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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 $\geqslant$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 $\geqslant$40% would suggest a drug activity, and $\leqslant$20% would suggest inactivity.

Keywords: Soft-tissue sarcoma; Progression-free rate; Response criteria; Phase II; End-point

1. 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 [2–4] 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.

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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.

2. 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 [6–17].

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).

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 1
Therapeutic regimen

Regimen	Treatment description
A	Dacarbazine 1.2 g/m^2, 20-min infusion, q 3 wks
B	Ifosfamide 5 g/m^2, 1-day infusion, q 3 wks
C	Ifosfamide 3 g/m^2 day, 4-h infusion, days 1, 2, 3, q 3 wks
D	Ifosfamide 12 g/m^2, 3-day infusion, q 4 wks
E	Mitozolomide 90 g/m^2, 1-h infusion, q 6 wks
F	Nimustine, 100 or 75 mg/m^2, slow i.v. injection, q 6 wks
G	Fotemustine, 100 mg/m^2, 1-h infusion, wk 1, 2, 3, 9, 12, 15 ...
H	Miltefosine, 50 mg, p.o., 3 times daily
I	L-MTP/PE, 4 mg, 30-min infusion, weekly
J	Temozolomide, 150 mg/m^{2}day, p.o., days 1, 2, 3, 4, 5, q 4 wks
K	Etoposide, 50 mg/m^2 day, p.o., days 1–21, q 4 wks
L	Tomudex, 3 mg/m^2, 15-min infusion, q 3 wks
M	Gemcitabine, 1250 mg/m^2, 30-min infusion, day 1, 8

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

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.

Table 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 chemotherapy 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	$\leqslant 3^{b}$	1^{a}	–	$\leqslant 4$	$\leqslant 4$	–	–	–	–	–	–	–
WBC (10^{b} 9/l)	$\geqslant 3$	$\geqslant 4$	$\geqslant 4$	>4	>4	>4	$\geqslant 4$	$\geqslant 4$	>3.5	$\geqslant 3.5$	$\geqslant 4$	$\geqslant 4$
PLA (10^{b} 9/l)	$\geqslant 100$	$\geqslant 100$	$\geqslant 100$	>125	>125	>150	$\geqslant 100$	$\geqslant 100$	>100	$\geqslant 100$	$\geqslant 100$	$\geqslant 100$
Haemoglobin (g/l)	–	–	–	–	–	>110						
Creatinine (micromol/l)	$\leqslant 150$	$\leqslant 150$		$\leqslant 150$	$\leqslant 150$	$\leqslant 132.6$	$\leqslant 150$	$\leqslant 150$	$\leqslant 150$	$\leqslant 150$	$\leqslant 120$	$\leqslant 120$
Creatinine clearance (ml/s)	–	–	$\geqslant 1.17$	–	–	$\geqslant 1$	–	–	>1	–	Or >1.08	Or >1.08
Bilirubin (micromol/l)	$\leqslant 25$	$\leqslant 25$	$\leqslant 30$	$\leqslant 25$	$\leqslant 25$		$\leqslant 25.6$	$\leqslant 25$	$\leqslant 25$	$\leqslant 20$	$\leqslant 30$	$\leqslant 30$
Albumin (g/l)	–	$\leqslant 25$	$\leqslant 25$	–	–		$\leqslant 25$	–	–	$\leqslant 30$	$\leqslant 25$	$\leqslant 25$
Transaminases (UNL[a])	–	–		–	–	$\leqslant 1.25$	–	–	<2	–	–	–
Alkaline phosphatases (UNL[a])	–	–		–	–	$\leqslant 1.25$						
Prior nephrectomy	–	–	No	–	–	–	–	–	–	–	–	–

wks, weeks; PS, Performance Status; WBC, white blood cells; PLA, platelets; UNL, upper normal limit.
[a] Single agent doxorubicin or epirubicin.
[b] Including at least doxorubicin, cyclophosphamide or ifosfamide.

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].

3. Results

3.1. 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.

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.

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

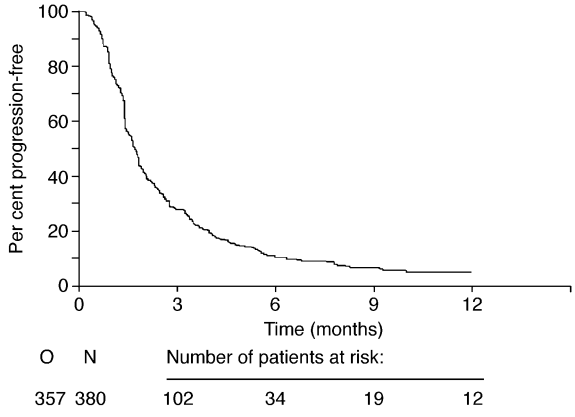

Fig. 1. Kaplan–Meier estimate of progression-free rate for the whole cohort of pretreated patients. O, observed; N, number.

Table 3
Patients characteristics: the following table indicates the proportion of patients (in%) included in each extreme category of the baseline variables

Trial	A	B/C	D	E	F	G	H	I	J	K	L	M
No. 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 (years)												
<40	42	20	28	28	15	36	38	42	25	35	14	16
>60	24	22	20	28	30	14	19	16	29	27	18	35
Initial diagnosis (months)												
<6	–	13	28	–	–	4	14	11	0	4	14	0
>24	–	34	36	–	–	46	48	32	52	38	18	52
Liver												
Involved	7	21	36	19	30	29	29	32	25	12	18	26
Histology												
Leiomyosarcoma	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 sarcoma	18	7	12	19	12	21	10	11	11	12	5	23
Neurogenic sarcoma	7	7	0	8	3	14	19	11	11	4	5	6
Liposarccma	2	13	4	8	6	4	10	5	11	12	14	10
Fibrosarcoma	2	1	0	4	9	0	14	0	4	0	5	0
Prior chemotherapy												
Adjuvant only	9	24	24	4	12	7	14	16	7	27	23	13
>1 regimen	–	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

MFH, malignant fibrous histiocytoma.

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

3.2. 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%).

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

Treatment	No. cases	3-month PFR (%)		6-month PFR (%)	
		Estimates	S.E.	Estimates	S.E.
Inactive regimen	234	21	3	8	2
Active regimen	146	39	4	14	3
All patients	380	28	3	10	2

S.E., standard error.

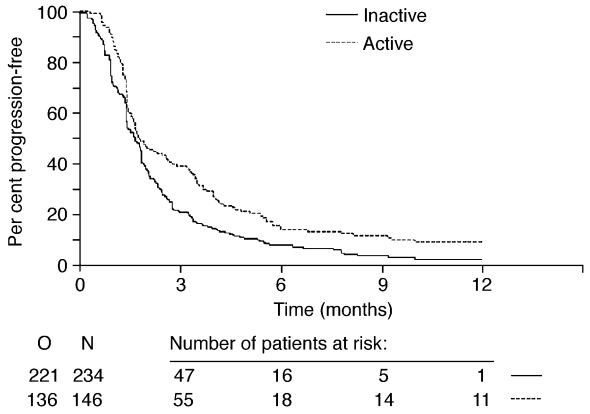

Fig. 2. Kaplan–Meier estimate of progression-free rate for patients pretreated with an inactive or with an active agent. O, observed; N, number.

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 subgroup, 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].

4. Discussion

4.1. 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%.

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

Histology	No. cases	3 month PFR (%)		6 month PFR (%)	
		Estimates	S.E.	Estimates	S.E.
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

MFH, malignant fibrous histiocytoma; S.E., standard error; GI, gastrointestinal.

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.

4.2. 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.

4.3. 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.

4.4. 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.

4.5. 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).

5. 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 endpoint 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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