Advanced soft tissue sarcoma: prognostic factors and aspects of trial methodology

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Advanced soft tissue sarcoma: prognostic factors and aspects of trial methodology

Vergevorderde weke delen sarcomen: prognostische factoren en studie-methodologische aspecten

Thesis

to obtain the degree of doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus
Prof.dr. S.W.J. Lamberts
And in accordance with the decision of the Doctorate Board

The public defence shall be held on
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by

Martine Marie Berthe Van Glabbeke
born at Etterbeek, Belgium

Doctoral Committee

Promotor	Prof.dr. J. Verweij
Other members:	Prof.dr. G. Stoter Prof.dr. A.A.M. Eggermont Prof.dr. A.T. van Oosterom

To the memory of my mother,

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Chapter I

Introduction to the thesis

Soft tissue sarcoma

Soft tissue sarcomas are rare tumors, and globally account for less than 1% of all malignancies. They develop from the cells of the soft supporting tissues of the body (also known as mesenchyma): fat, muscles, nerves, fibrous tissues, blood and lymph vessels.

Soft tissue sarcomas are therefore a heterogeneous group of tumors. They currently include more than 50 different histological subtypes. The classification of these tumors is complex and review of the histopathologic specimen by experienced pathologists is generally recommended for clinical practice and, a fortiori, for clinical research. Progress in the understanding of sarcoma has frequently resulted in identification of new histological subtypes or reclassification of existing ones. The development of immunochemistry, cytogenetic and molecular genetic has brought major progress in this field in the last 10 years. The latest available classification of soft tissue tumors has been issued by the World Health Organization in 2002 [1].

Several histological grading systems have been proposed, with either 3 or 4 classification levels**.** Most have been validated as prognostic factors for metastases free and overall survival in patients with untreated primary soft tissue sarcoma. The two most widely used grading systems are the one of the US National Cancer Institute (3 levels, based on the histological subtype, and corrected for tumor necrosis, mitotic rate, cellularity and/or pleomorphism for some subtypes), and the one of the French “Fédération Nationale des Centres de Lutte Contre le Cancer” (3 levels, based on tumor necrosis, mitotic rate and tumor differentiation, giving an equal weight to these 3 factors). The French system has been shown to better predict outcome, but both systems are still used. The two systems do overlap in approximately 2/3 of the cases [2].

Soft tissue sarcomas can occur in any site of the human body. According to the NCI webs site, almost half of them occur in extremities, 40% in trunk and retroperitoneum and 10% in head and neck; more recently, the WHO has reported a slightly different distribution: 75% are located in extremities, 10% in the trunk wall and 10% in the retroperitoneum. The two levels “CTOS code for anatomic site of disease” provides a standard classification system for the localization of the primary disease.

Diagnosis and treatment of primary disease

Soft tissue sarcomas are often diagnosed accidentally, because they generally develop without pain. Less than 1% of soft tissue tumors are malignant. Other soft tissue tumors are either benign or of intermediate malignancy (locally aggressive or rarely metastasizing), according to the last classification of soft tissue tumors [1]. The probability of malignancy of a newly diagnosed soft tissue tumor is related to size and depth, but, so far, malignancy can not be accurately predicted by clinical examinations and imaging techniques. A tumor biopsy is needed to confirm the histology, and this should preferably be performed in a specialized sarcoma center to avoid compromising the results of the subsequent surgery.

Primary treatment consists of radical surgery, eventually associated to radiotherapy. Unfortunately, a large proportion of the patients will subsequently relapse locally or develop metastases. Adjuvant chemotherapy has not been proved to increase overall survival, but a meta-analysis or adjuvant trials has demonstrated a significant improvement of disease free

survival (10% at 5 years), both in terms of control of the local tumor (5% at 5 years) and of the metastatic spread (9% at 5 years) [3].

Advanced disease and clinical trials

Inoperable locally advanced or metastatic disease at presentation, inoperable locoregional relapse and development of metastases are generally called “advanced disease”.

Systemic therapy is used for patients with advanced disease. Although responses and prolongation of progression free survival have been observed, this therapeutic approach is generally considered **as palliative**.

Cytotoxic agents that have demonstrated activity against soft tissue sarcoma are limited to doxorubicin, ifosfamide and dacarbazine. Multiple randomized clinical trials have been carried out to optimize the combination of these drugs as first treatment for advanced disease (generally called first line therapy). So far, no combination has been shown to significantly improve survival when compared to doxorubicin administered as a single agent at a dose of 75 or 80 mg/m^2 every 3 weeks.

Investigational new drugs are generally considered as therapeutic options after failure of the first line combination therapy. Most of the cytotoxic agents tested in the clinic against other malignancies have also been tested against soft tissue sarcoma in phase II trials, but none of them has showed any substantial activity in terms of objective response.

Targeted therapies have recently brought new expectations for the treatment of soft tissue sarcoma. Mechanisms of carcinogenesis and tumor growth have been extensively studied for sarcoma, making them ideal candidates for targeted therapies. These expectations have been substantiated by the documentation of the activity of imatinib mesylate for Gastro-Intestinal Stromal Tumors (GIST), a sarcoma entity that has been identified relatively recently and is known to be insensitive to chemotherapy. In a trial including 946 advanced GIST patients, the 2-years survival estimate is close to 70%, as compared to 20% with standard doxorubicin based chemotherapy [4]. The success of imatinib therapy for GIST is an encouraging example of the possibilities that can be offered by targeted therapies.

Specific histological subtypes are, so far, rarely addressed in clinical trials, and are not even often used for stratification. The difficulty to conduct histology specific studies resides in the limited potential accrual (in a subgroup of a rare disease), associated to the complexity and constant evolution of the histopathological classification. Inclusion of this heterogeneous group of diseases in clinical trials may have restricted the discovery of new agents to “**large spectrum**” drugs active against most of the frequent histological subtypes. Additionally, the referral pattern of individual centers and even of clinical research groups may be largely affected by the quality of the collaboration between medical oncologists and organ specialists at the institutional level. This may lead to “selection biases” and irreproducible results in clinical trials.

As an example, trials conducted in uterine leiomyosarcoma have shown a promising activity of the combination of docetaxel and gemcitabine, two agents that had failed “mixed histology” phase II studies [5].

Objective response to therapy has been used to document activity of new drugs since the recommendation of the WHO in 1979. “Response” is defined as an objectively documented decrease in the size of cancer lesions (subsequent to the administration of the drug), which translates a biological activity of the drug. WHO response criteria may not have been an optimal screening tool for new drugs in sarcoma: they used a complex response evaluation algorithm that was often misunderstood or misinterpreted; they ignored modern imaging techniques like computerized tomographic scans and magnetic resonance imaging, both largely used for the staging of soft tissue sarcoma; more importantly, they are not appropriate to document the activity of cytostatic agents (expected to stop tumor growth) that do not necessarily result in an immediate decrease of the size of the lesions. A few active agents may have been missed because of the use of inappropriate criteria.

Long disease stabilizations have been observed in recent phase II trials with trabectedin [6] and brostallicin [7], despite a limited number of objective responses. Both agents that are currently awaiting confirmation of their activity in controlled clinical trials.

The Soft Tissue and Bone Sarcoma Group (STBSG) of the European Organization for Research and Treatment of Cancer (EORTC) has conducted multiple clinical trials in soft tissue sarcoma, with a particular focus on patients with advanced disease. Those trials data have all been managed at the EORTC Data Center, using similar data collection forms, and similar database formats. A central pathology review by a panel of experts is mandatory for all trials subjects. The group has consistently used the French grading system since its first publication. As results, the group has accumulated a database of over 2000 patients treated with first line therapy for advanced soft tissue sarcoma, 380 patients from phase II trials in second or third line therapy, and 946 advanced GIST patients treated with imatinib in the largest clinical trial conducted so far.

Objectives of this thesis

Prognostic factors for newly diagnosed sarcoma patients have extensively been studied. Histological grading systems have been specifically designed to estimate the patients’ survival from primary disease presentation. Host (age, sex, performance status, biological parameters at diagnosis) and disease factors (histological type, anatomical localization of the primary disease, tumor size, depth and spread) have been explored in univariate and multivariate analyses. A staging system based on both clinical and pathological factors has been proposed, and its prognostic value has been validated. Other prognostic indexes are available for specific subgroups (based on tumor respectability, anatomical localization, histological subtypes).

None of this is available for patients with advanced disease treated with systemic therapy, and there are several reasons to believe that prognostic factors may be different in this population. Patients who reached the stage of advanced disease are an unfavorable selection of all patients with sarcoma. Prognostic factors at that time are expected to reflect both the natural course of the disease and the sensitivity to systemic therapy. Also, factors characterizing the previous evolution of the disease and the prior therapies need to be added to the list of variables that can affect the prognosis.

As only palliative treatments are available for advanced soft tissue sarcoma, there is an urgent need to explore new possible therapeutic options in well designed clinical trials. Targeted therapies are expected to play a major role in treatment of sarcoma in the future, but classical drug development methodology developed for cytotoxic drugs is probably not applicable to targeted therapies. A better understanding of the disease and of the factors likely to affect response to therapy would lead to optimization of the clinical trials designs, in terms of patients selection, stratification factors, selection of end-points for early drug development and historical references to assess the level or activity and toxicity of new agents.

The difficulties linked to the complexity of the histology, to the use of different grading system, and, most of all, to the lack of large series of consistently documented cases have all been, so far, obstacle to address those issues in a consistent way.

The EORTC prospectively obtained databases provided a unique opportunity to run retrospective analyses aiming at a better understanding of this complicated disease, and optimization of the design of future clinical trials that will be needed to improve the systemic therapy of these patients. This thesis describes part of this work.

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Chapter II

Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens. An EORTC STBSG study.

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Summary

PURPOSE: A total of 2,185 patients with advanced soft tissue sarcomas who had been treated in seven clinical trials investigating the use of doxorubicin- or epirubicin-containing regimens as first-line chemotherapy were studied in this prognostic-factor analysis.

PATIENTS AND METHODS: Overall survival time (median, 51 weeks) and response to chemotherapy (26% complete response or partial response) were the two end points. The cofactors were sex; age; performance status; prior therapies; the presence of locoregional or recurrent disease; lung, liver, and bone metastases at the time of entry onto the trial; long time period between the initial diagnosis of sarcoma and entry onto the study; and histologic type and grade.

RESULTS: Univariate analyses showed (a) a significant, favorable influence of good performance status, young age, and absence of liver metastases on both survival time and response rate, (b) a significant, favorable influence of low histopathologic disease grade on survival time, despite a significantly lower response rate, (c) increased survival time for patients with a long time period between the initial diagnosis of sarcoma and entry onto the study, despite equivalent response rates, and (d) increased survival time with liposarcoma or synovial sarcoma, a decreased survival time with malignant fibrous histiocytoma, a lower response rate with leiomyosarcoma, and a higher response rate with liposarcoma ($P < .05$ for all log-rank and χ^2 tests). The Cox model selected good performance status ($P < .0001$), absence of liver metastases ($P = .0001$), low histopathologic grade ($P = .0002$), long time lapse since initial diagnosis ($P = .0004$), and young age ($P = .0045$) as favorable prognostic factors of survival time. The logistic model selected absence of liver metastases ($P < .0001$), young age ($P = .0024$), high histopathologic grade ($P = .0051$), and liposarcoma ($P = .0065$) as favorable prognostic factors of response rate.

CONCLUSION: This analysis demonstrates that for advanced soft tissue sarcoma, response to chemotherapy is not predicted by the same factors as is overall survival time. This needs to be taken into account in the interpretation of trials assessing the value of new agents for this disease on the basis of response to treatment.

Introduction

For more than 20 years, the Soft Tissue and Bone Sarcoma Group (STBSG) of the European Organization for Research and Treatment of Cancer (EORTC) has been investigating different chemotherapy regimens for advanced and metastatic soft tissue sarcomas. In chemotherapy-naive patients with advanced disease (who had either relapsed after primary tumor surgery and/or radiotherapy or presented with inoperable or metastatic disease), successive clinical trials were performed that investigated a series of doxorubicin- or epirubicin-containing regimens (Table 1). None of the randomized trials has demonstrated the superiority of any of the investigated regimens, either in terms of response to chemotherapy or in terms of survival [1-7]. The data from all trials have been managed at the EORTC Data Center, resulting in the accumulation of an homogeneous database for more than 2,000 prospectively recruited patients. This accumulation presented a unique opportunity to conduct a retrospective analysis of prognostic factors influencing response to chemotherapy and overall survival time. Although the prognosis of patients with

primary disease, as well as that of patients amenable to metastasectomy, had previously been studied, no data are currently available from large series to predict the duration of survival and probability of response to chemotherapy of patients with advanced disease.

Table II-1: Therapeutic regimen

Regimen	Cycle description	Cycle duration
A	Doxorubicin 75 mg/m2	3 weeks
B	Doxorubicin 50 mg/m2 Ifosfamide 5 g/m2	3 weeks
C	Doxorubicin 75 mg/m2 Ifosfamide 5 g/m2 GM-CSF	3 weeks
D	Epirubicine 75 mg/m2	3 weeks
E	Epirubicine 150 mg/m2	3 weeks
F	Epirubicine 50 mg/m2, day 1-3	3 weeks
G	Doxorubicin 50 mg/m2 Dacarbazine 250 mg/m2, day 1-5 Cyclophosphamide 500 mg/m2 Vincristine 1.5 mg/m2	4 weeks
H	Doxorubicin 50 mg/m2 Dacarbazine 250 mg/m2, day 1-5 Cyclophosphamide 500 mg/m2, day 29 Vincristine 1.5 mg/m2, day 29	8 weeks
I	Doxorubicin 50 mg/m2 Dacarbazine 750 mg/m2 Cyclophosphamide 500 mg/m2 Vincristine 1.5 mg/m2	3 weeks

Patients and methods

Patients

Patients who had been treated in seven studies investigating doxorubicin- or epirubicin-containing regimens as a mode of first-line chemotherapy were included in this prognostic-factor analysis. The therapeutic regimens are described in Table 1.

End Points of the Analysis

The two end points of our study were response to chemotherapy and overall survival time. The aim of the study was to determine whether the factors that influenced response to

chemotherapy were the same as the factors that influenced survival time and to build a set of independent prognostic factors for each end point.

Survival time was computed from the date of randomization (in the randomized trials) or from the date of prospective registration (in the nonrandomized trials) to the date of death. Patients who were alive at the last follow-up date were censored.

Response to chemotherapy was evaluated according to World Health Organization (WHO) criteria [8] in all trials. Complete responses and partial responses were externally reviewed and validated on the basis of source documents. Response to therapy was analyzed as a binary variable: patients who achieved a complete or partial response were considered "responders," and patients with stable disease or progression were considered "failures."

Sample Size

A total of 2,233 patients were registered in the seven trials. Patients were included in the analysis presented here regardless of their eligibility status for each particular trial. For 48 patients, no follow-up data were available. Consequently, a total of 2,185 patients was included in the survival time analysis, and 446 patients were still alive at the time of their last follow-up. The analysis of response to chemotherapy included 1,922 cases. The 263 remaining patients were not assessable for this end point.

Investigated Cofactors

The factors routinely recorded as baseline data in the different trials were investigated as potential prognostic factors (demographic data, history of sarcoma, extent of disease at the time of trial inclusion, and histology). The demographic variables included age, sex, and performance status before the start of chemotherapy. Age was recoded into four categories (< 40, 40 to 50, 50 to 60, and > 60 years). Performance status was measured on the WHO scale except for two trials in which it was retrospectively converted from the Karnofsky scale to the WHO scale. Variables related to the history of sarcoma included prior surgery and prior radiotherapy, as well as the time since the first diagnosis of sarcoma. This last variable was recoded into six categories (< 3, 3 to 6, 6 to 12, 12 to 24, 24 to 60, and > 60 months). Prior chemotherapy was an exclusion criterion in all trials.

Data on the extent and localization of the disease included the presence of locoregional disease or local recurrence, as well as lung, liver, and bone metastases. Chest radiography, bone scans, and liver scans were mandatory at the time of entry onto all trials. Histologic subtype and histopathologic grade, as assessed by a panel of reference pathologists, were preferred over the use of local diagnosis, to ensure the consistency and homogeneity of the data. For practical reasons, only 70% of the cases could be reviewed. Analyses including these factors are therefore based on the subset of reviewed cases. Histologic subtypes were recoded as multiple binary variables.

Statistical Methods

All cofactors were first investigated as potential prognostic factors of survival and of response by univariate techniques. For survival time, the proportion of survivors was estimated by the Kaplan-Meier method [9] and the log-rank test was used for the

comparisons [10]. For ordered categorical variables (age group, performance status, histopathologic grade, time since initial diagnosis), the log-rank test for trend was used. The proportion of responders was estimated in contingency tables, and the categories were compared using the χ^2 test. For ordered categorical variables, the χ^2 test for trend was used [11]. Two multivariate models were built: a Cox model [12] for overall survival time, and a logistic model [13] for response to chemotherapy. All factors that presented with a significant or borderline prognostic value in the univariate analyses were initially included in the models. Nonsignificant factors were subsequently removed according to a backward selection procedure.

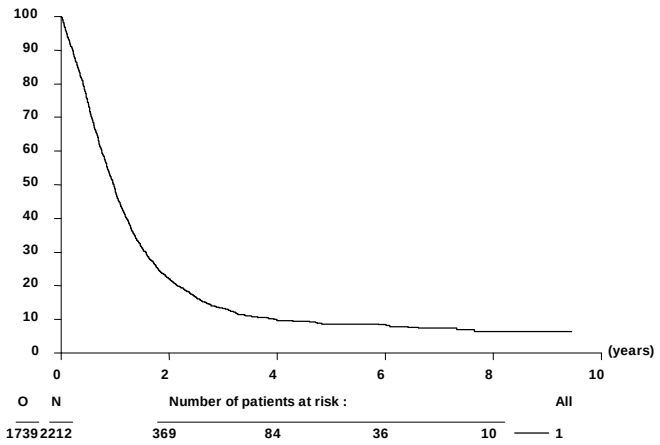
The results presented in this article are based on unadjusted analyses of categorical variables. The final multivariate models were later adjusted by therapeutic regimen and by study, which did not change any conclusion. Replacement of categorized variables by original continuous variables (age, time lapse since diagnosis) also did not change any conclusion.

Results

In the series of 2,185 patients with follow-up data, the median survival time was 51 weeks. The overall survival time for all patients is shown in Fig 1. Survival curves for the therapeutic arms of the different studies were all superimposable. Comparison of the therapeutic arms in all randomized trials showed no significant differences (Table 2).

Figure II-1:
Overall survival

O, observed failures;
N, number of patients



In the series of 1,922 patients who were assessable for response, an overall response rate of 26% was observed. This response rate varied largely from one study to the other, but, with the exception of one study, no statistically significant difference was observed between the randomized therapeutic arms in any of the studies (Table 2). These findings are in agreement with the individual study results from the original publications, which were based on eligible patients [1-7].

Table II-2: Results of previous studies

Study no.	Treat. Arm	No of cases	No eval. survival	No eval. resp.	Resp. rate	Median surv.	P-values: resp / surv
62861	G	191	184	151	34%	44 wks	P = 0.001 / P = 0.422
	H	121	118	93	15%	42 wks	
62801	A	106	101	85	25%	41 wks	P = 0.277 / P = 0.622
	D	104	102	84	18%	46 wks	
62842	B	203	195	177	34%	58 wks	
62851	A	295	289	266	23%	49 wks	P = 0.437 / P = 0.896
	B	297	287	254	28%	57 wks	
	I	157	157	146	27%	51 wks	
62883	C	111	111	99	46%	54 wks	
62901	A	112	111	99	13%	50 wks	P = 0.705 / P = 0.967
	E	111	109	97	16%	48 wks	
	F	111	109	93	17%	45 wks	
62903	B	157	155	145	23%	55 wks	P = 0.491 / P = 0.919
	C	157	157	133	26%	49 wks	
TOTAL		2233	2185	1922	26%	51 wks	

wks, weeks; eval., evaluable; resp., response; surv., survival

Univariate Analysis of Survival Time

The univariate analysis of survival time (Table 3) demonstrated a highly significant favorable prognostic value of young age, good performance status, absence of liver and bone metastases, low histopathologic grade, and long time lapse since the initial diagnosis of sarcoma. Patients with liposarcoma and those with synovial sarcoma had a significantly better survival time, whereas patients with malignant fibrous histiocytoma had a significantly worse survival time. The other investigated cofactors did not affect survival time.

Table II-3: Univariate analysis of survival time

		No of cases	No of death	1-yr surviv. estim.	2-yr surviv. estim.	Median survival time	P
Overall		2185	1739	48%	22%	51 wks	-
Age group	< 40 yrs	562	430	53%	24%	56 wks	<0.001
	40 - 50 yrs	434	354	52%	23%	55 wks	
	50 - 60 yrs	571	459	48%	22%	50 wks	
	> 60 yrs	564	446	39%	20%	41 wks	
Performance status	PS 0	894	672	59%	30%	65 wks	<0.0001
	PS 1	802	657	47%	19%	49 wks	
	PS 2	375	324	26%	9%	27 wks	
	PS 3	25	22	10%	-	9 wks	
Liver metastases	No	1637	1286	50%	24%	52 wks	<0.0001
	Yes	372	314	42%	13%	44 wks	
Lung metastases	No	976	772	48%	24%	50 wks	0.682
	Yes	1159	932	48%	20%	51 wks	
Bone metastases	No	1715	1370	49%	23%	52 wks	0.0023
	Yes	222	174	39%	14%	41 wks	
Histologic subtype	Leiomyos.	538	449	49%	20%	52 wks	0.438
	MFH	218	181	39%	18%	42 wks	0.012
	Synovial	120	92	67%	26%	69 wks	0.011
	Liposarc.	111	86	70%	37%	76 wks	0.0005
	Fibrosarc.	69	56	43%	18%	49 wks	0.591
	Other	506	403	40%	22%	42 wks	0.298
Tumor grade	I	176	122	64%	40%	79 wks	<0.0001
	II	457	377	52%	22%	54 wks	
	III	728	606	42%	17%	44 wks	
Time since initial diagnosis of sarcoma	< 3 mon	397	311	44%	21%	45 wks	<0.0001
	3-6 mon	146	116	34%	15%	36 wks	
	6-12 mon	253	216	36%	10%	37 wks	
	1-2 yrs	207	166	48%	18%	51 wks	
	2-5 yrs	207	147	62%	34%	71 wks	
	> 5 yrs	96	64	66%	34%	82 wks	

yr, year; surviv.estim., survival estimate

Multivariate Analysis of Survival Time

The final Cox model for overall survival time is described in Table 4. According to this model, good performance status (P < .0001), absence of liver metastases (P < .0001), low histopathologic grade (P = .0002), long time lapse since the first diagnosis of sarcoma (long disease-free interval) (P = .0004), and young age (P = .0045) were the only independent favorable prognostic factors of survival time.

Table II-4: Final Cox model for overall survival

Factor	Parameter estimate	Risk ratio	P-value
Performance status	0.415	1.515	< 0.0001
Liver involvement	0.379	1.461	< 0.0001
Tumor grade	0.215	1.240	0.0002
Delay since initial diagnosis of sarcoma	- 0.082	0.921	0.0004
Age	0.102	1.107	0.0045

The impact of each factor may be quantified by the increase in the "hazard ratio" (immediate risk of death) of two successive patient categories (ie, in performance status, PS 1 compared with PS 0). According to the final Cox model, this risk increased by 51.5% for performance status categories, 46.1% for liver involvement, 24% for histopathologic grade categories, and 10.7% for age categories and decreased by 7.9% for elapsed time categories.

The liposarcoma and malignant fibrous histiocytoma categories dropped out of the multivariate models when tumor grade was included. Indeed, these factors are correlated. The overall series included 13% of grade 1 tumors, 34% of grade 2 tumors, and 53% of grade 3 tumors. For liposarcoma, these figures were 39%, 34%, and 28%, respectively. For malignant fibrous histiocytoma, these figures were 8%, 24%, and 68%, respectively.

The synovial sarcoma category included only 1% of patients with liver involvement (v 19% in other histologic categories and 14% if the leiomyosarcoma category is excluded), as well as a high proportion (58%) of patients under 40 years of age (v 25% in other histologic categories). This factor dropped out of the final model, which included age and liver involvement. The overall survival for all independent prognostic subgroups is shown in Figures 2 through 7.

Figure II-2:
Overall survival by age group

O, observed failures;
N, total number of patients

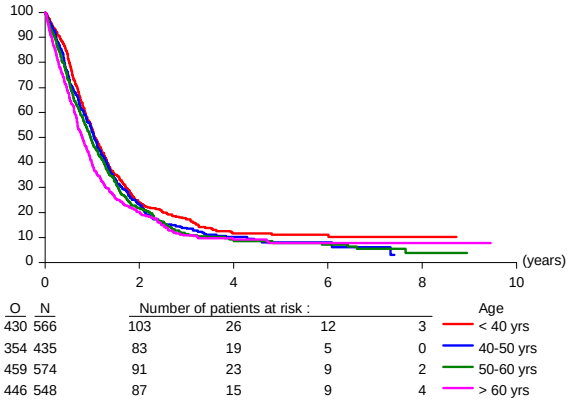


Figure II-3:
Overall survival by performance status

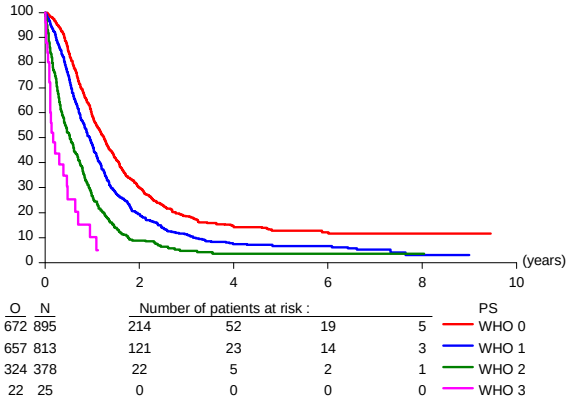


Figure II-4:
Overall survival by liver metastases

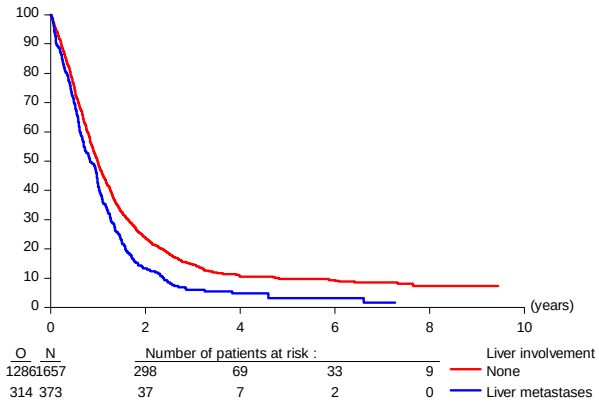


Figure II-5:
Overall survival by histopathological grade

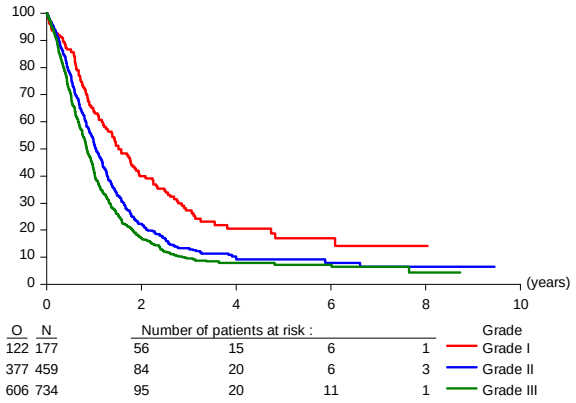


Figure II-6:
Overall survival by histologic cell type

Leio, leiomyosarcoma;
MFH, malignant fibrous histiocytoma;
Synov, synovial sarcoma;
Lipo, liposarcoma;
Fibro, fibrosarcoma

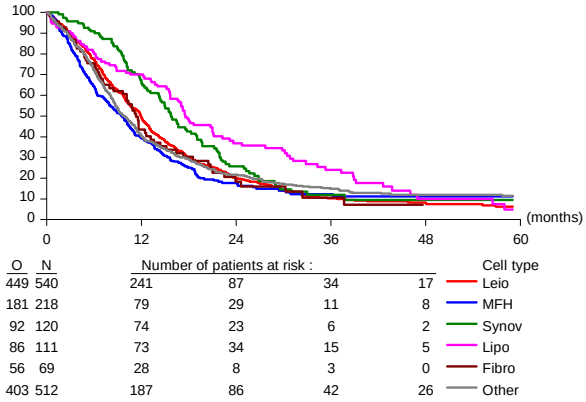


Figure II-7:
Overall survival by time elapsed since initial diagnosis of sarcoma

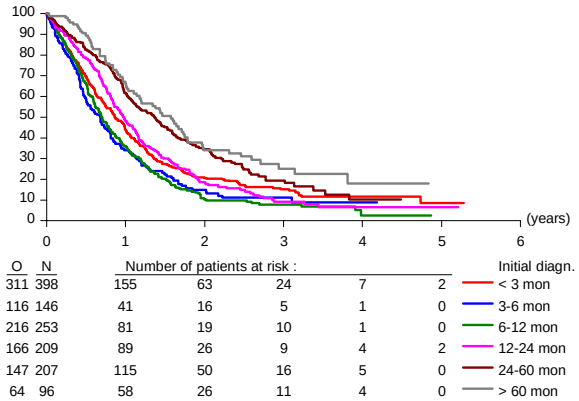


Table II-5: Univariate analysis of response to chemotherapy

		No of cases	No of responders	Response rate	P
Overall		2185	1739	48%	-
Age group	< 40 yrs	562	430	53%	0.001
	40 - 50 yrs	434	354	52%	
	50 - 60 yrs	571	459	48%	
	> 60 yrs	564	446	39%	
Performance status	PS 0	894	672	59%	0.001
	PS 1	802	657	47%	
	PS 2	375	324	26%	
	PS 3	25	22	10%	
Liver metast	No	1637	1286	50%	0.001
	Yes	372	314	42%	
Lung metastases	No	976	772	48%	0.021
	Yes	1159	932	48%	
Bone metastases	No	1715	1370	49%	0.109
	Yes	222	174	39%	
Histologic subtype	Leiomyos.	538	449	49%	0.002
	MFH	218	181	39%	0.716
	Synovial	120	92	67%	0.313
	Liposarc.	111	86	70%	0.049
	Fibrosarc.	69	56	43%	0.394
	Other	506	403	40%	0.038
Tumor grade	I	176	122	64%	0.008
	II	457	377	52%	
	III	728	606	42%	
Time since initial diagnosis of sarcoma	< 3 mon	397	311	44%	0.495
	3-6 mon	146	116	34%	
	6-12 mon	253	216	36%	
	1-2 yrs	207	166	48%	
	2-5 yrs	207	147	62%	
	> 5 yrs	96	64	66%	

Univariate Analysis of Response Rate

The results of the univariate analysis of response rate (Table 5) demonstrated a highly significant favorable prognostic value for the absence of liver metastases, young age, and good performance status. The response rates were also significantly higher for high-grade tumors and lower for leiomyosarcoma. The higher response rate of patients with lung metastases and those with liposarcoma is of borderline significance.

Multivariate Analysis of Response Rate

The final logistic model for response to chemotherapy is described in Table 6. According to this model, absence of liver lesions (P < .0001), young age (P = .0024), high histopathologic grade (P = .0051), and liposarcoma (P = .065) were the only independent favorable prognostic factors of response. The leiomyosarcoma category dropped out of the logistic model when liver involvement was included. In patients with liver lesions, leiomyosarcoma accounted for 62% of the cases; 11% of responses were observed versus 20% for other histologic categories. In patients without liver lesions, leiomyosarcoma only represented 29% of the cases, with a response rate of 29%, compared with 32% in other histologies. Performance status also dropped out of the final model.

Table II-6: Final logistic model for response to chemotherapy

Factor	Parameter estimate	Odds ratio	P-value
Liver involvement	0.963	2.620	< 0.0001
Age	0.184	1.202	0.0024
Tumor grade	- 0.297	0.743	0.0051
Liposarcoma	- 0.673	0.510	0.0065
(intercept)	1.202		

Discussion

Identification of prognostic factors in soft tissue sarcoma has been a field of extensive research in this rare group of malignant diseases, but it was primarily limited to the definition of staging systems for patients presenting for the first time with this disease [14-26]. The staging systems used in these analyses were usually based on a combination of clinical and histopathologic factors. Universally agreed-upon clinical prognostic factors include tumor size and quality of surgery (which obviously depends on tumor localization), whereas proposed histopathologic grading systems are usually based on mitotic count, tumor necrosis, and degree of differentiation [14]. In most of the studies, histopathologic grade was the most important prognostic factor, but Gaynor et al [20] also demonstrated that the prognostic value of this factor disappeared beyond 18 months. On behalf of the EORTC–Soft Tissue and Bone Sarcoma Group, van Unnik et al [14] have proposed a prognostic index, which is based on tumor size, mitotic count, and necrosis.

The prognostic factors for patients presenting with inoperable or metastatic disease and for patients developing metastases after surgery and/or radiotherapy may be different. So far, the prognostic factors for advanced and recurring cases have only been studied in the highly select population of patients amenable to metastasectomy [27-30]. In patients with advanced sarcomas who were not candidates for surgery, some data are available from studies that investigated specific chemotherapy regimens [1,31-33] but no large-scale analysis has been conducted so far. Our unique series of over 2,000 patients has been used to provide a model that predicts the probability of response to chemotherapy and the overall survival time in this population.

Despite the fact that age and performance status are generally not reported as prognostic factors for patients with primary disease, it is not surprising that these factors correlate with survival time in patients with advanced disease. This was also reported by Borden et al.[31] In our study, we have also demonstrated that age is highly predictive for response to first-line chemotherapy, but performance status does not add predictive information to the model. The absence of significant prognostic value for factors related to the nature and extent of previous therapy suggests that once a patient presents with inoperable advanced soft tissue sarcoma, prior modes of therapy do not have any further impact on the outcome.

Liver metastases had a very significant adverse predictive value for both response and survival. This might be explained by two hypotheses: (1) liver metastases are a sign of advanced disease, which explains the poor prognosis of those patients, or (2) the presence of liver metastases in itself is a poor prognostic factor, regardless of the degree of advancement of the disease, because liver metastases are apparently less chemosensitive than other lesions [33]. Both hypotheses need to be explored further.

Patients with a long time lapse since the first diagnosis of sarcoma had a better survival time than did patients recently diagnosed. This has also been reported with regard to other types of tumors, for which a long previous "disease-free survival" predicts a long survival time when patients relapse. Patients with a high histopathologic grade of disease had a significantly worse survival time than did the others, despite a significantly higher response rate. This is compatible with the recognition that high-grade tumors are more chemosensitive, but responses tend to be of short duration in these patients and are often followed by rapid progression.

The univariate analysis demonstrated the prognostic importance of histologic subtype. Patients with liposarcoma and synovial sarcoma had a significantly better survival time than did patients with other cell types, whereas patients with malignant fibrous histiocytoma had a worse survival time. Liposarcoma patients had a higher response rate, and leiomyosarcoma patients had a lower response rate. According to our analysis, liposarcoma appears in the form of chemosensitive tumors with a good prognosis of survival. The distribution of tumor grades in this histologic subtype explains the favorable survival time but is in contrast with the high response rate. Other histopathologic variables dropped out of the multivariate models, but the analysis presented here clarifies these findings on the basis of their correlation with other prognostic factors.

The lower probability of response to chemotherapy in leiomyosarcoma patients, which is in contrast with previously reported data [31,33] is linked to the increased frequency of liver metastases in these patients. Correlation of these two factors could be a result of the high

proportion of abdominal leiomyosarcoma cases in our series, which have a greater propensity for liver metastases. Because our data are up to 20 years old, the histologic entity of "gastrointestinal stromal sarcoma" had not been identified at the time of diagnosis of most of these patients, and these cases are probably included as leiomyosarcomas in our series. Unfortunately, we have not systematically recorded the site of origin of sarcoma in all trials and therefore cannot confirm this hypothesis. More recent data will enable us to study this issue further.

The decreased survival time in cases of malignant fibrous histiocytoma is obviously linked to the distribution of the histopathologic grades of these tumors. Synovial sarcoma usually involves young patients without liver metastases, which explains their good survival time. Finally, the overall survival time curve shows that a small proportion of patients is still surviving after 5 years and suggests that some of these patients may have been cured by chemotherapy.

In conclusion, this analysis demonstrates that for advanced soft tissue sarcomas, the probability of achieving response to chemotherapy is not predicted by the same factors as in overall survival time. While young age and the absence of liver metastases significantly affect both end points in a favorable way, low histopathologic grade has a favorable impact on survival time and an adverse impact on response rate. This should be taken into account in the interpretation of trials of new therapeutic agents in which the activity results are based on response.

The study also demonstrates the prognostic value of histologic subtypes of sarcoma. So far, we have been unable to confirm whether these factors add independent prognostic information to the described models, except for cases of liposarcoma, but we could demonstrate why they affected overall survival time and response to chemotherapy. Further investigations of the correlation between the histologic subtype, the site of origin of the disease, and the sites of the metastases should provide a better understanding of the behavior of the different histologic subtypes.

Author update (2002)

This analysis of a large database of patients with advanced soft tissue sarcoma documents the (expected) adverse prognosis of patients with old age or poor performance status, and, more interestingly, of patients with liver metastases.

This last finding could be explained by 3 hypotheses:

- liver metastases per se have a poor chemosensitivity (to anthracycline containing regimen),
- the presence of liver metastases is an indicator of advanced disease,
- patients with Gastro-Intestinal Stromal Tumors (GIST) in our population could have been entirely responsible for the apparent adverse prognostic value of liver metastases.

In order to explore the last hypothesis further, we have succeeded in identifying the site of the original tumor in 58 % of the patients and have subsequently been able to isolate a sub-

population of 1249 patients that does not include GIST cases. This sub-population excludes patients with tumors of gastro-intestinal, abdominal or unknown origin, who had either been classified by the review panel as "leiomyosarcoma" or "miscellaneous sarcoma", or had not been externally reviewed.

In this sub-population, the presence of liver metastases remains a significant prognostic factor, both in the univariate and multivariate analyses (table 1). This demonstrates that our original findings were not entirely due to the confounding effect of GIST cases, and that the two first hypotheses remain worth investigating.

Leiomyosarcoma from this sub-population originate mainly from the gynecological tract (58%) or the extremities (25%). Their response rate (28%) does not differ significantly (P=0.42, chi-square test) from the response rate in other cell types (30%). This is in contrast with the total population, where the low response rate of "leiomyosarcoma" is probably linked to the high proportion of abdominal and gastro-intestinal tumors and of liver metastases, as suggested in the discussion.

The original univariate analysis also highlights differences in response rate and survival between histologic subtypes. This variable is correlated with other prognostic factors and drops out of the multivariate models. However, as new therapeutic approaches in soft tissue sarcoma are targeting specific histologic subtypes, this paper, added to the more recent publication of progression free rates [34], provides useful historical data for early drug development.

Table II-7: Prognostic value of liver involvement

Parameter		Survival		Response	
Analysis		Univariate	Multivariate	Univariate	Multivariate
Original series (updated data)	Hazard / Odds ratio	1.374	1.450	3.236	2.899
	P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sub-population excluding possible GIST cases	Hazard / Odds ratio	1.312	1.412	1.807	1.792
	P-value	0.0082	0.0079	0.0178	0.0226

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Chapter III

Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy

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Abstract

Adult patients with metastatic or locally advanced irresectable soft-tissue sarcoma (ASTS) are generally considered as incurable. Whether some of these patients achieve long-term survival after first-line treatment with chemotherapy is not known. Patients with ASTS still alive 5 years after initial treatment with a doxorubicin-containing regimen, i.e. long-term survivors, were analysed among the 2187 patients included in first-line chemotherapy protocols between 1976 and 1990 in seven trials of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) group. 1888 patients were followed for at least 5 years. The initial clinical characteristics and the outcome of the long-term survivors were investigated. 66 of the 1888 patients were alive at 5 years and the projected 5-year survival was 8% in this series. Age or histological subtypes were similar in the long-term survivors compared with the other patients. The percentages of females (69%), of grade 1 tumours (35%), of patients with an initial performance status (PS) of 0 (63%) were significantly higher in the long-term survivors while liver metastasis (6% versus 21%) were significantly less frequent. Long-term survivors were observed in all subgroups of patients. 31, 31, 31 and 6% of the long-term survivors were in complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively, after the first-line regimen. A CR to a doxorubicin-containing regimen was the major parameter correlated to 5-year survival. In multivariate analysis using a logistic model, independent parameters correlated to 5-year survival were PS, female gender, grade I tumours, and the achievement of a CR after first-line treatment, which was retained as the most powerful predictor for 5-year survival. 10 of the 66 patients died after 5 years in this series, including 8 patients in PD or SD after first-line treatment versus 2 patients in PR or CR (P=0.01). 8% of patients with ASTS are alive 5 years after first-line chemotherapy with a doxorubicin-containing regimen. Long-term survivors are observed in all prognostic subgroups of patients, in particular those achieving a CR to first-line chemotherapy.

Introduction

The prognosis of patients with irresectable or advanced metastatic soft-tissue sarcoma (ASTS) remains poor with response rates to chemotherapy ranging from 20–35% in most series and a median survival of at best 12 months [1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11]. The treatment of ASTS is therefore generally considered as palliative. However, long-term survival can be achieved in patients with metastatic sarcoma in whom complete remission is achieved after complete resection of all metastases [12 and 13], as well as in patients with locally advanced disease when adequate surgery is rendered possible by preoperative chemotherapy [14]. However, whether long-term survival can be achieved in patients with irresectable metastatic or advanced sarcoma treated with chemotherapy has seldom been addressed in a large prospective series of ASTS [15]. If long-term survival can be achieved in some patients with ASTS treated with chemotherapy, the therapeutic strategy may be significantly modified for subsets of patients.

The objectives of this study were to evaluate the frequency and the clinical characteristics of long-term survivors in patients with ASTS. With this aim, we performed a retrospective study of long-term survivors in a database of 2187 patients treated with a doxorubicin-

containing regimen between 1976 and 1990 in trials carried out by the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) [2, 3, 4, 5, 6, 7 and 8].

Patients and methods

Database

This study was performed retrospectively using a database involving 2187 patients ASTS, treated with a doxorubicin-containing regimen as first-line chemotherapy, within 7 prospective EORTC STBSG studies between 1976 and 1990 [1, 2, 3, 4, 5, 6, 7 and 8] (Table 1). Of these 2187 patients, 1888 (86%) had a minimum follow-up of 5 years since the initiation of chemotherapy: 66 were alive at 5 years, and 1822 had died within the first 5 years. The chemotherapy regimens used in these studies were: doxorubicin single agent [2, 4 and 6], epirubicin single agent [2 and 6], doxorubicin and ifosfamide combinations [3, 4, 7 and 8], doxorubicin, vincristine, cyclophosphamide, dacarbazine (DTIC) combinations [1 and 4]; doses and schedules were previously reported [1, 2, 3, 4, 5, 6, 7 and 8]. Survival was not significantly different between the arms of the randomised studies. Inclusion and exclusion criteria in these seven trials were similar: patients with locally advanced irresectable ASTS and/or distant metastasis, aged between 15 and 75 years, with evidence of tumour progression within 2 months were included. The following tumour cell types were included: malignant fibrous histiocytoma (MFH), liposarcoma, rhabdomyosarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, angiosarcoma, haemangiopericytoma, neurogenic sarcoma, unclassified sarcoma, miscellaneous sarcoma including mixed mesodermal tumours of the uterus. Malignant mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, embryonal rhabdomyosarcoma were not included. Major exclusion criteria included a previous history of cardiovascular disease, renal failure, symptomatic or known Central Nervous System (CNS) metastases, abnormal serum bilirubin, and second primary malignant tumours (except adequately treated *in situ* carcinoma of cervix or basal cell carcinoma).

Analysis

The proportion of patients surviving at 5 years, their clinical characteristics at inclusion, their response to first-line treatment and their outcome beyond 5 years were investigated. These characteristics were compared with those of patients who died within 5 years after inclusion in the trial. Patients lost to follow-up within 5 years of inclusion were not considered in this analysis.

Statistics

The clinical characteristics of the patients were compared using the Chi square test or Fisher's Exact test for binary variables, the overall Chi-square test for categorical non-ordered variables and the Mantel and Haenszel Chi-square test for ordered categorical variables. Survival curves were plotted according to the method of Kaplan–Meier. Survival curves were compared using the log-rank test. Multivariate analysis of parameters correlated with 5-year survival was performed using a logistic regression model.

Chapter III

Results

The median overall survival of the series of 2187 patients was 354 days (11.7 months). 355 patients were still alive in October 2000. The survival estimate was 8% at 5 years, 7.6% at 6 years, 6.8% at 7 years and 5.6% at 8 years (standard error <1%). No deaths were recorded beyond 8 years; 9- and 10-year survival estimates were therefore also 5.6%. Among the 66 patients alive at 5 years, 10 died beyond 5 years after inclusion. The 6-, 7- and 8-year survival estimates for 5-year survivors were 94, 85 and 70%, respectively (Fig. 1).

Parameters correlated to 5-year survival

The follow-up of 299 patients was shorter than 5 years: these patients were not included in any further analyses. Parameters correlated to 5-year survival were therefore analysed in 1888 patients. The characteristics of the 66 patients alive at 5 years were compared with those of the 1822 patients who died within 5 years after registration (Table 1). 69% of 5-year survivors were females and 31% males (P=0.004). Age was not significantly different in the two groups. The proportion of patients with PS of 0 was significantly higher in the 5-year survivors compared with the remaining patients (63% versus 41%) (P=0.002). Five-year survivors more frequently had grade 1 tumours (35% versus 11%), and less frequently grade 3 tumours (38% versus 55%) (P<0.001) (Table 1). There were also significantly less liver metastases (6% versus 21%) in the 5-year survivors compared with other patients (P=0.003). In contrast, histological subtypes were not significantly different in the 5-year survivors compared with patients who died before 5 years (Table 1). Using a multivariate analysis with logistic regression, parameters (excluding response to chemotherapy) independently correlated to a poor 5-year survival rate were similar to those previously identified as independent prognostic variables for overall survival in the same series: male sex (Relative Risk RR: 2.1), higher tumour grade (RR: 2.3), liver metastases (RR: 4.5) and worse performance status (RR: 2.7) (data not shown). However, 5-year survivors were observed in all prognostic subgroups in this series (Table 1).

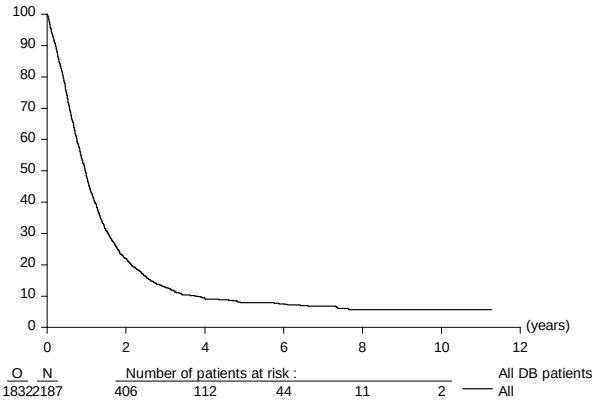
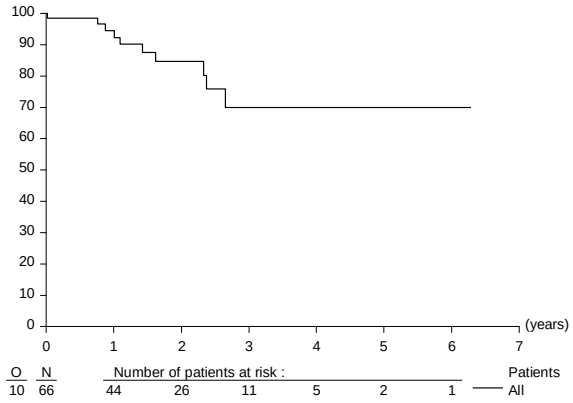


Figure III-1: Overall survival
a)in the whole series of 2187 patients;
b)after 5 years in the 66 patients alive after 5 years;
c)after 5 years in patients in CR, PR, NC and PD after first line therapy.

O, observed deaths,
N, number of patients



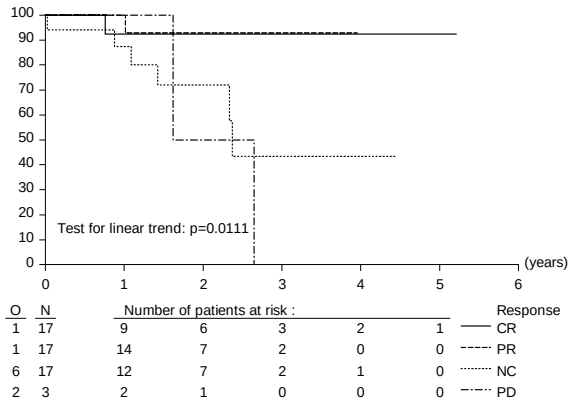


Table III-1: Clinical characteristics of 5 years survivors

Characteristics		5-years survivors N (%)	Others N (%)	P-value
Gender	Male	22 (33)	887 (49)	0.004
	Female	44 (67)	906 (51)	
Age (years)	< 40	22 (34)	858 (26)	0.13
	40 – 50	13 (20)	368 (21)	
	50 – 60	17 (26)	477 (27)	
	> 60	13 (20)	468 (26)	
Tumor grade	I	14 (35)	129 (11)	< 0.001
	II	11 (28)	389 (33)	
	III	15 (38)	644 (55)	
PS	0	40 (63)	720 (41)	0.002
	1	19 (30)	779 (45)	
	2	5 (8)	243 (14)	
	3	0 (0)	3 (0.2)	
Disease	Locally advanced	27 (44)	342 (20)	0.005
	Metastatic	28 (46)	1142 (68)	
	Both	6 (10)	190 (11)	
Lung metastases	No	33 (52)	774 (45)	0.24
	Yes	30 (48)	962 (55)	
Liver metastases	Yes	4 (6)	326 (21)	0.003
	No	59 (94)	1236 (79)	
Histology	MFH	6 (14)	185 (14)	0.946
	Fibrosarcoma	2 (5)	57 (4)	
	Liposarcoma	3 (7)	92 (7)	
	Leiomyosarcoma	13 (31)	471 (36)	
	Synovialosarcoma	2 (5)	95 (7)	
	Neurosarcoma	4 (10)	96 (7)	
	Others	12 (29)	316 (24)	

Characteristics		5-years survivors N (%)	Others N (%)	P-value
Study [reference]	62761 [2]	7 (3)	265 (97)	
	62801 [3]	0 (0)	168 (100)	
	62842 [4]	0 (0)	142 (100)	
	62851 [5]	44 (7)	596 (93)	
	62883 [6]	3 (3)	102 (97)	
	62901 [7]	5 (2)	277 (98)	
	62903 [8]	7 (3)	272 (97)	

Response to first-line chemotherapy and 5-year survival

Among the 66 patients with ASTS alive at 5 years, 17 (31%) had experienced complete response (CR) and 17 (31%) partial response (PR) to first-line chemotherapy, respectively (Table 2). This proportion was significantly higher than in other patients ($P<10^{-5}$). In addition, 17 (31%) of 5-year survivors had stable disease (SD) as their best response to first-line treatment and 3 (6%) had progressive disease (PD). The contribution of subsequent treatment cannot be assessed since it was not documented in the database (Table 2). When CR to first-line chemotherapy was introduced in the multivariate model, CR was found to be the most potent prognostic factor for 5-year survival (Table 3). However, here also, 5-year survival was observed in all subgroups, even in patients whose best response was PD after a first-line regimen containing doxorubicin. Of note, response to first-line chemotherapy still strongly influenced the outcome of these patients *after* 5 years: 2 of 3 patients with PD died between 5 and 7 years, compared with 6 of 17 patients in stable disease and 1 of 17 both for PR and CR patients (Fig. 1c, P=0.01).

Table III-2: Response to first line doxorubicin-containing regimen

Response to 1st line	5-years survivors (n=66)	Others (n=1822)	P-value	% of 5 years survivors amongst response subgroup
CR	17 (31%)	64 (4%)		17 / 81 (21%)
PR	17 (31%)	306 (19%)		17 / 323 (5%)
NC	17 (31%)	641 (39%)		17 / 658 (3%)
PD	3 (6%)	627 (38%)	0.00001	3 / 630 (0.5%)

Table III-3: Multivariate analysis of prognostic factors for 5-years survival

Variable	Parameter estimate	Standard error	Wald chi-square	P-value	Odds ratio	95% confidence interval
Intercept	2.8555	0.8128	12.3408	0.0004		
PS	0.7052	0.3113	5.1314	0.0235	2.024	1.08-3.74)
Grade	0.7790	0.2353	10.9625	0.0009	2.179	(1.36-3.52)
Female gender	-0.8286	0.3798	4.7589	0.0291	0.437	(0.30-0.93)
CR to 1st line	-2.1505	0.4634	21.5363	0.0001	0.116	(0.40-0.29)

Discussion

These results show that ASTS is not an incurable disease: 8% of these patients are alive 5 years after initial diagnosis, and the majority of them experience long-term survival afterwards. Several clinical parameters, such as gender, PS, tumour grade and liver metastasis were found to be correlated to 5-year survival in univariate and multivariate analysis, and independent prognostic factors for 5-year survival were actually similar to those correlated to overall survival since the inclusion in the trial within the same series [1]. However, the histological subtype, an important prognostic factor for overall survival during the first 5 years actually lost its predictive value afterwards and was found not to significantly influence 5-year survival in this study. This is likely to be related to the slower progression rate in liposarcomas compared with other sarcomas in patients with advanced disease within the first years; however, eventually a similar proportion of patient with liposarcoma relapse and die of their disease, compared with patients with other sarcoma subtypes. An important observation from this series is that 5-year survivors were observed in all subgroups of patients, even in those with high grade tumours, liver or bone metastasis, and poor performance status.

Clinical response to first-line regimen was found to be the most significant parameter correlated to 5-year survival. Actually, a major difference was observed between patients who achieved CR, and patients who achieved PR, SD, or PD, with a 21% (17/81) rate of 5-year survival for the former, compared with a $\leq$5% rate for the latter. Interestingly, the percentage of long-term survivors among patients who achieve CR following treatment with a first-line regimen in this series is very similar to that of other published series in which CR was achieved by other means, including surgery, or surgery plus chemotherapy. This percentage ranged between 20 and 30% in the surgical series reported by Putnam and colleagues [12], in a series of a combination of chemotherapy and surgery [13], in a series of patients treated with chemotherapy only reported by Yap and colleagues [15], and with high-dose chemotherapy in a series where this unusual strategy was tested [16, 17, 18, 19, 20 and 21].

It should be noted that the majority of long-term survivors did not achieve CR after first-line chemotherapy. It is likely that these patients have been proposed for second-line chemotherapy or resection of metastases sites. However, the second-line treatment was not documented in the database, and the contribution of these treatments to the favourable outcome of these patients (in particular, the CR or PR rates to these treatments) is not known. Nevertheless, long-term survival was exceptional (<=5%) in all subgroups of patients who did not achieve CR after first-line treatment. Overall, the patients in CR have a relative chance of achieving long-term survival which is 5.0-fold higher than patients in PR, 10-fold higher than patients in SD and 55-fold higher than patients in PD. Regarding long-term survival, three subgroups of patients may therefore be distinguished according to response to first-line chemotherapy: 1) patients in CR, 2) patients in PR or SD, who were found to have a comparable outcome in terms of 5-year survival, and 3) finally patients in PD. In view of these results, a major goal of the treatment of patients with ASTS could be to improve the *complete* response rate to chemotherapy or to combined strategies with chemotherapy and surgery. However, complete response rates are low in ASTS, ranging from 0 to 10% with single agent or combination regimens in large series [1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11]. Another relevant parameter could be the rate of "non-progressive" disease, combining stable disease, partial and complete responses: not surprisingly, these three subgroups include almost all long-term survivors in the present series. Despite a large number of phase II trials, recent agents have shown a limited efficacy on ASTS [22, 23, 24 and 25]. Therefore, strategies combining chemotherapy with surgery on multiple tumour sites to improve the rate of long-term survivors deserve to be evaluated to increase CR rate.

However, the long-term survival of patients who achieve CR remains unsatisfactory since 80% of these patients will relapse and die of their disease afterwards. Strategies to reduce the relapse rates in these potentially curable patients are therefore needed. High-dose chemotherapy has been proposed with this aim in mind in selected patients: five year survival rates over 50% were reported in some of these small uncontrolled studies [15, 16, 17, 18, 19, 20 and 21]. Whether this only reflects a selection of patients still requires to be tested in a prospective randomised trial.

In conclusion, these results indicate that a significant proportion of patients with ASTS can achieve long-term survival and probably cure after first-line chemotherapy with anthracyclines. Long-term survivors are observed in all subgroups of patients, even in those with a well established unfavourable prognosis, such as liver metastasis, and high grade tumours. The achievement of CR is the major parameter correlated to long-term survival and future clinical trials should include complete response as a major endpoint in the evaluation of therapeutic strategies.

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Chapter IV

RECIST vs. WHO: Prospective comparison of response criteria in an EORTC phase II clinical trial investigating ET-743 in advanced soft tissue sarcoma

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Abstract

The present study was set up just after the publication of the response evaluation criteria in solid tumors (RECIST) as a prospective validation exercise in soft tissue sarcoma. Forty-nine patients were entered into a phase II clinical trial aiming at determining the activity and safety of ET-743 (Ecteinascidin) in second line advanced soft tissue sarcoma. Response to treatment and progression were monitored following the WHO criteria and RECIST. Discordances between WHO and RECIST criteria for the best response were reported for two cases: one no-change (WHO) reported as partial response (RECIST) and one progression (WHO) reported as no-change (RECIST). In terms of date of progression, 3 patients progressed on WHO criteria while they were still stable with RECIST. Overall the results of the study would not have changed if RECIST had been used instead of WHO criteria.

In conclusion, response criteria as defined by RECIST are adequate to measure response and progression in non-GIST soft tissue sarcoma and can be used instead of the modified WHO criteria.

Introduction

Response evaluation criteria in solid tumors (RECIST) was introduced in February 2000 to facilitate and improve the evaluation and the reporting of responses in early clinical trials aiming at determining the level of anti-tumor activity of new anti-cancer agents [1]. The new criteria gave much more precision as to how tumor lesions should be assessed and how responses should be reported, also taking into account modern imaging techniques. RECIST uses a uni-dimensional measure (the longest diameter) to quantify measurable tumor lesions as opposed to the bi-dimensional method (cross-sectional longest diameters) usually employed with most other sets of response criteria [2], [3] and [4]. On the basis of previous studies [3] and [5], RECIST defines measurable lesions as lesions with a minimum size depending on the method of investigation. Following a principle already implemented in the SWOG response criteria [3], the rules defining objective progression were voluntarily scaled down as compared to the WHO criteria so that the increase in measurable overall tumor burden should be greater with RECIST (20% in one dimension is equivalent to 44% in 2 dimensions) than with WHO criteria (25% in 2 dimensions) to qualify for progression. Following this last criterion, there was some concern that time to progression could be longer using RECIST as opposed to WHO criteria and this was identified up front as an issue requiring some attention in future trials before drawing definitive conclusions.

The objective measurement of tumor lesions has been used for decades in advanced soft tissue sarcoma to screen new agents or new regimens. The original WHO criteria have been adapted (modified WHO criteria) to improve the accuracy of response assessment in this tumor type [5] and [6]. The aim of the current study was to test RECIST in a prospective trial in parallel with WHO criteria and establish new references (using RECIST) in this tumor type for future trials if significant differences were identified compared with modified WHO criteria.

Patients and methods

The present study was conducted in the framework of a non-randomised phase II study investigating the anticancer activity and safety of Ecteinascidin (ET-743 – a novel tetrahydroisoquinoline compound isolated from the marine ascidian *Ecteinascidia turbinata*) in pre-treated advanced soft tissue sarcoma. The clinical trial was conducted by the EORTC Soft Tissue and Bone Sarcoma Group (STBSG). After the publication of the RECIST in February 2000, the original clinical trial protocol was officially amended to extend the sample size and collect information prospectively and in parallel about response and progression as assessed both by RECIST and WHO criteria. Patients eligible for entry in the study were required to have histologically proven measurable metastatic or unresectable loco-regional recurrent soft-tissue sarcoma. Mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, embryonal rhabdomyosarcoma and dermatofibrosarcoma were excluded. Patients with gastro intestinal stromal tumors (GIST) were treated in a separate study.

All patients were to have a documented progressive disease at inclusion, with defined target lesions at physical examination, on X-rays and CT scan. For the purpose of this project, the eligibility criteria required the presence of at least one measurable lesion fulfilling the definition of both (modified) WHO criteria and RECIST. The protocol specified that maximum three target lesions per organ and maximum five target lesions overall were to be reported and used for assessing response. WHO criteria were used as reference criteria for therapeutic decisions (discontinuation of treatment).

Other eligibility criteria were standard and have been outlined in detail in a previous paper together with the results of the therapeutic activity of ET-743 [7].

ET-743 was administered at a dose of 1.5 mg/m^2 intravenously as a 24 h continuous infusion every 3 weeks using a central venous line.

Response to treatment was evaluated every 2 cycles (every 6 weeks), with repeated clinical and relevant radiological assessments based on disease extension at presentation. For all responding patients, the hospital records and all available films were reviewed by two independent investigators. A response was accepted only if they reached consensus. In the absence of consensus the worst response category was assigned. Patients were considered evaluable for response if they had received a minimum of two cycles of treatment. In case of rapidly progressive disease after one course, the patient was removed from study and classified as treatment failure. If response had not been assessed, patients were included in the following categories: early death from toxicity in case of death occurring within 6 weeks due to signs of toxicity; early death from malignant disease if death occurred within 6 weeks after commencing chemotherapy due to soft tissue sarcoma and without signs of toxicity; a further classification was early death from other cause if death occurred in the same period of a cause not related to malignant disease. Patients who had stable disease or exhibited complete or partial responses remained on treatment until treatment completion (6 cycles), disease progression, unacceptable toxicity or patient refusal. Patients with evidence of drug related clinical benefit were allowed to continue on therapy after 6 cycles.

The Simon two stage design has been separately applied to each patient cohort (one cohort before and one cohort after the amendment) to allow determination of response rates and progression with RECIST. All analyses presented in this paper are exploratory and descriptive and have been produced using VISTA, the software developed by EORTC to handle clinical trial data.

Results

Between March 2000 and November 2000, 49 patients were recruited by 7 participating centers. Two patients were initially declared ineligible by the study coordinator for the main efficacy analysis. One patient had a lung target lesion with a longest diameter of 17 mm on CT scan while the selection criteria required at least one target lesion >20 mm and another patient had only one target lesion that had been previously irradiated. However, considering an intent to treat analysis for all patients for whom we had data on both WHO and RECIST evaluations, these patients have been included in the present analysis. The original localisation of the disease is described in Table 1.

Table IV-1: Primary sites of disease

	n = 49 (%)
Head and neck	2 (4)
Trunk	7 (14.3)
Visceral intra-abdominal	5 (10.2)
Retroperitoneum	6 (12.2)
Uterus	8 (16.3)
Girdle	5 (10.2)
Lower arm	16 (32.6)

Most of the patients had either one (21 patients/42.9%) or two (14 patients/28.6%) different anatomic sites involved (considering target and non-target lesions) and only 10 (20.4%) and 4 (8.2%) patients had 3 or 4 different sites involved, respectively. Twenty-nine patients had only one target lesion and 11 patients had 2 target lesions (Table 2). Target lesions were located in one organ only for 44 patients (Table 3) and the distribution of lesions per organ/system is described in Table 4. Following the modified WHO criteria used for decision making in this protocol 2 patients presented a partial remission (PR), 30 patients achieved no-change (NC) and in 17 patients progressive disease was recorded as best overall response. The comparison of response assessment between WHO criteria and RECIST is described in Table 5. Discordances between WHO criteria and RECIST for the best response were reported for two cases: one no change (NC) (WHO) reported as partial response (PR) (RECIST) and one progressive disease (PD) (WHO) reported as NC (RECIST).

Table IV-2: Number of target lesions per patient

WHO	RECIST					
	1	2	3	4	5	Total
1	29 (100%)					29 (59.2%)
2		11 (100%)				11 (22.4%)
3			7 (100%)			7 (14.3%)
4				1 (100%)		1 (2%)
5					1 (100%)	1 (2%)
Total	29	11	7	1	1	49

Table IV-3: Number of target lesions by organ per patient

Lesions	Organs			
	1	2	3	Total
1	29 (65.9%)			29 (59.2%)
2	7 (15.9%)	4 (100%)		11 (22.4%)
3	7 (15.9%)			7 (14.3%)
4			1 (100%)	1 (2%)
5	1 (2.3%)			1 (2%)
Total	44	4	1	49

Table IV-4: Organ/system involved (patients may have more than 1 site involved)

Involved sites	Any lesions (*n* = 49)	Target lesions (*n* = 49)
Primary	18	11
Lymph nodes	6	3
Lung	33	22
Liver	9	6
Skin	1	–
Other soft tissue sites	16	15
Bone	6	–

Table IV-5: Best response to therapy WHO *vs.* RECIST

WHO	RECIST			
	PR	NC	PD	Total
PR	2			2 (4.1%)
NC	1	29		30 (61.2%)
PD		1	16	17 (34.7%)
Total	3 (6.1%)	30 (61.2%)	16 (32.6%)	49

PR, partial response; NC, no change; PD, progressive disease.

The progression status evaluated according to WHO criteria or RECIST is presented in Table 6. In this analysis, 15 patients were not evaluable for the comparison RECIST/WHO. Two patients stopped treatment for toxicity reasons before progression and 13 patients progressed after the end of the planned treatment period and had no comparative measurements recorded at the time of progression. Among the remaining 34 patients, 3 patients were identified as PD following the WHO criteria while they were still stable (NC) following RECIST. For 2 of these patients, therapy was discontinued (as per protocol) at the time of WHO progression. One patient died rapidly and the other patient survived another year. The third patient was continued on therapy for another 6 months despite WHO progression (erroneously reported as NC (WHO) by the investigator but truly NC following RECIST) achieving a partial remission (WHO and RECIST) that remained stable for another year. In the present study, the decision rules set up for the further development of ET-743 would not have been affected if RECIST had been used instead of the modified WHO criteria.

Table IV-6: Timing of progression with RECIST and WHO criteria

	Progression, *n* = 49 (%)
Non-evaluable	15 (30.6)
Same date of progression	31 (63.3)
Progression with new lesion(s)	18 (58)
Progression by increase of pre-existing of tumor burden	13 (42)
Progression by RECIST after progression by WHO	3 (6.1)

Discussion

The present study is interesting for several reasons including that this is the first study prospectively testing both RECIST and WHO criteria in advanced soft tissue sarcoma. Using the response rate to decide whether or not to continue or stop further investigations with ET-743 the same decision would have been taken whether WHO criteria or RECIST had been used. These decision rules were built into the protocol. However based upon the observed specific character of the anti-tumor activity generated by ET-743 (long lasting absence of progression), in further planning more attention was given to the time to progression and progression rate (or rate of progression arrest) to quantify the activity of ET-743. As WHO criteria were initially designated as the criteria on which the therapeutic decisions should be taken, it has not been possible to assess and compare progression rates obtained with the two sets of response criteria especially for long lasting disease stabilisation after treatment completion. Should RECIST have been selected as the principal criteria for this study a long and difficult debate would have followed whether the very long time to progression was only due to the use of RECIST instead of WHO criteria, or due to the intrinsic anti-tumor activity of ET-743. This constitutes clearly one of the limitations of this study as is the case for all prospective validation studies published so far [8], [9], [10], [11], [12], [13], [14] and [15]. This study, albeit relatively small, suggests that for screening types of trials such as the phase II study design, the simpler RECIST is as satisfactory as the more complex WHO criteria, particularly for development planning. This study does not enable us to assess whether if RECIST was used as principal selection criteria for response, if it would have cut down the number of eligible patients compared to WHO criteria (with no minimum size for tumor lesion) since the WHO modified criteria used in this study (and previous studies in the same tumor type) are even more strict in the selection of patients than RECIST.

It is also important to note that, as in many other tumor types, progression is identified with the appearance of a new lesion in a majority of patients (58% in this study) as opposed to an objective increase in existing tumor burden. This confirms that although a relative precision is needed to measure the overall tumor burden, the true impact of measurement errors as well as the importance given to the magnitude of tumor burden increase (25% in 2 dimensions with WHO or 20% in one dimension with RECIST) on the correct estimation of the progression rate is relatively small. In the present study, only three patients (6.1%) were identified as progressing according to the modified WHO criteria while they were still considered as stable using RECIST. The natural history of these three patients (after being identified as progressing following the WHO criteria) supports the concept on which the progression rule in RECIST has been elaborated. That is to say that prolonging the time to progression by requiring a larger increase in tumor burden than with former WHO criteria may have almost no impact on patients truly progressing (the delay between WHO and RECIST progression will be very small). However, it may on the other hand help patients who might still benefit from further treatment and who are therefore less exposed to unfortunate therapeutic decisions based on measurement imprecision or errors.

Even though up to five target lesions could be reported as per protocol the large majority of patients had less than 3 target lesions reported and almost all of them were situated in the same organ/system. It is, however, difficult to interpret these data without knowing the real

number of potential target lesions at baseline. One could indeed be victim of under-reporting of target lesions or on the contrary conclude that the problem of having to follow a lot of target lesions (up to five following this protocol) is not a true problem in this tumor type.

Of the eight currently published prospective validation studies comparing WHO criteria to RECIST, four involve primary lung cancer [8], [11], [13] and [14], one involves metastatic colorectal cancer [9], and one lung and liver lesions from breast cancer [10], and finally two involve mesothelioma [12] and [15]. Apart from the mesothelioma studies all indicate a similar outcome in terms of response rates regardless whether RECIST or WHO criteria are used. Because of the particular characteristics of mesothelioma, it can be expected that both RECIST and WHO are not adequate to measure the true tumor burden. Several solutions have been proposed but there is currently no consensus on a preferred system. Three of the studies performed provide information on WHO criteria and RECIST in terms of progression [9], [10] and [13] but as indicated and importantly, none of these studies used RECIST as primary criteria and, therefore, the overall conclusion drawn from comparing RECIST and WHO criteria remains slightly biased. In two studies [9] and [10], as in the current one, few patients with PD using WHO criteria would still have been considered as stable with RECIST. In one (small) study [13], there was no difference in time to progression when using either RECIST or WHO criteria. Apart from mesothelioma, all other studies performed confirmed that RECIST (and the uni-dimensional approach) is suitable to measure response and progression. In conclusion, our study confirms that RECIST can be used for decision making in screening studies in soft tissue sarcomas. Putting this study in perspective with other studies in more common tumor types supports the implementation of RECIST as standard criteria for response evaluation but also for monitoring progression.

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Chapter V

Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas

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Abstract

We have estimated progression-free rates (PFR) for various groups of soft-tissue sarcoma patients from our clinical trials database, to provide reference values for conducting phase II studies with PFR as the principal end-point. In 146 pretreated patients receiving an active agent, the PFR estimates were 39 and 14% at 3 and 6 months; with inactive regimens (234 patients), those estimates were 21 and 8% respectively. In 1154-non-pretreated patients, PFR estimates varied from 77% (synovial sarcoma) to 57% (malignant fibrous histiocytoma (MFH)) at 3 months, and from 56% (synovial sarcoma) to 38% (MFH) at 6 months. In 61 leiomyosarcomas from gastrointestinal origin, the corresponding figures were 44 and 30%, respectively. Consequently, for first-line therapy, a 6-month PFR of >=30–56% (depending on histology) can be considered as a reference value to suggest drug activity; for second-line therapy, a 3-month PFR of >=40% would suggest a drug activity, and <=20% would suggest inactivity.

Introduction

Response to therapy, based on a measured decrease in the size of cancer lesions, is considered to be the most effective end-point to document biological anticancer activity of cytoreductive agents and consequently to identify potential new cytoreductive drugs. The response evaluation criteria in solid tumours (RECIST) criteria [1] provide a harmonised method of response evaluation. For non-cytoreductive anticancer agents, biological activity is frequently not expected to translate into shrinkage of lesions, but rather in stabilisation of disease. The RECIST guidelines recognise that progression-free survival and/or time to progression may be a valuable alternative end-point to provide an initial estimate of the biological effect for these agents.

The classical phase II designs [2, 3 and 4] are applicable to any situation where the activity of the new agent is characterised by a binary variable that objectively defines ‘success’ versus ‘failure’ for each patient. Our proposal is to consider absence of progression (or the progression-free rate (PFR)) at a fixed time point as a primary end-point of phase II trials with non-cytotoxic drugs. This is one of the different approaches proposed by Korn [5] for phase II clinical trials with cytostatic agents.

In the above-mentioned designs, the sample size and decision rules are computed on the basis of the ‘success’ rates expected after treatment with an active therapeutic agent (P1), as well as treatment with an inactive agent (P0). These reference rates will obviously differ if the definition of ‘success’ is changed from objective response to progression-free status.

In soft-tissue sarcomas, only three cytotoxic drugs (doxorubicin, ifosfamide and dacarbazine) have, so far, demonstrated activity. New non-cytotoxic agents, often targeting specific histological subtypes, are now being explored. In addition, given the low objective response rate observed with the above three agents, for new cytotoxic agents information on PFRs will be relevant. The aim of this study was to provide appropriate baseline references for conducting phase II trials with PFRs as end-points in this disease.

In this study, we have explored the Soft Tissue and Bone Sarcoma Group (STBSG) database to estimate the PFRs that can be reasonably expected from an active agent or

combination, and from an inactive agent in soft-tissue sarcoma. This will guide the choice of the ‘P0’ and ‘P1’ parameters of phase II statistical designs.

Patients and methods

The European Organization for Research and Treatment of Cancer (EORTC) STBSG has investigated in prospective clinical trials different new agents and combination therapies for soft-tissue sarcoma, both in pretreated and non-pretreated patients [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and 17].

Pretreated patients included in this analysis had been included in 12 clinical trials and treated with 11 different agents, according to the 13 therapeutic regimens detailed in Table 1 (one regimen per trial, except for a randomised trial with regimens B and C).

Table V-1: Therapeutic regimen

Regimen	Treatment description
A	Dacarbazine 1.2 g/m2, 20 min infusion, q 3 wks
B	Ifosfamide 5 g/m2, 1 day infusion, q 3 wks
C	Ifosfamide 3 g/m2.day, 4 hours infusion, days 1,2,3, q 3 wks
D	Ifosfamide 12 g/m2, 3 days infusion, q 4 wks
E	Mitozolomide 90 g/m2, 1 hour infusion, q 6 wks
K	Etoposide, 50 mg/m2.day, p.o., d1-21, q 4 wks

q, every; wks, weeks; i.v., intravenous; p.o., orally;
L-MTP/PE, liposomal muramyl tripeptide phophatidylethanolamide

All of the studies required histological evidence of soft-tissue sarcoma of one of the following cell types: malignant fibrous histiocytoma (MFH), liposarcoma, rhabdomyosarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, angiosarcoma including haemangiopericytoma, neurogenic sarcoma, unclassified sarcoma, and miscellaneous sarcoma including mixed mesodermal tumours of the uterus. Malignant mesothelioma, chrondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma and embryonal rhabdomyosarcoma were excluded. Other criteria included the presence of at least one bidimensionally measurable lesion (according to the World Health Organization (WHO) criteria), evidence of progression within 4 or 6 weeks prior to treatment, absence of symptomatic Central Nervous System (CNS) metastases, and informed consent. Eligibility in terms of age and performance status, as well as upper and lower limits of haematological and biological parameters varied slightly amongst the trials, as shown in Table 2. Extent of allowed prior chemotherapy varied largely between protocols. Although not formally required in all trials, most patients were pretreated with at least one chemotherapy regimen. Non-pretreated patients were excluded from the present

analysis, as well as patients that were not eligible for the trial, and patients who did not receive any protocol treatment.

Table V-2: Selected patient populations

Trial regimen	A	B-C	D	E	F	G	H	I	J	K	L	M
Evidence of progression within	4 wks	6 wks	6 wks	4 wks	4 wks	2 mon	4 wks	6 wks	6 wks	6 wks	6 wks	6 wks
Age (years)	15-75	15-75	15-65	15-75	15-75	18-75	15-75	15-75	17-75	15-75	15-75	15-75
PS	0-1	0-1	0-1	0-1	0-2	0-2	0-2	0-2	0-1	0-1	0-1	0-1
Prior chemo. Regimen	--	1		--	--	0-1	0-1					
single agent			0-2					0-2	0-2	0-2	2	2
OR multidrug			0-1					0-1	0-1	0-1	1	1
Prior drugs	≤ 3**	1*	--	≤ 4	≤ 4	--	--	--	--	--	--	--00
WBC (10**9/l)	≥ 3	≥ 4	≥ 4	> 4	> 4	> 4	≥ 4	≥ 4	> 3.5	≥ 3.5	≥ 4	≥ 4
PLA (10**9/l)	≥ 100	≥ 100	≥ 100	> 125	> 125	> 150	≥ 100	≥ 100	> 100	≥ 100	≥ 100	≥ 100
Hemoglobin (g/dl)	--	--	--	--	--	> 11						
Creatinine (micromol/l)	≤ 150	≤ 150		≤ 150	≤ 150		≤ 150	≤ 150	≤ 150	≤ 150	≤ 120	≤ 120
Creatinine (mg/dl)	--	--		--	--	≤ 1.5						
Creatinine clearance (ml/min)	--	--	≥ 70	--	--	≥ 60	--	--	> 60	--	Or > 65	Or > 65
Bilirubine (micromol/l)	≤ 25	≤ 25	≤ 30	≤ 25	≤ 25		≤ 20	≤ 25	≤ 25	≤ 20	≤ 30	≤ 30
Bilirubine (mg/dl)	--	--		--	--	≤ 1.5						
Albumine (g/l)	--	≤ 25	≤ 25	--	--		≤ 25	--	--	≤ 30	≤25	≤ 25
Transaminases (* UNL)	--	--		--	--	≤ 1.25	--	--	< 2	--	--	--
Alkaline phosph. (*UNL)	--	--		--	--	≤ 1.25						
Prior nephrectomy	--	--	No	--	--	--	--	--	--	--	--	--

wks, weeks; PS, Performance Status; chemo, chemotherapy; WBC, white blood cells; PLA, platelets; UNL, upper normal limit.

The 1154 non-pretreated cases included in this analysis were selected from the previously reported cohort of more than 2000 cases [18]. Therapeutic regimens have been previously described. Patients selected for this analysis had an externally confirmed diagnosis of the six most frequent histological subtypes.

Response to therapy was evaluated according to the WHO criteria in all trials. Complete and partial responses were reviewed by at least two investigators of the group. This review process was recently validated by an external radiologist [19]. Patients were followed for progression every 6 weeks. In most studies, patients were also followed for survival after progression.

Data have been collected in a consistent way for all of these trials, and we have selected from the resulting database the following groups of patients:

- Patients treated with an active drug (ifosfamide or dacarbazine) after failure of an anthracycline-containing regimen (146 cases); PFRs observed in this group provide reference values for the parameter P1 in pretreated patients.
- Patients that, after failure to prior chemotherapy, were treated within nine studies on investigational agents that unfortunately did not demonstrate substantial antitumour activity at the tested dose and schedule (234 cases): PFRs observed in this group provide reference values for the parameter P0 in pretreated patients.
- Patients treated with a first-line active drug or combination (anthracycline-containing regimen), with an externally confirmed diagnosis of leiomyosarcoma (531 cases), MFH (217 cases), synovial sarcoma (115 cases), liposarcoma (110 cases), fibrosarcoma (68 cases) and neurogenic sarcoma (113 cases): these groups provide reference values for the parameter P1 in non-pretreated patients, for the six most frequent histological subgroups.

Understandably, we do not have any data on patients treated with first-line inactive agents or combinations, and we are therefore unable to provide reference values for the parameter P0.

In view of the large number of histological subtypes of soft tissue sarcomas, the database of pretreated cases was not large enough to allow us to provide separate estimates for the different tumour types.

In all groups of patients, the 3-month and 6-month PFRs have been evaluated by the Kaplan–Meier method [20]. Standard errors were estimated by the Greenwood formula [21]. For pretreated patients, the prognostic value of baseline characteristics was estimated in univariate (logrank test [22]) and multivariate (Cox regression [23]) analyses.

The following factors were explored (when available): age, performance status at the start of therapy, type of prior therapy, number of prior therapeutic regimens and agents, presence of liver metastases and time elapsed since the initial diagnosis of sarcoma.

For non-pretreated patients, we have previously published a detailed prognostic factor analysis on the complete database [18].

Results

Pretreated patients

From the 11 investigated agents, only two demonstrated significant antitumour activity, in terms of objective responses: ifosfamide and dacarbazine; these were considered as 'active drugs' in our analysis. For the nine other agents, no or few responses were observed at the investigated dose and schedule, and we therefore considered these as 'inactive regimens'.

A total of 380 patients were included in this analysis, 146 of them treated with active drugs (ifosfamide or dacarbazine) and 234 treated with inactive regimens. Patient characteristics are summarised in Table 3.

Table V-3: Patients characteristics

Trial		A	B/C	D	E	F	G	H	I	J	K	L	M
# cases		45	76	25	26	33	28	21	19	28	26	22	31
Sex	Males	56	47	56	46	42	61	57	47	46	50	68	48
Performance status	0	36	33	32	35	18	21	43	21	32	28	45	32
	2+	16	5	0	0	21	25	14	16	4	0	0	0
Age	< 40 yrs	42	20	28	28	15	36	38	42	25	35	14	16
	> 60 yrs	24	22	20	28	30	14	19	16	29	27	18	35
Initial diagnosis	< 6 mon	--	13	28	--	--	4	14	11	0	4	14	0
	> 24 mon	--	34	36	--	--	46	48	32	52	38	18	52
Liver	Involved	7	21	36	19	30	29	29	32	25	12	18	26
Histology	Leiomyo.	30	45	24	23	39	29	24	32	21	31	32	35
	MFH	18	11	8	12	9	18	19	16	11	12	5	0
	Synovial	18	7	12	19	12	21	10	11	11	12	5	23
	Neurogen.	7	7	0	8	3	14	19	11	11	4	5	6
	Liposarc.	2	13	4	8	6	4	10	5	11	12	14	10
	Fibrosarc.	2	1	0	4	9	0	14	0	4	0	5	0
Prior chemo-therapy	Adjuv.only	9	24	24	4	12	7	14	16	7	27	23	13
	> 1 regim.	--	0	1	--	--	4	0	11	32	12	32	32
	1 drug	17	100	36	--	0	25	38	58	39	8	36	42
	2 drugs	67	0	32	--	18	64	48	37	54	77	41	48

mon, months; yrs, years; Leiomyo, leiomyosarcoma; MFH, malignant fibrous histiocytoma; Neurogen., neurogenic sarcoma; Liposarc., liposarcoma; Fibrosarc., fibrosarcoma

The Kaplan–Meier estimate of the PFR is shown in Fig. 1 for the whole cohort of patients and in Fig. 2 for the two groups of patients separately. The 3-month and 6-month PFRs were 39 and 14%, respectively, for patients treated with an active drug, and 21 and 8%, respectively, for patients treated with an inactive regimen. For the whole cohort, the rates were 28 and 10%, respectively. Detailed results are shown in Table 4.

Figure V-1: Progression-free rate for the whole cohort of pretreated patients.

Kaplan-Meier estimate;
O, observed events;
N, number of patients

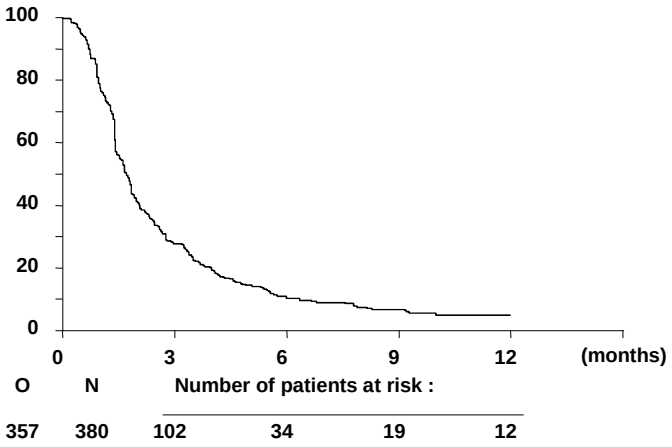

Figure V-2: Progression-free rate for patients pretreated with an inactive or with an active agent.

Kaplan-Meier estimate;
O, observed events;
N, number of patients

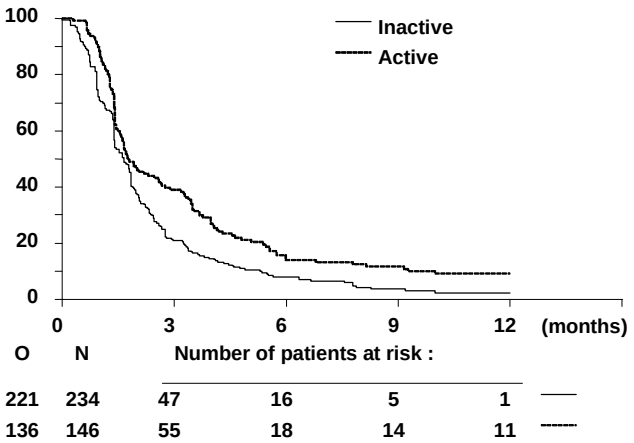

Table V-4: Progression free rates (PFRs) in pretreated patients

Type of drug	# cases	3 months PF rate		6 months PF rate	
		Estimates	Std error	Estimates	Std error
Inactive	234	21 %	3 %	8 %	2 %
Active	146	39 %	4 %	14 %	3 %
All patients	380	28 %	3 %	10 %	2 %

Only three prognostic factors emerged from the univariate analysis, and they all remained significant (or of borderline significance) in the multivariate Cox model:

- Treatment with an active drug (*P*<0.0001)
- Interval since the initial diagnosis of disease (*P*=0.014) and
- Performance status (*P*=0.08).

Non-pretreated patients

In this group of patients, the 3-month PFRs varied from 77% (synovial sarcoma) to 57% (MFH) and the 6-month PFRs from 56% (synovial sarcoma) to 38% (MFH), the standard error (S.E.) was <5% in all estimates except for fibrosarcoma (6%).

Most of the trials were conducted before the identification of gastrointestinal stromal tumour (GIST) as a separate entity, and these cases were consequently classified as 'leiomyosarcoma' in our database. However, a gastrointestinal origin of disease was documented in 61 leiomyosarcomas, and we assumed that most of those cases would today be classified as GIST. In this sub-group, 3-month and 6-month PFRs were 44 and 30%, respectively (S.E.=6%). Detailed results are shown in Table 5.

The prognostic factors of response and survival were the same as those already reported for the whole cohort [18].

Table V-5: Progression-free rates (PFRs) in non pretreated patients

Histology	# cases	3 months PF rate		6 months PF rate	
		Estimates	Std error	Estimates	Std error
Leiomyosarcoma (all)	531	58 %	2 %	40 %	2 %
MFH	217	57 %	3 %	38 %	3 %
Synovial sarcoma	115	77 %	4 %	56 %	5 %
Neurogenic sarcoma	113	67 %	5 %	45 %	5 %
Liposarcoma	110	64 %	5 %	55 %	5 %
Fibrosarcoma	68	62 %	6 %	45 %	6 %
Leiomyosarcoma from GI origin	61	44 %	6 %	30 %	6 %

PF rate, progression free rate ; MFH, malignant fibrous histiocytoma; GI, gastrointestinal.

Discussion

Relevance of the results

Our proposal is to use PFRs retrospectively estimated from our database as reference values for the P0 and P1 parameters in the statistical design of future phase II trials. These estimates are, however, provided with a standard error around 5%.

Phase II trials are screening studies, designed to decide if a new agent is worth further investigation in an appropriate phase III programme. The decision is based on observations assumed to reflect biological antitumour activity, but not necessarily a therapeutic benefit. If results of the phase II trial are consistent with the level of activity expected from an active drug, the new agent deserves further testing. If results of the phase II trial are consistent with the level of activity expected from an inactive drug, the new agent is rejected from further testing. The sample size is computed to ensure that these two decision rules are mutually exclusive. It should be underlined that a phase II trial is considered as positive when the drug activity is consistent with the one of an active agent with a confidence level (β) as low as 5 or 10%.

Therefore, we feel that parameters estimated from clinical trial data with an error rate of 5% may be used as a guide to proceed with the clinical development programme of a new agent, but not to prove the therapeutic value of the drug. However, even with a drug like dacarbazine, by many still considered as an active drug in this group of diseases, the responses observed were not durable leading to a shorter progression-free time than observed with some investigational agents. In addition, recent results using some new cytotoxic agents suggest that response is not the best end-point for phase II studies on which to base important drug development decisions.

Selection of the appropriate time point for evaluation

The selection of an appropriate time point for PFR evaluation is a compromise between the need to avoid false-positive trials, and practical complications linked to a long period of observation. If the disease is slowly progressing, absence of documented progression at the first disease evaluation (generally 6–8 weeks after the start of treatment) may not reflect any drug activity, but only the natural course of the disease. Our data showed little discrimination between active and inactive regimens at this time point. However, it is expected that all patients should be evaluable, and, therefore, would be treated until the evaluation point in the absence of progression. A study requiring a long treatment and follow-up period would be difficult to conduct. Therefore, we propose to evaluate the progression status 3 and 6 months after the start of treatment.

Despite a close study monitoring, it may be difficult to avoid losing a few patients to follow-up before documented progression. These patients will therefore not be fully evaluable for the primary end-point, and the sample size should be accordingly increased. However, instead of excluding these patients from the analysis, the success rate can be estimated by an actuarial method (preferably Kaplan–Meier), and these patients would be censored at the date of the last follow-up. The Greenwood formula can be used to estimate the standard error. Green [24] has proposed methods to adapt the decision rules of several phase II

designs when the attained sample size is not the one that was initially planned. These methods can be extended to actuarial estimates of success rates.

Assessment of progression-free status

The primary end-point of a clinical trial needs to be objectively assessable. The RECIST criteria provide a method for progression evaluation. According to these guidelines, several events are considered as evidence of progression: appearance of new lesions, increase of at least 20% in the sum of the diameters of the target lesions, and unequivocal increase in the size of non-measurable disease. This last criterion needs to be confirmed by an external review. Therefore, in trials using these types of end-points, an external review may still be needed. It should also be underlined that measurable disease at trial entry is still required.

Stable disease cannot be considered as evidence of the treatment activity if the disease was not progressing before the start of treatment. Therefore, only patients with documented progressive disease should be selected for these trials. This requires at least two sets of objective tumour measurements before inclusion, which would restrict the eligible population.

Selection of the statistical design

The most popular statistical designs for phase II trials are the two steps optimal and minimax designs proposed by Simon [2]. The 'success rate' must be evaluated on a first patient cohort before the decision to proceed to the full size study, which requires the interruption of the trial until the first cohort has reached the evaluation time point. This is also true for the Bryant and Day two-step design [25] that also controls for toxicity. The complexity will be increased further for designs that have three or more steps, such as those proposed by Ensign [26] and Fleming [3].

Fleming [3] has also proposed a single step design based on a similar hypothesis. This simplifies the conduct of the trial because it does not need to be interrupted, but the absence of an early stopping rule may be unethical in early phase II trials, when the investigational agent has not yet demonstrated any activity.

The design proposed by Gehan [4] is sometimes used in early phase II trials, when a decision rule is not crucial. This method tests the compatibility of the observed success rate with the rate of an active agent, but does not formally reject agents with a positive, but low, success rate. As our data show that a small proportion of patients remain disease-free at 3 or 6 months, even when treated with an inactive regimen, this design is not appropriate when activity is characterised by the absence of progression.

Other end-points

Other end-points are currently used for phase II trials on non-cytotoxic drugs, or in situation where objective responses are not expected.

One of them is the 'clinical response benefit' where success is defined as the occurrence of either an objective response (according to RECIST criteria), or the absence of progression at a predefined time point (fixed between 3 and 6 months). The difference with our proposal is that patients who respond rapidly after the start of treatment, but progress before this

fixed time point are considered as successes. This design is probably more relevant to trials on rapidly progressing disease, when very few responses are expected, but disease stabilisation would be considered as a success. It is, however, difficult to provide objective reference of 'success rates' with this end-point from existing data. It will also be difficult to use censored progression data in the analysis.

Mick and colleagues have proposed to use a 'growth modulation index', defined as the ratio between the time to progression observed with the new agent, and time to progression observed with the most recent prior anticancer treatment of the same patient [27].This method is theoretically very attractive, but only applicable to patients who have already failed a prior treatment, and for whom the time to previous progression was accurately documented. This restricts both the types of studies (on pretreated patients) and the eligible population (data availability).

Conclusions

To conclude, for phase II trials of non-cytotoxic agents in soft-tissue sarcoma, we propose to use standard phase II designs, with 3-month or 6-month PFRs as the principal end-points. Reference values for the P0 and P1 parameters have been evaluated from the STBSG database for different groups of patients. Confirmation of these values from other databases would be useful. Time to progression is more difficult to evaluate than objective response, and its use as a principal end-point should be restricted to situations where a decrease of the tumour volume is not expected. Phase II trials conducted with this end-point are still simple screening studies and are not intended to provide more information than a justification to further investigate a new treatment. Sufficiently powered phase III trials remain the only way to document the therapeutic benefit provided by a new agent.

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Chapter VI

Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: an EORTC-ISG-AGITG study

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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.

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).

Table VI-1: Distribution of cofactors

Factor	N	%	Randomized arm (N)	
			400 mg od.	400 mg bid.
Age (years):				
Median / range	59 (18-91)			
< 40	72	7.6%	38	34
40-50	176	18.6%	87	89
50-60	228	24.1%	122	106
60-70	282	29.8%	138	144
> 70	188	19.9%	88	100
Gender				
Male	573	61.3%	283	290
Female	373	38.7%	190	183
Performance score (WHO)				
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				
Gastrointestinal	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 (days)				
Median / range	338 (6–10092)			
< 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

Factor	N	%	Randomized arm (N)	
			400 mg od.	400 mg bid.
Diameter of largest lesion (mm)				
Median / range	78 (<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 HGB (mmol/l)				
Median / range	7.9 (4.7-15.6)			
< 7	245	25.9	124	121
7 – 8	245	25.9	127	118
8 – 8.8	236	24.9	104	132
> 8.8	220	23.3	118	102
Baseline granulocytes (10^9/l)				
Median / range	4.8 (1.5-30.6)			
< 4	318	33.6	172	146
4 – 5	196	20.7	99	97
5 – 6.5	195	20.6	94	101
> 6.5	237	25.1	108	129
Baseline platelets (10^9/l)				
Median / range	297 (28-1245)			
Baseline creatinine (µmol/l)				
Median / range	79.6 (35-795.6)			
Baseline bilirubin (µmol/l)				
Median / range	10 (1.7-138.8)			
Baseline albumin (g/l)				
Median / range	39.2 (4.1-70.0)			
< 35	189	20.0	99	90
35 – 39	181	19.1	86	95
39 – 43	222	23.5	108	114
> 43	155	16.4	79	76
Unknown	199	21.0	101	98

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.

Table VI-2: Prognostic factors for initial resistance

Factor	Univariate analysis		Multivariate model	
	Odd ratio	P-value	Odd-ratio	P-value
Lung metastases	0.323	< 0.0001	0.332	0.0001
Baseline hemoglobin	1.421	< 0.0001	1.380	0.0004
Baseline granulocytes	0.926	0.0049	0.935	0.0208
Baseline platelets (/100)	0.845	0.0082		
Performance status	0.734	0.0079		
Baseline albumin	1.040	0.0186		
Liver metastases	1.611	0.0212	1.816	0.0055
Time since GIST diagnosis (m)	1.297	0.0488		

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).

Table VI-3: Prognostic factors for late resistance

Factor	Univariate analysis		Multivariate model	
	Hazard ratio	P-value	Hazard ratio	P-value
Baseline granulocytes	1.064	< 0.0001	1.051	0.0009
Diameter of the largest lesion	1.033	0.0001	1.023	0.0095
Baseline white blood cells	1.051	0.0001		
Performance status	1.241	0.0014		
Gastric primary	0.712	0.0042	0.731	0.0088
Bowel primary	1.385	0.0053		
Baseline albumin	0.976	0.0095		
Prior chemotherapy	1.298	0.0184		
Dose of imatinib	0.779	0.0202	0.754	0.0093

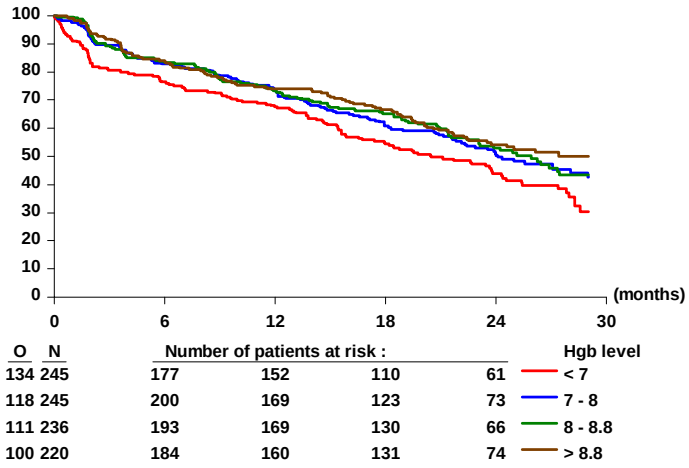
Impact of the Most Significant Cofactors

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 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.

Figure VI-1: Progression-free survival by hemoglobin level

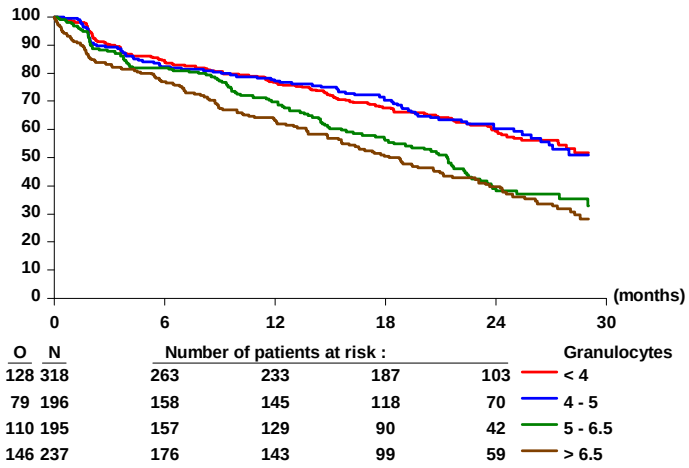
(mmol/l)



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 x 10^9/L.

Figure VI-2: Progression-free survival by granulocytes count

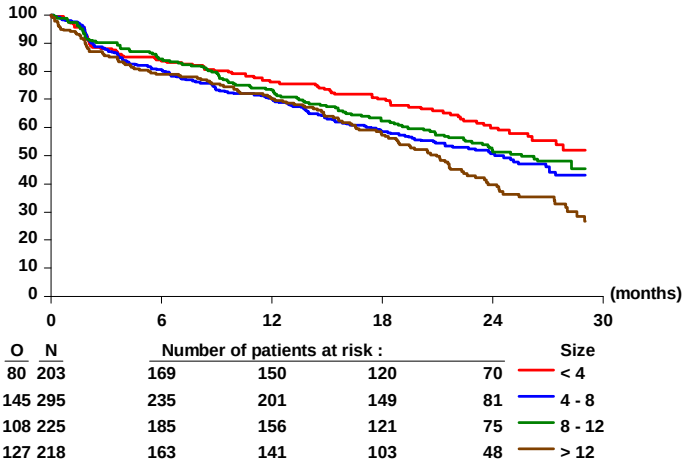
(10^9/l)



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).

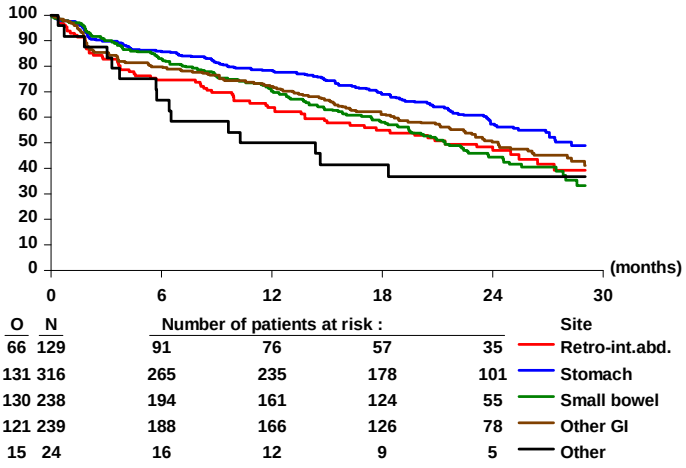
Figure VI-3: Progression-free survival by size of lesions

(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.

Figure VI-4: Progression-free survival by site of primary disease



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.

Table VI-4: Subgroup analysis

	Number of cases		Hazard ratio			Wald test
Subgroup	Total	Failures	Estimate	Confidence interval		P-value
All patients	946	463	0.801	0.667	0.961	0.017
Bas. granulocytes < 5 10^9/l	514	207	0.874	0.665	1.15	0.3368
Bas. granulocytes > 5 10^9/l	432	256	0.678	0.530	0.867	0.0020
Largest diameter < 120 mm	728	336	0.793	0.640	0.982	0.0337
Largest diameter > 120 mm	218	127	0.796	0.560	1.131	0.2025
Stomach origin	316	131	0.836	0.593	1.179	0.3077
Small bowel origin	238	130	1.025	0.726	1.446	0.8886
Other GI origin	239	121	0.576	0.400	0.828	0.0029

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 x 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.

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 x 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.

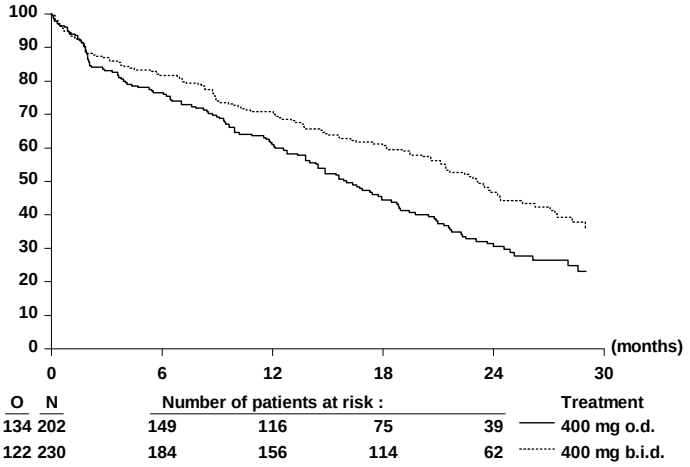


Figure VI-5: Progression free survival by dose level in patients with granulocytes >= 5 x 10^9/L

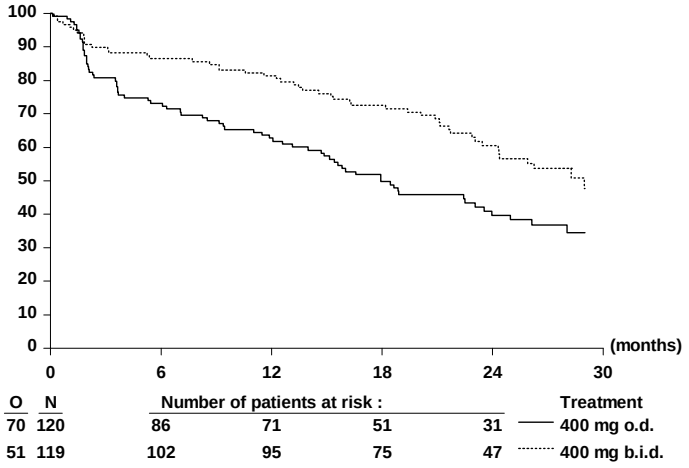


Figure VI-6: Progression free survival by dose level in patients with tumors of GI origin outside of the stomach or small bowel

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* 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 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.

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 x 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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Chapter VII

Predicting toxicities for patients with advanced gastro-intestinal stromal tumors (GIST) treated with imatinib: an EORTC-ISG-AGITG study.

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Abstract

The aim of this analysis is to identify prognostic factors of toxicity to imatinib treatment.

It is based on 942 GIST patients randomized to receive imatinib at different doses [1]. The correlation between toxicities occurring with a CTC grade 2+ (non hematological) or grade 3+ (hematological) and imatinib dose, age, sex, performance status, original disease site, site and size of lesions at trial entry, baseline hematological and biological parameters was investigated.

Anemia was correlated to dose and baseline hemoglobin level and neutropenia to baseline neutrophil count and hemoglobin level.

The risk of non hematological toxicities was dose dependent and higher in females (edema, nausea, diarrhea), and in patients with advanced age (edema, rash fatigue), poor performance status (fatigue and nausea), prior chemotherapy (fatigue), tumor of identified gastro-intestinal origin (diarrhea) and small lesions (rash).

We are proposing a multivariate risk calculator that can be used in the clinic for individual patients.

Introduction

GastroIntestinal Stromal Tumors (GIST) are a subset of soft tissue sarcomas classified relatively recently, that have proven to be insensitive to chemotherapy and radiotherapy [1].

Imatinib is a small molecule tyrosine kinase inhibitor 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. Treatment with imatinib has increased the two years survival expectation of patients with advanced or metastatic GIST from less than 20% to approximately 70% [2, 3]

However, the optimal dose of imatininb for the treatment of GIST is still unclear. According to an EORTC phase I study, the highest feasible dose of imatinib in GIST is 400 mg bid [4]. One randomized phase II trial (400 mg od vs 300 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 daily dose of 400 mg.

Formal comparison of the standard dose (400 mg od) versus the highest feasible dose (400 mg bid) has been addressed in two large randomized 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 largely 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 were reported in the two large randomized trials: 10% and 44% respectively for the standard and the high dose arm (absolute proportion) in the SWOG study [9]; 13% and 49% (6 months cumulative incidence) in the EORTC/ISG/IGITG study (2); in this last study, respectively 32% and 50% of the patients experienced at least one CTC grade III or IV toxicity during therapy; anemia, edema,

fatigue, nausea, abdominal pain, diarrhea, neutropenia and rash were all recorded in more than 1/3 or the patients and all were dose dependent except for neutropenia and abdominal pain [2].

A similar toxicity profile has been reported in other imatinib trials, in GIST and other tumor types [4, 5, 6, 10, 11, 12].

The aim of the current study is 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.

Material and methods

In the EORTC-ISG-AGITG phase III trial, 946 patients with advanced or metastatic GIST were randomized 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 WHO performance score up to 3, normal hematological and renal function , and liver function tests within 2.5 time the upper normal value (or 5 times in case of liver metastases). Any prior therapy was allowed and there was no upper age limit.

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

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

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

In the present study, we have analyzed the occurrence of the principal toxicities: grade 2 (or more) edema, fatigue, nausea, diarrhea and skin rash; grade 3 (or 4) anemia and neutropenia. Leucopenia and vomiting were not analyzed, because of their obvious correlation with neutropenia and nausea. Abdominal pain was not analyzed, because if was difficult to distinguish disease-related from treatment-related events.

We first estimated the cumulative incidence of all events 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, we used logistic regression models 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 hemoglobin 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 GI site, "abdominal" not further specified), and laboratory parameters at study entry (white blood cell count –WBC-, absolute neutrophil count –ANC-, platelets, hemoglobin, bilirubin, creatinine, 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 web-site of the EORTC (www.eortc.be).

To validate the final risk models (and the risk calculator), we have used the data of a phase I and a phase II study conducted in soft tissue sarcoma by the EORTC Soft Tissue and Bone Sarcoma Group [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 edema and fatigue; estimated probability above 20% and under 20% for the other studied events. The observed occurrence of those events (and the estimated 95% confidence interval) has been tabulated for each risk group and compared to the model prediction.

Results

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 respectively 99%, 90% and 81% of the patients have been followed for 1, 2 and 3 years. At 1 year, only 27% of the patients had either discontinued protocol therapy or crossed-over to the high dose.

Table VII-1: Distribution of CTC grades

Grade	0	1	2	3	4	Total
Neutropenia	547 (58.07)	179 (19.00)	149 (15.82)	**41 (4.35)**	**26 (2.76)**	942
Anemia	65 (6.90)	438 (46.50)	313 (33.23)	**89 (9.45)**	**37 (3.93)**	942
Edema	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
Diarrhea	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

Description of toxicities

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

The hematological toxicities included in this analysis are anemia (94% all grades / 13% grade 3 or higher) and neutropenia (42% / 7%), and the non hematological toxicities are edema (80% all grades / 35% grade 2 or higher), skin rash (37% / 15%), fatigue (75% / 36%) and gastro-intestinal: nausea (56% / 20%) and diarrhea (54% / 18%).

Cumulative incidence of events

The cumulative incidence of the different types of toxities (overall, and for each therapeutic arm) is shown on figures 1, 2 and 3.

At one year, the most frequent toxicities (edema 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.

Figure VII-1: Cumulative incidence of toxic events – All patients

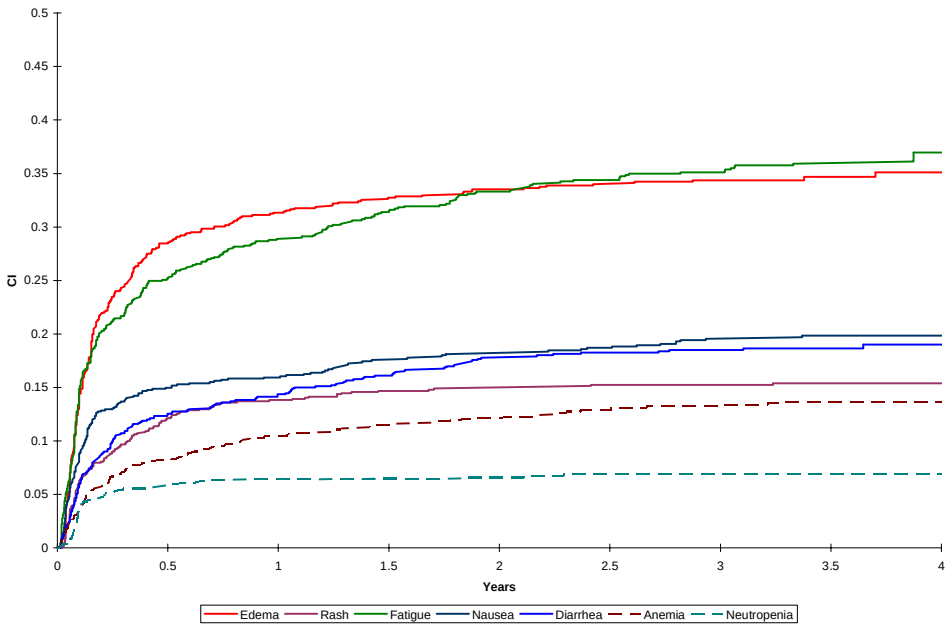


Figure VII-2: Cumulative incidence of toxic events – 400 mg o.d.

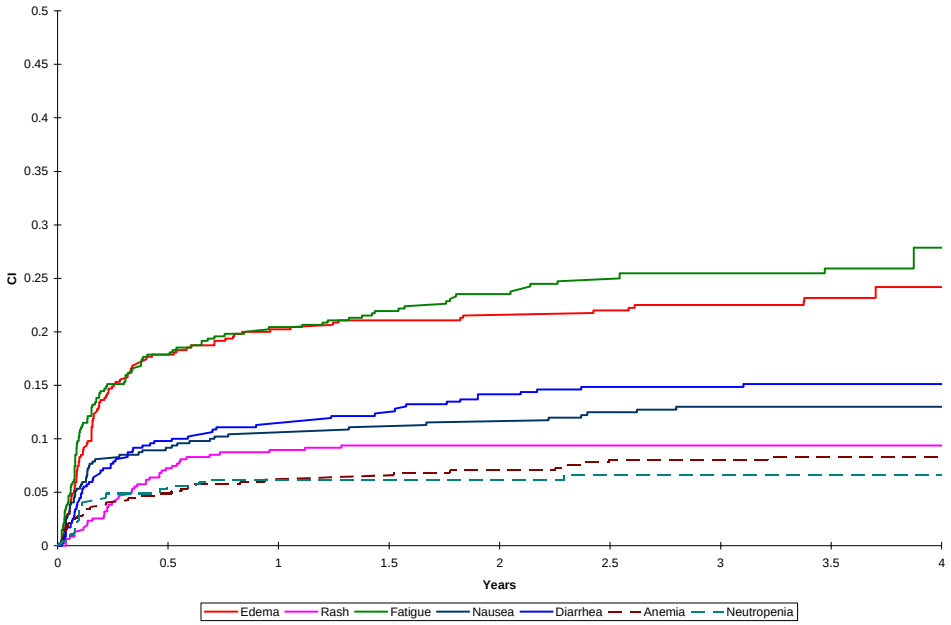
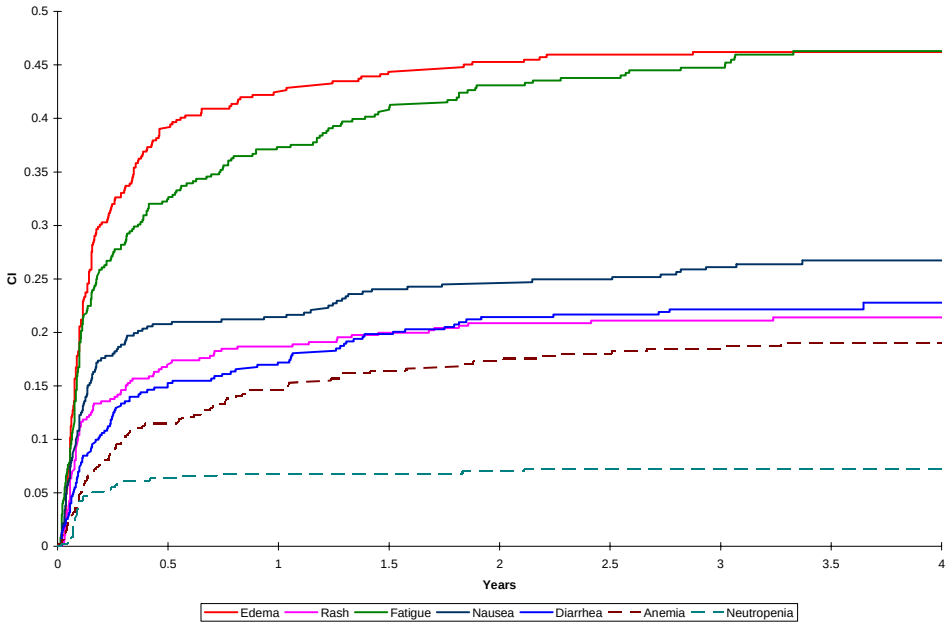


Figure VII-3: Cumulative incidence of toxic events – 400 mg b.i.d.



Identification of risk factors

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

For anemia, only high dose and baseline low hemoglobin 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 hemoglobin level was significantly correlated with dose ($p<0.0001$), initial hemoglobin level ($p<0.0001$) and initial albumin level ($p=0.0001$).

In the multivariate logistic model the prognostic factors for neutropenia were baseline low ANC and low hemoglobin levels.. Neutropenia was not dose dependant ($p=0.93$). In linear regression models, nadir ANC was only correlated with initial ANC.

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

For rash, high dose, advanced age and small size of lesions turned out to be independent prognostic factors. As patients with large lesions progress earlier than patients with small lesions [7], we investigated whether, in patients with small lesions, the increased risk of developing rash could be explained by a longer exposure to imatinib: we first added the factor “total treatment duration” to the logistic model: this factor turned out to be significant, but the factor “size of lesions” kept its significance level. We also ran the model 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 turned out to be independent prognostic factors. Small bowel origin adds information of borderline significance ($p=0.012$) to this model.

Finally, the independent prognostic factors for diarrhea are high dose, female sex and identified gastro-intestinal site of primary disease.

Table VII-2: Results of the prognostic factors analyses

	Anemia		Neutropenia		Fatigue	
	U	M	U	M	U	M
Dose level	****	<0.0001			****	<0.0001
Age					***	0.0023
Sex					*	
Perf. status	****				****	0.0003
Size of lesions	**					
Prior radio.					**	
Prior chemo.	*				**	0.0007
Initial HGB	****	<0.0001	*	0.0022	****	
Initial ALB	****				***	
Initial ANC	***		***	<0.0001		
Initial WBC	*		****			

	Edema		Rash		Nausea		Diarrhea	
	U	M	U	M	U	M	U	M
Dose level	****	<0.0001	****	<0.0001	****	<0.0001	**	0.0028
Age	***	0.0011	****	<0.0001				
Sex	****	<0.0001	*		****	<0.0001	*	0.0098
Perf. Status	*				****	<0.0001		
Primary : GI			*				*	0.0084
Prim: abdomen			*				*	
Prim: stomach			*				*	
Prim: bowel					**			
Size of lesions			**	0.0008				
Prior surgery					*			
Prior chemo.			**					
Initial HGB					**			
Initial ALB	**				**			
Initial ANC					**			
Initial WBC					*			

U: univariate models; M: multivariate models; radio., radiotherapy; chemo., chemotherapy; prim., primary; HGB, hemoglobin; ALB, albumin; ANC, absolute neutrophils count; WBC, white blood cells

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.

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

Table VII-3: Multivariate models and risk calculator

	Intercept	Dose (1=400 od, 2=400 bid)	Age (in years)	Sex (1=male, 2=female)	PS (WHO scale)	GI origin (0=no, 1=yes)	Tumor size (in mm)	Prior chemo. (0=no, 1=yes)
Edema	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			
Diarrhea	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)
Anemia	-1.94	- 0.993	0.715	0
Neutropenia	-1.618	0	0.36	0.292

Table VII-4: Examples of result for individual patients

Patients characteristics		Dose	Probability of grade 3 (or 4) toxicity (%)	
HGB (mmol/l)	ANC (10**9/l)	(mg/day)	Anemia	Neutropenia
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

Patients characteristics						Dose	Probability of grade 2 (or higher) toxicity (%)				
Age (years)	Sex	PS (WHO)	Prior chemo.	Lesion size (mm)	GI origin	(mg/ day)	Edema	Fati- gue	Skin rash	Nau- sea	Diar- rhea.
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

We have validated this model using data of 91 patients with advanced or metastatic sarcoma treated with imatinib at doses ranging from 400 to 1000 mg/day. We have used the calculator 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 really observed in all risk groups is shown in table 5.

The observed proportion of toxicities corresponds to the model for all except 3 groups, where the estimated 95% confidence interval still overlaps with the predicted chance range.

Table VII-5: Results of the validation

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

* 95% confidence interval: 27.7% - 59%

Risk estimated by the model		> 20%	< 20%	TOTAL
Skin rash	Nr cases	33	58	91
	Observed events	15 (45.5%)	10 (17.2%)	25 (27.5%)
Nausea	Nr cases	62	29	91
	Observed events	21 (33.9%)	10 (34.5%)*	31 (34.1%)
Diarrhea	Nr cases	38	53	91
	Observed events	16 (42.1%)	11 (20.8%)**	27 (29.7%)
Anemia	Nr cases	24	67	91
	Observed events	7 (29.2%)	9 (13.4%)	16 (17.6%)
Neutropenia	Nr cases	1	90	91
	Observed events	0	12 (13.3%)	12 (13.2%)

* 95% confidence interval: 17.9% - 54.3%; ** 95% confidence interval: 10.8% - 34.1%

Discussion

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

A randomized trial from 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 unacceptable for a 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 of 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 rechallenging 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 do therefore consider our data as

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 analyzed 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 one 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 diarrhea, and $p<0.0001$ for all other toxicities), with the exception of neutropenia ($p=0.93$). For GIST patients, this was previously reported in a phase I dose escalation study [4], in a randomized phase II study [5] and in two randomized phase III studies [2, 3]. No randomized data are available for leukemia, but most series also suggest that toxicities are dose dependent: nausea, edema, diarrhea and rash [17], nausea, edema and diarrhea [18] and anemia [19]. In only one Philadelphia chromosome-positive chronic phase 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.

Neutropenia 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 neutropenia 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 previous explored in patients treated with imatinib for GIST, but some data are available from CML studies: the cumulated data of 3 phase II trials (532 cases) has been analyzed by Hensley [11] and Cohen [12], while Cortes [19] focused on anemia 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 leukemia.

Advanced age was reported as a significant risk factor for edema [11, 12] and anemia [19], and female sex as a significant risk factor for neutropenia, edema, nausea and fatigue [12], for rash [12, 22] and for anemia [19]. For non hematological side effects, we observed the same correlations (but sex dropped out of the multivariate model for fatigue and rash). Hensley has identified a correlation between drug exposure (steady state plasma concentration) and edema, but this factor was not independent from age and sex [11]. In a GIST study, Judson has 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 anemia and neutropenia, we did not find any correlation with age and sex, but only with low baseline hemoglobin and neutrophils levels. AUC has also been reported to be higher in patients with baseline low hemoglobin level [14] and high granulocytes counts [15], so the prognostic value of baseline hemoglobin for neutropenia may be explained by a higher drug exposure and a possible role of hemoglobin 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 diarrhea in patients with tumors of identified gastro-intestinal origin has not been previously reported, but the last two factors could obviously not be explored in leukemia patients.

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 above 60 years old 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 had to be rejected, as tumor 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 dataset. 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 are proposing to estimate the probability of experiencing toxicities for individual patients on the basis of the final logistic models issued from this analysis. The coefficients of all models are included in table 3, and we are also proposing an interactive risk calculator (using the same coefficients), programmed in Excel. This simple tool can be used in clinical practice to customize treatment for individual patients.

Those models have been estimated on the basis of the largest available series of GIST patients treated with imatinib. They has been validated on the basis of a small series of 91 sarcoma patients treated at doses ranging from 400 mg to 1000 mg. Results of those validation tests are generally good (except for the underestimation of edema and nausea in the low risk groups), considering the limited sample size of the validation set. In our validation data set, the occurrence of edema was not correlated with sex, which can explain the discrepancy with our edema model. We expect to be able to further validate our models 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 imatininb. Based on those results, we propose a simple tool to calculate the risk of the principal toxic events for individual patients.

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Chapter VIII

Summary and conclusions

A general description of soft tissue sarcomas and their treatments is given in Chapter 1. The chapter also provides an introduction to the work on prognostic factors that is described in this thesis.

In chapter 2, we have identified the characteristics of the patients (and of their disease) influencing the survival expectation and the probability to respond to first line chemotherapy for advanced disease. Not surprisingly, advanced age is an adverse prognostic factor of survival and response to therapy. Poor performance adversely affects survival but not the probability of response to first line therapy. The number and size of the lesions does not affect response and neither survival, at the time of diagnosis of advanced disease. The survival prognosis is more favorable if the sarcoma was diagnosed at least 2 years before chemotherapy was needed. Patients who were initially diagnosed with low grade disease have a longer survival expectation, despite the fact that they respond less frequently to chemotherapy; and they are probably not appropriate candidates to test the activity of new drugs, especially if response is used as principal end-point.

The presence of liver metastases shortens the survival expectation, and decreases the probability of response. This suggested that either liver metastases are less chemo-sensitive, or that they represent an even more advanced stage of the disease, but alternatively, we could initially also not exclude that most of the patients with liver metastases could have had GIST, a histological sub-type known not to respond to chemotherapy. In an updated analysis, we excluded possible GIST patients and still observed a disadvantage in survival and response in patients with liver metastases. We concluded that the adverse prognostic effect of liver metastases in the series is not fully explained by the presence of GIST.

For randomized trials allowing entrance of patients with the various tumor types, the prognostic factors identified in this work should be used to stratify the treatment allocation (correcting the randomization process to ensure that those factors are evenly distributed between the two randomized arms).

The probability of response and the survival expectation is not the same for the different histological subtypes, but baseline characteristics (age, tumor grade and liver metastases) also differ between those groups. Knowing the exact subtype does generally not improve the estimation of the response probability and survival expectation if the other factors are already taken into account, except for liposarcoma for which the probability for response is higher. However, the estimation of response and survival for the different subtypes provides useful references for future histology specific trials.

In chapter 3, we have observed that 8% of the patients treated with a first chemotherapy for advanced disease are still alive after 5 years, which contrasts with the median survival of approximately one year in this population.

Those long term survivors more frequently are women, patients with a good initial physical performance, with a low grade tumor, and/or patients who had a complete response to treatment (complete disappearance of all lesions and of all cancer symptoms). A few deaths were still observed after 5 years, mostly in patients who had not responded to initial chemotherapy.

We concluded that a small proportion of patients with advanced soft tissue sarcoma can be cured with chemotherapy, in contract with the general opinion that systemic chemotherapy for advanced disease can only be palliative.

In chapter 4, we have investigated the possibility to use of the new "Response Evaluation Criteria for Solid Tumors" (RECIST) for soft tissue sarcoma. We retrospectively evaluated the results of the STBSG phase II study on the drug "ET-743" (now known as trabectedin) using RECIST instead of the WHO criteria used for the primary evaluation of the study results (in accordance with the protocol). This study was specifically designed to validate the new criteria, and objective measurements of all target lesions were reported on the data forms for the two methods.

There were only minor differences between the two evaluations, and the conclusions of the study would not have been modified by the use of RECIST. This validates the use of RECIST in soft tissue sarcoma, and the STBSG subsequently adopted the new criteria for phase II studies on cytotoxic drugs.

In chapter 5, we are proposing to use the progression free status of the patient at a fixed time point as primary end-point for phase II trials in soft tissue sarcoma. We have estimated the proportion of patients with stable disease (no measured increase in the size of the lesions) 3 and 6 months after start of chemotherapies in various groups of patients.

After failure of a first line chemotherapy regimen, 39% of the patients treated with agents known to induce responses (ifosfamide and dacarbazine) had a stable disease at 3 months, while this figure was only 21% for patients treated with investigational agents that ultimately failed to induce responses. We concluded that progression free rate at 3 months is an appropriate criterium to evaluate the activity of a new drug used as second or third line therapy. The estimation of the progression free rates was precise enough to be used as reference values for the design of phase II trials.

For patients treated with a first line chemotherapy regimen, the size of the database was sufficient to provide specific reference values for the principal histological subtypes (for active combinations only). Those references values have become extremely useful for the evaluation of targeted therapies, which are not expected to be cytotoxic.

In chapter 6, we investigated prognostic factors of resistance to imatinib mesylate in patients with advanced GIST. We have analyzed the data of the phase III study comparing the outcome of two daily doses of imatinib. The impressive activity of this drug in this disease is translated by an interruption of the tumor growth in most patients. However, a small proportion of the patients appear to be completely insensitive to the drug (early resistant), and progress rapidly. Patients with initial disease stabilization may relapse later; it is believed that tumor regrowth (late resistance) is induced by a different biological mechanism than the initial disease.

The proportion of "progression free" patients drops rapidly during the first 3 months, and more slowly thereafter. Based on this observation, we have considered progression within 3 months of start of therapy as "early resistance" and progression after 3 months as "late resistance". We have independently analyzed prognostic factors for early and late resistance.

Early resistant patients were those with an initial low hemoglobin and high granulocyte count. Prognostic factors for late resistance were high initial granulocyte count, large lesions and original localization of the disease outside of the stomach. We suggested that hemoglobin level could have an impact on the transport of the drug from the blood to the tumor, that the biological mechanism of tumor growth could vary between tumors of different anatomical origin, and that large tumors could more frequently induce secondary mutations that would lead to tumor regrowth.

Early resistance was independent of the daily dose, but late resistance was dose dependent, particularly in some of the prognostic subgroups. A subsequent analysis of the genetic mutations in the original tumor blocks showed large correlations between the types of mutations and the original localization of the disease.

In chapter 7, based on the data of the same study, we have identified patient's characteristics that influenced the occurrence of the principal toxicities. Women and patients with advanced age or poor performance status have generally a higher chance to experience edema, skin rash, fatigue, nausea and/or diarrhea during treatment with imatinib mesylate, but those factors do not influence the probability of all toxicities with the same magnitude. Additionally, diarrhea is more frequent in patients with a tumor originally located in the gastro-intestinal tract, skin rash in patients with small lesions, and fatigue in patients who have received prior chemotherapy. All toxicities are highly dose dependant (except neutropenia), but, again, the impact of the dose is not of the same magnitude for all toxicities.

We have subsequently generated multivariate models to estimates the probability of the different toxicities for individual patients. Those complex models have been integrated into an Excell program that can be used in clinical practice.

Those models have been validated with the data of the prior phase I / II study of imatinib mesylate conducted by the STBSG.

Future perspectives

Based on the exploration of the databases accumulated by the EORTC STBSG, the studies described in this thesis will contribute to:

Better prediction of the outcome of available treatments for advanced soft tissue sarcoma and GIST, on the basis of patients and disease characteristics at treatment start:

- Response probability and survival expectation for patients receiving doxorubicin based combinations as fist line therapy for advanced disease
- Progression free rate for patients treated with active and inactive drugs after failure to first line therapy, and for individual histological subtypes in first line therapy
- Early and late resistance to imatinib mesylate for patients with advanced GIST
- Occurrence of the principal toxicities of imatinib mesylate for patients with advanced GIST

Generation or confirmation of hypotheses that will contribute to the understanding of those diseases:

- Liver metastases from soft tissue sarcoma are either relatively insensitive to chemotherapy, or characterize an even more advanced stage of disease that is beyond chemo-sensitivity
- Systemic chemotherapy is curative for a small proportion of patients with advanced soft tissue sarcoma
- Hemoglobin may play a significant role in the transport of imatinib mesylate from the blood to the tumor
- The biological mechanisms of tumor growth in GIST are not evenly distributed between tumors of different anatomical origin
- Large GIST lesions could more frequently induce secondary mutations

Optimization of the design of future clinical trials to appropriately explore new potential systematic treatments:

- Trials comparing first line chemotherapy regimen should be stratified by age group, histological grade of disease and presence of liver metastases
- Patients with low grade tumors should not be included in trials using response to therapy as the primary end-point
- RECIST provide an appropriate primary end-point for testing cytotoxic drugs in soft tissue sarcoma
- Progression free rate at 3 months is an appropriate end-point for testing cytostatic drugs and targeted therapies in soft tissue sarcoma; appropriate reference values are available for this end-point
- Reference values are also provided to conduct histology specific phase II trials in first line therapy with targeted therapies. The favorable toxicity profile of these agents and the limited activity of chemotherapy can justify such trials.

In the first part of this thesis, we have focused on patients treated with doxorubicin containing combinations as first line therapy for advanced soft tissue sacoma. Ifosfamide is the second active drug in this disease, and a large number of patients treated with this drug are now documented in our database. We will investigate whether the prognostic factors for response and survival are the same in this population, which may help to select the most appropriate first line therapy for future patients.

RECIST is certainly not an appropriate end-point for the screening of new targeted therapies in GIST. Progression free rate at 3 months may be an appropriate alternative, but we will explore the actual measurements of the disease and investigate whether they can provide more reliable and specific criteria to document early resistance.

It has been demonstrated that resistance of GIST to imatinb could be overcome by increasing the daily dose; prognostic factors of first objective progression may ultimately not affect overall survival. When a sufficient follow-up will be available, we will identify

prognostic factors of survival and compare them to the prognostic factors of early and late progression.

Prognostic factors of early and late resistance in GIST have not yet been validated and prognostic factors of toxicity have been validated in a very small dataset. A second study of imatinib in GIST was conducted in US and Canada, using a nearly identical clinical trial protocol. After publication of the results of this second study, we are expecting to be able to use its data to confirm our models.

Chapter IX

Samenvatting en conclusies

Een algemene beschrijving van weke delen sarcomen en hun behandelingen word gegeven in **Hoofdstuk 1**. Dit hoofdstuk geeft ook een inleiding tot het werk over prognostische factoren dat in dit proefschrift beschreven is.

In Hoofdstuk 2 hebben we de kenmerken van patiënten (en hun ziekte) geïdentificeerd die de overlevingkans en de kans op respons op eerste lijns behandeling voor vergevorderde ziekte (niet meer volledig chirurgisch te verwijderen of uitgezaaid) beïnvloeden. Zoals verwacht, is gevorderde leeftijd een ongunstige prognostische factor voor overleving en voor respons op behandeling. Slechte klinische conditie heeft een ongunstige invloed op overleving maar niet op de kans op respons op eerste lijns behandeling. Het aantal en de grootte van de kwaadaardige lesies heeft geen invloed op respons of overleving. De overlevingskans is beter als het sarcoom meer dan twee jaar voorafgaand aan de chemotherapie gediagnosticeerd wordt. Patiënten met een tumor van lage maligniteidsgraad hebben een langere overlevingskans, hoewel ze minder vaak goed op chemotherapie reageren; ze zijn misschien geen goede kandidaten om de activiteit van nieuwe geneesmiddelen te testen, vooral als respons op behandeling gebruikt wordt als voornaamste eindpunt.

De aanwezigheid van levermetastasen vermindert de overlevingskans, en de kans op respons. Dit suggereert dat levermetastasen minder chemosensitief zijn, ofwel dat ze een kenmerk zijn van een vergevorderd stadium van de ziekte, maar we konden oorspronkelijk niet uitsluiten dat de patiënten met levermetastasen meestal gastrointestinale stroma tumoren (GIST) hadden, een bekend chemotherapieresistent histologisch subtype sarcoom. Daarom zijn in een latere analyse alle mogelijke GIST patiënten uitgesloten, en desondanks bleef er een slechtere overleving en respons bij patiënten met levermetastasen. Wij concluderen dat de tegenstrijdige prognostische invloed van levermetastasen in onze data niet volledig door de aanwezigheid van GIST verklaard wordt.

Voor gerandomiseerde klinische studies die insluiten van de verschillende histologische subtypen toestaan, zouden de prognostische factoren die we hebben geïdentificeerd in onze studie, gebruikt kunnen worden als stratificatiefactoren voor behandelingsallocatie (om zo het randomisatie proces te verbeteren en zeker te zijn dat deze factoren gelijk verdeeld zijn tussen de gerandomiseerde groepen).

De kans op respons en de overlevingsverwachting zijn niet identiek voor de verschillende histopathologische subtypen, maar de basis kenmerken leeftijd, tumorgraad en levermetastasen verschillen ook tussen deze groepen. Kennis van het preciese subtype verbetert gewoonlijk de inschatting van de overlevingskans en kans op respons overigens niet, als de andere prognostische factoren al bekend zijn, met uitgezondering van liposarcomen die een hogere responskans hebben. Maar de inschatting van responskans en overlevingkans voor verschillende histologische subgroepen verschaft een goede referentie voor toekomstige klinische onderzoeken bij gedefinieerde histologische subgroepen.

In het onderzoek beschreven in **Hoofdstuk 3** vonden wij dat 8% van de patiënten die behandeld werden met een eerste lijn chemotherapie voor vergevorderde ziekte na 5 jaar nog in leven waren, terwijl de gemiddelde overleving slechtsongeveer 1 jaar is in deze populatie.

Deze lange termijn overlevers zijn vaker vrouwen, patiënten met een goede initieele klinische conditie, een lage tumorgraad, en/of patiënten die een complete respons hadden op behandeling (verdwijnen van alle lesies en kanker symptomen). Sommige patienten overleden meer dan 5 jaar na de behandeling. Meestal betrof dit patiënten met een partieele respons of de initieele chemotherapie.

Daaruit hebben we kunnen afleiden dat een klein aantal van de patiënten met vergevorderde ziekte kan genezen worden met chemotherapie, in tegenstelling tot de algemeen gehandteerde veronderstelling dat systemische behandeling voor vergevorderde ziekte alleen palliatief zal zijn.

In Hoofdstuk 4, hebben we het mogelijk gebruik van de nieuwe “Response Evaluation Criteria for Solid Tumors” (RECIST) voor weke delen sarcomen onderzocht. We hebben daarvoor de STBSG fase II studie met het geneesmiddel “ET-743” (nu ook bekend als trabectedin) retrospectief geanalyseerd, en RECIST gebruikt in plaats van de WHO criteria die waren gebruikt voor de oorspronkelijke evaluatie. Deze studie was speciaal ontworpen om de nieuwe criteria te valideren, en objectieve metingen van alle doel lesies met beide methoden waren verzameld op de studie formulieren.

Er waren maar kleine verschillen tussen beide evaluaties, en de conclusies van het onderzoek zouden niet verschillend zijn als de RECIST methode gebruikt zou zijn. Daarmee kunnen we het gebruik van RECIST voor weke delen sarcomen valideren. De STBSG heeft dus de nieuwe criteria aanvaard voor toekomstige fase II studies met celdelingremmende geneesmiddelen (cytostatica).

In Hoofdstuk 5 stellen we voor de progressievrije status op een bepaald tijdpunt als primair eindpunt te gebruiken in fase II studies bij weke delen sarcomen. We hebben percentage patiënten met stabiele ziekte (zonder toename van de omvang van de lesies) 3 en 6 maanden na het begin van chemotherapie geschat in verschillende patiëntengroepen.

Na het niet meer werken van de eerste lijn chemotherapie combinatie, had 39% van de patiënten die behandeld werden met een geneesmiddel dat bekend actief is bij weke delen sarcoom (ifosfamide en dacarbazine) een stabiele ziekte na 3 maanden, terwijl dit slechts 21% was voor patiënten die behandeld werden met nieuwe geneesmiddelen die achteraf geen activiteit bleken te hebben. Wij concluderen dat stabiele ziekte na 3 maanden een goed eindpunt is om de activiteit van tweede of derde lijn behandeling te evalueren. De schatting van het percentage progressievrije patiënten was nauwkeurig genoeg om gebruikt te worden als referentiewaarde voor het ontwerpen van fase II studies.

Voor patiënten behandeld met eerste lijn (aciteve) chemotherapie combinaties, was de steekproefgrootte van de databank voldoende om specifieke referentiewaarden te geven voor de meeste histologische subtypes. Deze referentiewaarden zijn nu heel nuttig voor de evaluatie van nieuwe, moleculair doelgerichte geneesmiddelen, die zijn niet celdodend (cytotoxic) zijn.

In Hoofdstuk 6 hebben we prognostiche factoren onderzocht voor resistentie op imatinib mesylaat behandeling van patiënten met vergevorderde GIST. We hebben de data van een fase III studie bestudeerd, die het effect van twee verschillende doses imatinib vergeleek. De indrukwekkende werkzaamheid van dit geneesmiddel is leidt tot een onmiddellijke stopzetting van de tumorgroei bij de meeste patiënten. Maar een klein gedeelte van GIST

patiënten schijnen totaal resistent te zijn tot dit geneesmiddel (vroeg-resistent) en tonen een snelle progressie. Patiënten met een aanvankelijk goede respons,kunnen later recidiveren; men denkt dat deze recidieven (late resistentie) veroorzaakt woren door een verschillend biologisch mechanisme dan vroege resistentie.

Het percentage van progressievrije patiënten vermindert snel gedurende de eerste 3 maanden, en daarna veel langzamer. Op grond van deze observatie hebben we ziekteprogressie gedurende de 3 eerste maanden als “vroege resistentie” geclassificeerd, en ziekteprogressie na de 3 eerste maanden als “late resistentie”. We hebben prognostische factoren van vroege- en late resistentie onafhankelijk onderzocht.

Vroeg resistente patiënten hadden een aanvankelijk laag hemoglobine gehalte en een hoog granulocyten aantal. Prognostische factoren voor late resistentie waren hoog granulocyten aantal, grote lesies en primaire tumor lokalisatie buiten de maag. We veronderstellen dat het hemoglobinepeil het geneesmiddeltransport van het bloed tot de tumor kan beïnvloeden, dat de biologische werkwijze van tumorgroei kan verschillend zijn voor ziektes van verschillende primaire lokalisaties, en dat grote tumoren vaker secondaire genetische mutaties kunnen herbergen die zouden leiden tot recidiveren van de tumor.

Vroege resistentie was onafhankelijk van de dagelijkse dosis imatinib, maar late resistentie was dosisafhankelijk, meestal in bepaalde prognostische subgroepen. Een verder onderzoek van genetische mutaties in de oorspronkelijke tumorblokken toonde belangrijke correlaties tussen de mutatietypen en de oorspronkelijke ziektelokalisatie.

In Hoofdstuk 7 hebben we, gebaseerd op data van dezelfde studie, de patiënten karakteristieken geïdentificeerd die het optreden van de belangrijkste bijwerkingen beïnvloeden. Vrouwen en patiënten van gevorderde leeftijd of met een slechte klinische conditie hebben gewoonlijk meer kans op oedeem, huiduitslag, vermoeidheid, misselijkheid en/of diarree gedurende de behandeling met imatinib mesylaat, maar deze factoren geven niet dezelfde mate van kans op de verschillende bijwerkingen. Diarree is ook meer frequent bij patiënten met een tumor van gastrointestinale oorspong, huiduitslag bij patiënten met kleine letsels, en moeheid bij patiënten die eerder werden behandeld met chemotherapie. Alle bijwerkingen (uitgezonderd neutropenie) zijn geheel dosisafhankelijk maar, ook hier is de invloed van de dosis is niet van dezelfde omvang op alle bijwerkingen.

We hebben daarom multivariaat modellen ontworpen om de kans van alle bijwerkingen te schatten voor individuele patiënten. Deze ingewikkelde modellen zijn samengevoegd in een Excell programma dat gebruikt kan worden door de behandelend arts. Deze modellen werden gevalideerd met de data van de vroegere fase I / II studie van EORTC-STBSG met imatinib mesylaat.

Toekomstperspectieven

Op basis van de onderzoeken met de databank van de EORTC STBSG, zullen de studies beschreven in dit proefschrift bijdragen tot:

Betere voorspelling van de uitkomst van beschikbare behandelingen voor vergevorderde weke delen sarcomen en GIST, op basis van patiënten en ziekte kenmerken voor de behandeling:

- Responskans en overlevensverwachting van patiënten die doxorubicine combinaties krijgen als eerste lijn behandeling voor vergevorderde ziekte.
- Progressievrije percentage voor de patiënten behandeld met actieve en inactieve geneesmiddelen, na falen van eerste lijns behandeling, en voor verschillende histopathologische subtypes.
- Vroege en late resistentie op imatinib mesylaat voor patiënten met vergevorderde GIST.
- Inschatting van de belangrijkste bijwerkingen voor patiënten met vergevorderde GIST behandeld met imatinib mesylaat.

Ontwikkeling of bevestigen van hypotheses die tot het begrip van deze ziektes zullen bijdragen:

- Of levermetastasen van weke delen sarcomen relatief ongevoelig voor chemotherapie zijn, danwel een kenmerk van een vergevorderd ziektestadium zijn, buiten bereik van chemosensitiviteit.
- Systemische chemotherapie is curatief voor een klein aantal patiënten met weke delen sarcomen.
- Hemoglobine kan een belangrijke rol spelen bij het transport van imatinib mesylaat van het bloed naar de tumor.
- De biologische tumorgroei in GIST is niet gelijk tussen de tumoren van verschillende primaire tumor localisaties.
- Grote GIST lesies kunnen vaker secundaire mutaties veroorzaken.

Optimalisatie van toekomstige klinische studie-opzet om nieuwe potentiële systemische geneesmiddelen te onderzoeken:

- Studies die eerste lijns chemotherapie combinaties vergelijken zouden gestratifieerd moeten worden voor leeftijd, histologische tumorgraad en de aanwezigheid van levermetastasen.
- Patiënten met laag gradige tumoren zouden niet geincludeerd moeten worden in studies die respons op behandeling als primaire eindpunt gebruiken.
- RECIST geeft ons een gevalideerd primair eindpunt om celdodende geneesmiddelen te bestuderen.
- Stabiele ziekte (progressievrije status) na 3 maanden is een gevalideerd eindpunt om celdelingremmende en doelgerichte geneesmiddelen te bestuderen bij weke delen sarcomen; referentiewaarden zijn nu beschikbaar voor dit eindpunt.
- Referentiewaarden zijn ook verzameld om eerste lijn celdelingremmende en doelgerichte geneesmiddelen te bestuderen in fase II studies. De gunstige bijwerking profielen van deze nieuw medicijnen en de beperkte werkzaamheid van chemotherapie rechtvaardigen dergelijke studies.

In het eerste gedeelte van dit proefschrift hebben we onze aandacht gevestigd op patiënten die met eerste lijn doxorubicine combinaties behandeld worden voor vergevorderde weke delen sarcomen. Ifosfamide is het tweede actieve geneesmiddel voor deze ziekte, en gegevens van een groot aantal patiënten die met dit geneesmiddel behandeld zijn nu in onze gegevensbank beschikbaar. We zullen onderzoeken of prognostische factoren voor respons en overleving dezelfde zijn, dit om te helpen de beste eerste lijn behandeling voor toekomstige patiënten te kiezen.

RECIST is zeker geen voldoende eindpunt voor screening van nieuwe doelgerichte geneesmiddelen in GIST. Progressievrije status na 3 maanden mag een geldig eindpunt zijn, maar we willen ook de huidige tumormetingen onderzoeken en bestuderen of zij meer betrouwbare en specifieke criteria kunnen leveren om vroege resistentie vast te stellen.

Er werd aangetoond dat GIST resistentie op imatinib tegengewerkt kan worden door de dagelijkse dosis te verhogen; prognostische factoren voor eerste objectieve progressie mogen uiteindelijk de overleving niet beïnvloeden. Als genoeg follow-up beschikbaar is zullen we de prognostische factoren voor overleving karakterisere, en vergelijken met prognostische factoren voor vroege en late resistentie.

We hebben prognostische factoren voor vroege en late resistentie in GIST tot op dit ogenblik nog niet gevalideerd, en prognostische factoren voor bijwerkingen alleen op basis van een kleine gegevensbank gevalideerd. Een tweede studie met imatinib bij GIST is , met een bijna identiek opzet, in VS en Canada uitgevoerd; we verwachten dat het mogelijk zal zijn de gegevens van deze tweede studie te gebruiken om onze modellen te bevestingen.

Curriculum Vitae

Martine Van Glabbeke is born in Etterbeek (Belgium) on August 29th, 1951. After obtaining her high school degree from the “Athénée Royal de Watermael-Boitsfort” in 1969, she started studying applied sciences at the “Université Libre de Bruxelles” and obtained the degree of Civil Engineer in Chemistry, (“Ingénieur Civil Chimiste”, “Burgerlijke Ingenieur in Scheikunde”) in 1974, after the successful defense of a thesis entitled “Contribution to the study of the Belousof reaction: kinetic study of an oscillating reaction”. She also obtained post-graduate certificates in computer sciences, automation and corrosion in 1975, and a post-graduate master degree in statistics in 1982, both from the “Université Libre de Bruxelles”. She started working at the EORTC Data Center as a computer analyst in 1975, and became a biostatistician in 1978. In 1989, she was nominated Assistant Director of the EORTC Data Center. She has been the biostatistician of several EORTC groups since 1978 (Early Clinical Trials Group, Clinical Screening Group, Radiotherapy Group) and is still the biostatistician of the EORTC Lymphoma Group and the EORTC Soft Tissue and Bone Sarcoma Group, that she joined in 1983. She is currently heading the Protocol Development Unit of the EORTC Data Center. She has been a faculty member of various courses organized by the European School of Oncology, the EORTC Educational Office, and the Federation of European Cancer Societies, and currently co-Chairs the FECS-AACR-ASCO Flims Workshop on “Methods in Clinical Cancer Research”. She is a member of the American Society of Clinical Oncology, and of the Connective Tissue Oncology Society, for which she has served as board member from 1999 to 2002. Her principal hobbies are navigation and sailing.

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This thesis reflects the cooperative work of a multidisciplinary international group of scientists with a strong common objective, namely the EORTC Soft Tissue and Bone Sarcoma Group. I would like to express my gratitude to the members of this group, not only for letting me use the database they have accumulated in more than 30 years of clinical research, but mostly for their active contribution as co-authors of different chapters of this thesis, and, more generally, for their friendly support in all circumstances.

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On the worldwide scene, I am also grateful to the members of the Connective Tissue Oncology Society, which offers a unique forum for discussion, exchange of ideas and initiation of common projects for all scientists interested in sarcoma; large parts of this thesis have been presented at meetings of this society and have received an interesting feed-back.

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Of course, none of this would have been possible without the European Organisation for Research and Treatment of Cancer. Since 1975, I enjoy working at EORTC, applying my mathematical and statistical background to clinical cancer research, a field that brings so much personal satisfaction; this work also offers me the privilege to collaborate with investigators from multiple countries and share the richness of our cultural differences. I would like to thank Pr.Françoise Meunier, the EORTC Director General, as well as Dr.Patrick Therasse, the Director of the EORTC Data Center for allowing me to write and defend this thesis, based on my experience acquired with EORTC. I would mainly like to thank them for fighting every day to offer European scientists this unique infrastructure for conducting cancer clinical research across national borders and across specialties, in a scientifically independent way.

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The quality of most publication is directly linked to the quality of the underlying database. The analyses supporting this thesis are based on data organized, assembled, verified, queried and corrected by Anne Kirkpatrick, Catherine Hermans and Michelle Brown, whom I would first like to thank for the excellent quality of their work. I would also like to tell them and my other (past and present) colleagues from the “sarcoma team” that I do particularly appreciate the friendship we have developed in all those years.

On the personal side, I would like to thank my parents who have taught me, from my early childhood, to rely on my own judgment, and use it in an objective way. They were both supporters of the “number is all” theory, so my interest for mathematics (and logics) has probably a double genetic origin, enhanced by what some would qualify as “early intoxication”. However, they taught me that the important characteristic of this game called “mathematics” is its ability to solve a large variety of problems, if appropriately applied. They offered me a large horizon of possibilities, amongst with I selected biostatistics, a fascinating application that leads to biology and medicine.

Last but not least, an enormous amount of gratitude goes to my beloved husband, Guy Joly, who has supported and encouraged me through those busy but exciting years. Guy, I know that I had to dedicate to this project a large amount of time and attention that I have deprived you from, and that I have borrowed from our common projects. But you know that I would probably not have been able to keep my balance and complete this thesis without your critical and wise suggestions, or without your loving presence at my side. I would certainly not have been able to enjoy this day if I had not been able to share it with you. Although I know that it is only a modest compensation, I hope that you will be proud of your wife.