline haematological and biological parameters was investigated. Anaemia was correlated with dose and baseline haemoglobin level, and neutropaenia with baseline neutrophil count and haemoglobin level. The risk of non-haematological toxicities was dose dependent and higher in females (oedema, nausea, diarrhoea), and in patients of advanced age (oedema, rash fatigue), poor performance status (fatigue and nausea), prior chemotherapy (fatigue), tumour of identified gastrointestinal origin (diarrhoea) and small lesions (rash). A multivariate risk calculator that can be used in the clinic for individual patients is proposed.

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1. Introduction

Gastrointestinal stromal tumours (GIST) are a subset of soft tissue sarcomas classified relatively recently, which have proven to be insensitive to chemotherapy and radiotherapy.[1]

Imatinib is a small molecule tyrosine kinase inhibitor active against BCR-ABL, KIT and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. KIT is expressed in the vast majority of GISTs and is frequently mutated, leading to constitutive activation in these tumours. Treatment with imatinib has increased the 2 year' survival expectation of patients with advanced or metastatic GIST from less than 20% to approximately 70%.[2,3]

However, the optimal dose of imatinib for the treatment of GIST is still unclear. According to a European Organisation for Research and Treatment of Cancer (EORTC) phase I study, the highest feasible dose of imatinib in GIST is 400 mg bid.[4] One randomised phase II trial (400 mg once daily (od) versus 300 twice daily (bid)) and one single-arm phase II trial (400 mg bid) have shown activity at all dose levels.[5,6] The drug has been registered for the treatment of GIST at a dose of 400 mg od.

Formal comparison of the standard dose (400 mg od) versus the highest feasible dose (400 mg bid) has been addressed in two large randomised phase III trials. These trials have not demonstrated a survival benefit, despite a small progression-free survival advantage for the high-dose arm.[2,3] Exploratory analyses have suggested that the dose-response relationship differs greatly between prognostic subgroups.[7,8]

Although all trials report that the drug is well tolerated at the explored dose levels, a substantial proportion of dose reduction was reported in the two large randomised trials: 10% and 44% respectively for the standard and the high-dose arm (absolute proportion) in the Southwest Oncology Group (SWOG) study;[9] 13% and 49% (6 months' cumulative incidence) in the study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC–ISG–AGITG);[2] in this last study 32% and 50%, respectively, of the patients experienced at least one Common Toxicity Criteria (CTC) grade III or IV toxicity during therapy; anaemia, oedema, fatigue, nausea, abdominal pain, diarrhoea, neutropaenia and rash were all recorded in more than one-third of the patients and all were dose-dependent except for neutropaenia and abdominal pain.[2]

A similar toxicity profile has been reported in other imatinib trials, in GIST and other tumour types.[4–6,10–12]

The aim of the current study was to identify factors that influence the occurrence of the principal toxic events in GIST patients treated with imatinib, and to provide models to predict the probability of observing those toxicities in individual patients.

2. Materials and methods

In the EORTC–ISG–AGITG phase III trial, 946 patients with advanced or metastatic GIST were randomised to be treated with imatinib at a dose of 400 mg od (standard dose arm) or 400 mg bid (high-dose arm). In case of progressive disease in the standard dose arm, a cross-over to 400 mg bid was scheduled.

Eligibility criteria included a World Health Organisation (WHO) performance score of up to 3, normal haematological and renal function, and liver function tests within 2.5 times the upper normal value (or 5 times in the case of liver metastases). Any prior therapy was allowed and there was no upper age limit.

Toxicities were assessed weekly during the first 2 months of therapy, monthly up to 6 months and 3-monthly thereafter, using the CTC, version 2.0.

Treatment had to be withheld until recovery in the case of grade 2 non-haematological and grade 3 haematological toxicity; the dose had to be reduced in case of recurrence of those events, and in case of grade 3 non-haematological toxicity. No dose reduction was required for anaemia, but transfusions and/or epoetin were allowed.

Other eligibility criteria, evaluation criteria and efficacy results have been described elsewhere.[2]

In the present study, the occurrence of the principal toxicities were analysed: grade 2 (or more) oedema, fatigue, nausea, diarrhoea and skin rash; grade 3 (or 4) anaemia and neutropaenia. Leucopaenia and vomiting were not analysed, because of their obvious correlation with neutropaenia and nausea. Abdominal pain was not analysed, because it was difficult to distinguish disease-related from treatment-related events.

The cumulative incidence of all events was estimated across time, using competing risk methods. Per protocol discontinuations and dose escalations (because of progression) were considered as competing risks.

For the prognostic factors analyses, logistic regression models were used to predict the absolute occurrences of events. Potential prognostic factors were first selected by univariate analysis. All factors significant at the 0.05 level in univariate logistic models were subsequently included in a multivariate regression model; factors significant at the 0.01 level have been retained in the final model.

For haemoglobin level and neutrophil counts, the correlation between the nadir and the initial value was further explored by linear regression.

The following variables were investigated as potential prognostic factors: age, sex, performance status, time since initial diagnosis of GIST, prior therapies (surgery, radiotherapy, chemotherapy), site of disease origin (stomach, bowel, other gastrointestinal site, 'abdominal' not further specified), and laboratory parameters at study entry (white blood cell count (WBC), absolute neutrophil count (ANC), platelets, haemoglobin, bilirubin, creatinine, and albumin).

An interactive risk calculator has subsequently been designed on the basis of the final logistic models, using Microsoft Excel. Individual patient's characteristics are entered by the user, and the calculator estimates the probability of each toxicity for this patient. This risk calculator can be downloaded from the EORTC website (www.eortc.be/tools/imatinibtoxicity).

In order to validate the final risk models (and the risk calculator), data from a phase I and a phase II study conducted in soft tissue sarcoma by the EORTC Soft Tissue and Bone Sarcoma Group were used.[4,6]

For each side-effect, patients of the validation set have been classified in risk groups according to our models:

estimated probability above 40%, between 20% and 40% and under 20% for oedema and fatigue; estimated probability above 20% and under 20% for the other events studied. The observed occurrence of those events (and the estimated 95% confidence interval) has been tabulated for each risk group and compared with the model prediction.

3. Results

3.1. Duration of protocol therapy and follow-up

The present analysis is based on the 942 patients who received at least one administration of imatinib. At the time of this analysis, 310 patients were still receiving the protocol therapy (without cross-over), but the median follow-up was 42 months and 99%, 90% and 81% of the patients have been followed for 1, 2 and 3 years, respectively. At 1 year, only 27% of the patients had either discontinued protocol therapy or crossed-over to the high dose.

3.2. Description of toxicities

The worst grade of reported toxicities are listed in Table 1.

The haematological toxicities included in this analysis are anaemia (94% all grades/13% grade 3 or higher) and neutropaenia (42%/7%), and the non-haematological toxicities are oedema (80% all grades/35% grade 2 or higher), skin rash (37%/15%), fatigue (75%/36%) and gastrointestinal: nausea (56%/20%) and diarrhoea (54%/18%).

3.3. Cumulative incidence of events

The cumulative incidence of the different types of toxicities (overall, and for each therapeutic arm) is shown in Figs. 1 and 2(a and b).

At 1 year, the most frequent toxicities (oedema and fatigue) had each occurred in 20% of the patients in the standard dose arm, and in respectively 42% and 37% of the patients in the high-dose arm.

Table 1 – Distribution of Common Toxicity Criteria (CTC) grades

Grade	0	1	2	3	4	Total
Neutropaenia	547 (58.07)	179 (19.00)	149 (15.82)	41 (4.35)	26 (2.76)	942
Anaemia	65 (6.90)	438 (46.50)	313 (33.23)	89 (9.45)	37 (3.93)	942
Oedema	191 (20.28)	426 (45.22)	265 (28.13)	57 (6.05)	3 (0.32)	942
Fatigue	238 (25.27)	369 (39.17)	249 (26.43)	84 (8.92)	2 (0.21)	942
Diarrhoea	434 (46.07)	334 (35.46)	137 (14.54)	36 (3.82)	1 (0.11)	942
Nausea	411 (43.63)	347 (36.84)	155 (16.45)	29 (3.08)	–	942
Rash	595 (63.16)	203 (21.55)	107 (11.36)	36 (3.82)	1 (0.11)	942

Numbers are given as totals (%).

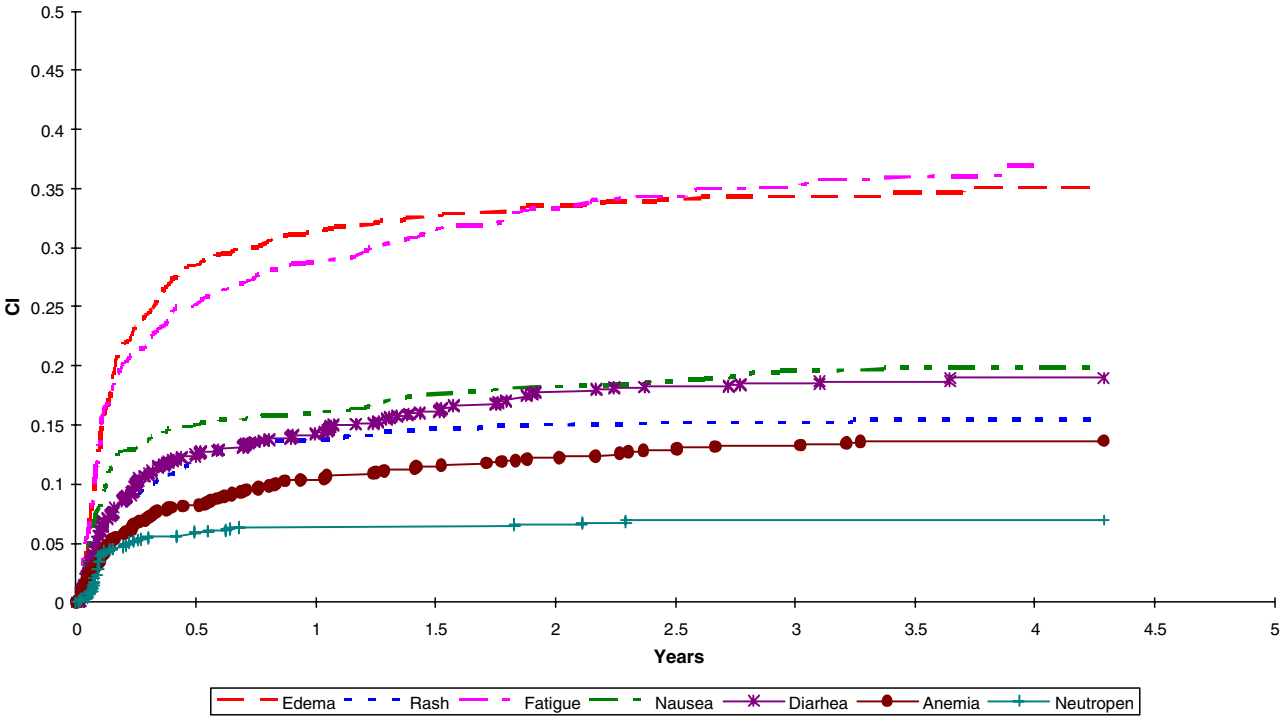

Fig. 1 – Cumulative incidence of toxic events – all patients.

3.4. *Identification of risk factors*

Results of the univariate and multivariate prognostic factor analyses are summarised in Table 2 for each toxicity.

For anaemia, only high-dose and baseline low haemoglobin level were independently significant at the 0.01 level in the multivariate logistic model. The factor 'low initial albumin level' added borderline significant information to this model (0.02). In linear regression models, nadir haemoglobin level was significantly correlated with dose ($P < 0.0001$), initial haemoglobin level ($P < 0.0001$) and initial albumin level ($P = 0.0001$).

In the multivariate logistic model the prognostic factors for neutropaenia were baseline low ANC and low haemoglobin levels. Neutropaenia was not dose-dependant ($P = 0.93$). In linear regression models, nadir ANC was correlated only with initial ANC.

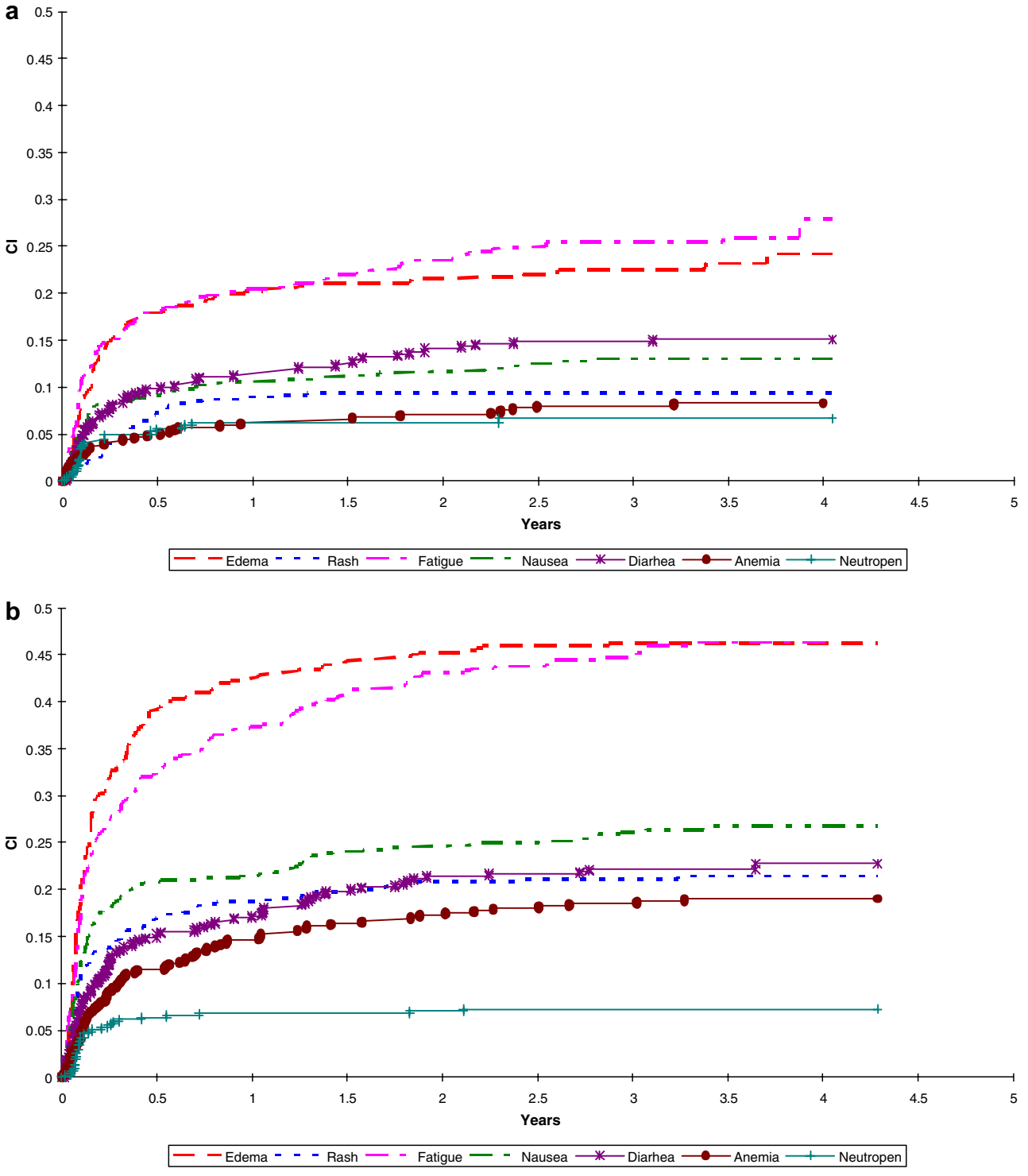

Fig. 2 – (a) – Cumulative incidence of toxic events – 400 mg od. (b) – Cumulative incidence of toxic events – 400 mg bid.

Independent prognostic factors for oedema included high dose, advanced age and female sex. An alternative model included high dose, female sex and baseline low albumin level (which is correlated with advanced age).

For rash, high dose, advanced age and small size of lesions were independent prognostic factors. As patients with large lesions progress earlier than patients with small lesions,[7] it was investigated whether, in patients with small lesions, the increased risk of developing rash could be explained by a longer exposure to imatinib: first the factor 'total treatment duration' was added to the logistic model: this factor turned out to be significant, but the factor 'size of lesions' kept its significance level. The model was also run on the subset of patients treated for more than 6 months, and for more than 12 months: in both subgroups, the (small) size of the lesions remained a significant risk factor.

For fatigue, high dose, advanced age, poor performance status and prior chemotherapy contributed to the final multivariate model.

For nausea, high dose, female sex and poor performance status were independent prognostic factors. Small bowel origin adds information of borderline significance ($P = 0.012$) to this model.

Finally, the independent prognostic factors for diarrhoea are high dose, female sex and identified gastrointestinal site of primary disease.

The final regression models (see coefficients in Table 3) enable one to compute, for individual patients, a 'risk score', for each toxicity investigated in this study. These scores can be converted (by logistic transformation) into estimations of the probability to experience the toxicities. The models have also been programmed in an Excel spreadsheet that can be

Table 2 – Results of the prognostic factors analyses

	Anaemia		Neutropaenia		Oedema		Rash		Fatigue		Nausea		Diarrhoea	
	U	M	U	M	U	M	U	M	U	M	U	M	U	M
Dose level	****	<0.0001			****	<0.0001	****	<0.0001	****	<0.0001	****	<0.0001	**	0.0028
Age					***	0.0011	****	<0.0001	***	0.0023				
Sex					****	<0.0001	*		*		****	<0.0001	*	0.0098
Performance status	****				*				****	0.0003	****	<0.0001		
Primary: GI							*						*	0.0084
Primary: abdominal							*						*	
Primary: stomach							*						*	
Primary: bowel											**			
Size of lesion	**						**	0.0008						
Prior surgery											*			
Prior radiotherapy									**					
Prior chemotherapy	*						**		**	0.0007				
Initial HGB	****	<0.0001	*	0.0022					****		**			
Initial ALB	****				**				***		**			
Initial ANC	***		***	<0.0001							**			
Initial WBC	*		****								*			

U, univariate models; M, multivariate models; WBC, white blood cell count; ANC, absolute neutrophil count; HGB, haemoglobin level; ALB, albumin level.
Conventional coded significance levels are provided for the univariate analysis (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$), while the exact significance levels are provided for all factors that remained in the final multivariate logistic models.

Table 3 – Multivariate models and risk calculator

	Intercept	Dose (1 = 400 od, 2 = 400 bid)	Age (years)	Sex (1 = male, 2 = female)	PS (WHO scale)	GI origin (0 = no, 1 = yes)	Tumour size (mm)	Prior chemotherapy (0 = no, 1 = yes)
(a) Coefficients for the models of non-haematological toxicities								
Oedema	4.54	–1.1	–0.0187	–0.775				
Fatigue	3.48	–0.924	–0.0178		–0.325			–0.517
Skin rash	4.77	–0.954	–0.0343				0.00631	
Nausea	4.64	–0.96		–0.963	–0.404			
Diarrhoea	3.53	–0.514		–0.441		–0.723		

	Intercept	Dose (1 = 400 od, 2 = 400 bid)	Baseline HGB (mmol/l)	Baseline ANC (10**9/l)
(b) Coefficients for the models of haematological toxicities				
Anaemia	–1.94	–0.993	0.715	0
Neutropaenia	–1.618	0	0.36	0.292

WHO, World Health Organisation; GI, gastrointestinal; ANC, absolute neutrophil count; HGB, haemoglobin level; od, once daily; bid, twice daily.

Table 4 – Examples of results for individual patients

Patients' characteristics						Dose	Probability of grade 2 (or higher) toxicity (%)				
Age (years)	Sex	PS (WHO)	Prior chemotherapy	Lesion size (mm)	GI origin	(mg/d)	Oedema	Fatigue	Skin rash	Nausea	Diarrhoea
(a) Non-haematological toxicities											
60	M	1	No	80	Yes	400	18	24	9	9	14
						800	39	44	21	21	21
40	M	1	No	80	Yes	400	13	18	5	9	14
						800	31	36	12	21	21
75	M	1	No	80	Yes	400	22	29	15	9	14
						800	46	51	31	21	21
60	F	1	No	80	Yes	400	32	24	9	21	20
						800	58	44	21	40	29
60	M	0	No	80	Yes	400	18	18	9	6	14
						800	39	36	21	15	21
60	M	2	No	80	Yes	400	18	30	9	13	14
						800	39	52	21	28	21
60	M	1	Yes	80	Yes	400	18	34	9	9	14
						800	39	57	21	21	21
60	M	1	No	25	Yes	400	18	24	13	9	14
						800	39	44	28	21	21
60	M	1	No	200	Yes	400	18	24	5	9	14
						800	39	44	11	21	21
60	M	1	No	80	No	400	18	24	9	9	7
						800	39	44	21	21	11

Patients characteristics		Dose	Probability of grade 3 (or 4) toxicity (%)	
HGB (mmol/l)	ANC (10**9/l)	(mg/d)	Anaemia	Neutropaenia
(b) Haematological toxicities				
8	5	400	6	6
		800	14	6
6	5	400	20	12
		800	41	12
9	5	400	3	4
		800	8	4
8	3	400	6	1
		800	14	11
8	9	400	6	2
		800	14	2

PS (WHO), World Health Organisation performance score.
ANC, absolute neutrophil count; HGB, haemoglobin level.

used in the clinic. Table 4 shows the obtained estimations for a few typical patients.

This model was validated using data of 91 patients with advanced or metastatic sarcoma treated with imatinib at doses ranging from 400 to 1000 mg/d. The calculator was used to estimate the probability of observing toxicities for all patients included in this data-set, and accordingly classified patients in risk groups. The proportion of toxicities actually observed in all risk groups is shown in Table 5.

The observed proportion of toxicities corresponds to the model for all except three groups, where the estimated 95% confidence interval still overlaps with the predicted chance range.

4. Discussion

Analyses of toxicity of cancer therapies generally focus on CTC grade 3 or 4 (grade 4 for haematological toxicities). In this study, we analysed the occurrence of grade 2 (or higher) non-haematological toxicities and grade 3 (or 4) haematological toxicities.

A randomised trial from the French Sarcoma Group has demonstrated that imatinib therapy should be continued indefinitely, even after complete response.[13] Toxicities generally considered as acceptable for a limited treatment period may be less acceptable for chronic therapy, and lead to dose reductions or even treatment discontinuation. A previous analysis has shown that the proportion of patients with toxicity seems to decrease with time[1] and toxicities do not substantially increase when the dose is escalated from 400 mg od to 400 mg bid.[16] This may be explained by an increase in the drug clearance and a subsequent lower drug exposure.[15] However, not all patients recover when the dose is maintained and recurrence of toxicity has been documented after re-challenging the patient at the same dose.[22]

More than 75% of the toxicities occurred within 1 year of treatment start, and at least 1 year of follow-up is available for 99% of the patients. We therefore consider our data to be

Table 5 – Results of the validation

Risk estimated by the model		> 40%	20–40 %	<20%	TOTAL
Oedema	Cases (*n*)	43	42	6	91
	Observed events	18 (41.9%)	18 (42.9%)*	0	36 (39.6%)
Fatigue	Cases (*n*)	60	30	1	91
	Observed events	38 (63.3%)	10 (33.3%)	0	48 (52.7%)

Risk estimated by the model		> 20%	<20%	TOTAL
Skin rash	Cases (*n*)	33	58	91
	Observed events	15 (45.5%)	10 (17.2%)	25 (27.5%)
Nausea	Cases (*n*)	62	29	91
	Observed events	21 (33.9%)	10 (34.5%)[a]	31 (34.1%)
Diarrhoea	Cases (*n*)	38	53	91
	Observed events	16 (42.1%)	11 (20.8%)[b]	27 (29.7%)
Anaemia	Cases (*n*)	24	67	91
	Observed events	7 (29.2%)	9 (13.4%)	16 (17.6%)
Neutropaenia	Cases (*n*)	1	90	91
	Observed events	0	12 (13.3%)	12 (13.2%)

95% confidence interval 27.7–59%.
a 95% confidence interval 17.9–54.3%.
b 95% confidence interval 10.8–34.1%.

mature, despite the fact that 310 of the 942 evaluable patients were still receiving protocol therapy.

For the identification of prognostic factors, we neglected the possible impact of treatment discontinuations, but simply analysed the occurrences of toxicities as binary variables, using logistic regression models. Unfortunately, no reliable and easily interpretable multivariate model is available for this competing risk situation. As 73% of the patients were still receiving protocol therapy 1 year after treatment start, it is unlikely that this choice is influencing the conclusions, especially as the variables that we have identified as prognostic factors for toxicity (age, sex, performance status, prior chemotherapy) do generally not influence progression-free survival, the principal cause of treatment discontinuations.[7]

Our results confirm that all investigated toxicities are highly dose dependent ($P = 0.005$ for diarrhoea, and $P < 0.0001$ for all other toxicities), with the exception of neutropaenia ($P = 0.93$). For GIST patients, this was previously reported in a phase I dose escalation study,[4] in a randomised phase II study[5] and in two randomised phase III studies.[2,3] No randomised data are available for leukaemia, but most series also suggest that toxicities are dose-dependent: nausea, oedema, diarrhoea and rash,[12] nausea, oedema and diarrhoea[18] and anaemia.[19] In only one Philadelphia chromosome-positive chronic phase chronic myeloid leukemia (CML) study of 144 cases,[20] toxicities were not more frequent with high-dose imatinib (400 mg bid) than in an historical series of 50 patients treated at standard dose (400 mg od), but those data should be interpreted with caution, because of the limited sample size and the use of historical controls.

Neutropaenia was completely dose-independent in our study. This was also the case in phase I CML trials.[17,18] It should be noted that the reported frequency of neutropaenia largely differed between diseases: 7% grade 3–4 in our study, as compared with 62%, 59%, 35% and 13% in large CML phase II trials, for decreasing stages of the disease, respectively.[11]

Risk factors for toxicity have not been explored previously in patients treated with imatinib for GIST, but some data are available from CML studies: the cumulated data of three phase II trials (532 cases) has been analysed by Hensley[11] and Cohen,[12] while Cortes[19] focused on anaemia in a partially overlapping population (338 cases); Valeyrie[22] has studied cutaneous toxicities on a smaller series (54 cases) of patients treated for Philadelphia chromosome-positive leukaemia.

Advanced age was reported as a significant risk factor for oedema[11,12] and anaemia,[19] and female sex as a significant risk factor for neutropaenia, oedema, nausea and fatigue,[12] for rash[12,22] and for anaemia.[19] For non-haematological side-effects, we observed the same correlations (but sex dropped out of the multivariate model for fatigue and rash). Hensley identified a correlation between drug exposure (steady state plasma concentration) and oedema, but this factor was not independent of age and sex.[11] In a GIST study, Judson observed that the drug clearance was lower and, subsequently, the area under the concentration curve higher for female patients, and for patients with low baseline albumin levels.[14] Those two findings suggest that drug exposure may be higher in female and/or elderly patients, who are consequently at a higher risk of toxicity.

For anaemia and neutropaenia, we did not find any correlation with age and sex, but only with low baseline haemoglobin and neutrophils levels. Area under the curve (AUC) has also been reported to be higher in patients with baseline low haemoglobin level[14] and high granulocytes counts,[15] so the prognostic value of baseline haemoglobin for neutropaenia may be explained by a higher drug exposure and a possible role of haemoglobin in drug transport and delivery.[23,24]

The increased risk of fatigue and nausea in patients with a poor performance status, the increased risk of fatigue for patients who have received prior chemotherapy and the increased risk of diarrhoea in patients with tumours of identified gastrointestinal origin has not been reported previously, but the last two factors could obviously not be explored in patients with leukaemia.

More surprising is the decreased risk of skin rash for patients with large lesions, and for patients with prior

chemotherapy; the last factor dropped out of the multivariate model because it was associated with age (patients over 60 years of age were less frequently pre-treated). As progression tends to occur earlier in patients with large lesions,[7] we investigated whether the decreased risk of rash could be due to a limited duration of the drug exposure: this hypothesis was rejected, as tumour size remained a significant risk factor when treatment duration was entered in the model, or when patients with short treatment duration (<6 or <12 months) were excluded from the data-set. In the CML studies a higher risk of toxicity was reported for patients with advanced disease, but the dose of imatinib may have been an important confounding factor.[10,11] So far, we are unable to explain this correlation.

We intend to estimate the probability of individual patients experiencing toxicities on the basis of the final logistic models issued from this analysis. The coefficients of all models are included in Table 3, and we also propose an interactive risk calculator (using the same coefficients), programmed in Excel. This simple tool can be used in clinical practice to customise treatment for individual patients.

Those models have been estimated on the basis of the largest available series of GIST patients treated with imatinib. They have been validated on the basis of a small series of 91 sarcoma patients treated at doses ranging from 400 to 1000 mg. Results of those validation tests are generally good (except for the underestimation of oedema and nausea in the low-risk groups), considering the limited sample size of the validation set. In our validation data-set, the occurrence of oedema was not correlated with sex, which may explain the discrepancy with our oedema model. We expect to be able to validate our models further when data from larger series of patients become available.

In conclusion, this study has identified factors that can potentially increase the risk of encountering toxicities in patients with advanced or metastatic GIST treated with imatinib. Based on those results, we propose a simple tool to calculate the risk of the principal toxic events for individual patients.

Conflict of interest statement

J. Verweij, P. Casali, P. Reichard, A. van Oosterom, I. Judson and JY Blay have received research grants, travel support or/and honoraria for speaking engagements and as members of various Novartis advisory boards. The EORTC–IST–AGITG study was funded by an unrestricted grant from Novartis Oncology. However, the study was conducted independently under the supervision of the steering committee. Novartis was not involved in study design, data collection or data analysis.

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