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Acknowledgements—We would like to thank Elisabet Anderbring, Inger Bodin, Bo Carlsson, Ruth Detlofsson, Inger Foskolos and Marianne Lagnefeldt for their skilful technical assistance. Drs Farkas Vanky, Jan-Olof Fernberg, Anders Österborg, Karl Merk, Magnus Björkholm and Bengt Simonsson are thanked for their help in obtaining blood, bone marrow and tumour samples. This study was supported by grants from the Swedish Cancer Society and The Cancer Society of Stockholm.

Eur J Cancer, Vol. 29A, No. 14, pp. 1943–1947, 1993.
Printed in Great Britain

0959-8049/93 $6.00 + 0.00

Selection of Large and Objectively Measurable Target Lesions in EORTC Phase II Trials: Impact on Recruitment and Response Rate

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The EORTC has recently issued minimum requirements for target lesions in phase II trials, aiming at a decrease in measurement errors [minimum size, computer tomography (CT) scan or ultrasound for deep lesions]. Their impact on recruitment and response has been retrospectively studied in a trial of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), investigating high-dose chemotherapy in patients with advanced soft tissue sarcoma, where 46/103 objective responses were seen, including 10 complete responses. For the 20 patients who did not satisfy the criteria, a similar objective response rate and a significantly higher complete response rate were reported. Among 265 target lesions, the same trends were observed when comparing small to large lesions, for different tumour sites. For deep lesions clinically assessed, significantly higher response rates were reported than for those measured by CT scans or ultrasound. The new stricter EORTC criteria improve the reliability of measurements and have been adopted for future phase II trials of the STBSG. This will not result in the selection of potentially poor responders. Less than 20% of the present recruitment will be lost.
Eur J Cancer, Vol. 29A, No. 14, pp. 1943–1947, 1993.

INTRODUCTION

BECAUSE OF the number of compounds with potential activity against cancer, the methodology of screening and early development of new agents is important if the delay between discovery and application in large numbers of patients is to be minimised. At the clinical level, drugs with potential value are first evaluated in a limited number of patients for toxicity (phase I) and for antitumour activity (phase II). Only agents which have successfully completed these trials (i.e. the clinical screening phases) will be further developed and tested on a large scale (phase III). Phase II trials are crucial, because the decision to either terminate the development of a new agent, or invest large amounts of energy and money in its development and evaluation relies on their results.

Despite a seemingly well established methodology [1], comparison of published results of phase II trials often reveals important differences in response rates reported for a particular drug in a specific tumour type. Differences in the doses and schedules chosen for the trial, but also in the selection of the patients, are factors known to influence the conclusions of the trials [2–4]. Differences in response criteria play a role in this heterogeneity, but, surprisingly, critieria used for the evaluation are frequently not reported properly [5].

A factor which is rarely reported is the type of lesions which are chosen as "targets" for the response evaluation. The principal end-point of phase II trials is the "response to treatment", conventionally defined by the WHO response criteria [6]. Patients eligible for phase II trials may have both measurable and non-measurable disease. For the sake of objectivity, only measurable lesions are generally used to evaluate the "response to treatment"; other lesions are only followed to confirm a complete response (all signs of disease must have disappeared) or to downgrade a case to progression (clear progression of any lesion, measurable or not, results in a classification as progression). Practically, a few easily measurable lesions are chosen before the start of treatment, and carefully measured at each evaluation: they are called "target", "index" or "indicator" lesions. All other lesions are only followed to ensure that they are not progressing (or that they have totally disappeared in case of complete response in the targets).

Particular attention has been paid recently to the reproducibility of measurement of target lesions. Their initial size is important: it has been demonstrated both by mathematical models and by practical experience that the error of measurement in small lesions may lead to a high percentage of false positive and false negative response assessments [7, 8]. Recently, the development of sophisticated investigation techniques has enabled the measurement of specific lesions with better precision. Comparison with clinical measurements has shown that the reliability of clinical evaluation for deep lesions was low.

However, if only large lesions can be used as targets, patients with small lesions would become ineligible for phase II trials. Confining the methods of investigation to those considered as reliable may also influence the possible recruitment to trials and increase the cost of treatment (e.g. repeated CT scans).

Minimum requirements for target lesions have recently been produced by the EORTC [9, 10]. The aim of the present study is to validate this policy, by investigating how it affects the recruitment as well as the response rate in a phase II trial conducted by an International Clinical Cooperative Group.

MATERIALS AND METHODS

In most EORTC phase II protocols conducted before 1991, the only requirement in terms of targets was the presence of at least one bi-dimensionally measurable lesion. Stricter recommendations have recently been issued, generally limiting the eligibility of targets to the following types of lesions:

1. A skin metastasis of at least 2.5 cm (largest diameter).
2. (a)A palpable lymph node of at least 2.5 cm.
   (b)A lymph node of at least 2.5 cm, measured by CT scan or ultrasound.
3. A lung metastasis of at least 2 cm, not adjacent to any other structure.
4. A liver metastasis of at least 2.5 cm, measured by CT scan or ultrasound.
5. A soft tissue lesion of at least 2.5 cm, measured by CT scan or ultrasound.

The impact of those recommendations has been retrospectively assessed in a phase II trial of high-dose chemotherapy as first line treatment for advanced soft tissue sarcoma. This study was selected because of its relatively large sample size (103 evaluable patients), and its high response rate (45%). It was planned before these recommendations were published, and conducted by the EORTC Soft Tissue and Bone Sarcoma Group [11].

Patients selected for this trial had to have histologically confirmed soft tissue sarcoma with progressive metastatic or local/locoregionally advanced disease, not previously treated with chemothereapy. Other selection criteria included age 18–75 years, performance status 0 or 1 (WHO scale), serum creatinine < 150 μmol/l, bilirubin < 25 μmol/l, white blood cell count $> 4 \times 10^9$/l and platelet count $> 100 \times 10^9$/l [11].

The protocol required the presence of at least one measurable lesion, progressing within 4 weeks prior to therapy, and not previously irradiated. Lesions considered as measurable were those that could be measured in their two largest perpendicular diameters, as well as liver enlargement measured as the sum of the distances from the inferior liver edge to the xiphoïd notch and right costal margin in the mid clavicular line in mid respiration. Osseous lesions and pleural effusions were not considered as measurable.

The chemotherapy regimen consisted of doxorubicin (75 mg/m^2, day 1) and ifosfamide (5 g/m^2, day 1), plus granulocyte–macrophage colony stimulating factor (GM-CSF) (250 μg/m^2/day, days 1–14), and was repeated every 3 weeks. The first assessment of response had to take place prior to the third cycle, or 6 weeks after the first treatment. Response was defined according to the WHO criteria [6]. Among the 103 evaluable patients in the study, a complete response (CR) rate of 10% (10 CR) and an overall response rate of 45% [10 CR + 36 partial response (PR)] were observed. One patient was not evaluable for response. Results have been published elsewhere [11].

Each lesion considered as a target had to be fully described on the case report form, before the start of treatment, and at each evaluation of the disease. The localisation of the lesion, the method of measurement and the two largest diameters had to be reported. We could, therefore, retrospectively assess, for each lesion, if it conformed to the new EORTC guidelines, in terms of minimal size and method of measurement. The response of all individual lesions had to be assessed at each evaluation of the disease status (according to the WHO guideline), and the corresponding measurements were reported on the case report form.

As a first step, we evaluated the percentage of non-compliers, i.e. patients who would have been ineligible, according to the new EORTC requirements. All reported target lesions were compared to those criteria. Lesions conforming to those criteria are referred as "acceptable". The number of acceptable lesions was counted for each patient. Patients without any acceptable lesions were considered as "non-compliers". Those cases were individually reviewed, to identify the type of target lesions used for those patients and to investigate which of the new criteria was the most restrictive.

The complete (CR) and overall (CR + PR) response rates were estimated in the groups of patients with and without

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Received 17 May 1993; accepted 10 June 1993.

acceptable target lesions, and compared between those two populations by a χ^2 test.

In a second step, we considered all lesions reported as targets by the investigator as separate entities, and analysed them site by site. The proportion of acceptable lesions was evaluated separately for lung lesions, soft tissue, liver, lymph nodes and skin lesions. The response rate of acceptable and non-acceptable lesions was evaluated in each of the sub-groups, and correlated with the inadequate characteristic. Again, the χ^2 test was used for comparison of response rates.

RESULTS

Analysis of individual patients

Patients included in the trial were reported to have 0 to 6 lesions conforming to the new criteria. The distribution of acceptable lesions is reported in Table 1. The majority of the cases were reported to have 1 (40.4%) or 2 (25%) acceptable lesions. A total of 20 patients (19.2%) did not have any acceptable lesions, and were therefore considered as non-compliers.

Among those 20 non-compliers, 10 had only lung lesions with a largest diameter < 2 cm (one to four lesions). 6 patients had only soft-tissue lesions not measured by CT scans or ultrasound. 2 patients had only lymph nodes < 2.5 cm and 1 patient a skin lesion < 2.5 cm. 1 patient had no lesion in any of the allowed sites. Therefore, the small size of the lesions was the rejection criteria for 13 non-compliers (65%), while the inappropriate method of measurement disqualified 6 other cases (30%).

Among the 83 evaluable cases with acceptable lesions, 35 (42.2%) responded, 3 (3.6%) with a CR and 32 (38.6%) with a PR. Alternatively, among the 20 patients without acceptable lesions, 11 (55%) responded, 7 (35%) with a CR and 4 (20%) with a PR. The overall response rate is not significantly different between compliers and non-compliers ($P = 0.32$), but the complete response rate is significantly higher in non-compliers ($P < 0.001$). These results are shown in Table 2.

Analysis of individual lesions

A total of 265 target lesions have been reported for the 104 eligible patients. About half of them were lung metastases (132/265) while soft tissue (48), liver (36) and lymph node (28) lesions each accounted for more than 10%.

Only 152 (57%) of the lesions used as targets conformed to the new criteria. This proportion varied between the different sites, ranging from 69% (25/36) in liver metastases to 50% (7/14) in skin lesions, as shown in Table 3.

Among 132 measured lung metastases, 59 (45%) were < 2 cm in their largest diameter; one single dimension was reported in only 1 case. A complete response rate of 40% was observed for the lesions under 2 cm, as compared with 25% in larger lesions ($P = 0.09$). In contrast, an overall response rate of 58% was observed in small lesions, which is not significantly different from the 68% observed in large lesions ($P = 0.66$). These results are shown in Table 4. Because lung metastases represent half of the lesions used to evaluate this phase II trial, the trends in the analysis of the overall response by patient and by individual lung lesion is similar.

Among the 48 soft tissue target lesions, 16 (33%) were not assessed by either CT scan, or ultrasound, while two were only measured in one single diameter. Both complete and overall response rates were significantly lower in the lesions measured by CT scans or ultrasound than in the lesions measured in two dimensions by other methods: for complete responses, 14% vs. 47% ($P = 0.03$) and for overall response, 46% vs 80% ($P = 0.05$). The results are shown in Table 5.

A total of 36 liver metastases were used as targets in this trial: in only 3 cases was liver enlargement clinically measured. Among the 33 lesions measured by CT scan or ultrasound, 8 were < 2.5 cm in their largest diameter. Overall response rate was 29% in both groups, while complete response rate was 14% in small lesions vs. 4% in large lesions. This difference is not

Table 1. Conformity to new requirements

No. acceptable lesions	Cases	Percent
0	20	19.2
1	42	40.4
2	26	25.0
3	10	9.6
4	3	2.9
5	2	1.9
6	1	1.0

Table 2. Overall response

	Acceptable target lesions		
Response	Yes	No	Total
CR	3	7	10
	3.6%	35.0%	9.7%
PR	32	4	36
	38.6%	20.0%	34.9%
NC	34	6	40
	41.0%	30.0%	38.8%
PD	14	3	17
	16.9%	15.0%	16.5%
Total	83	20	103

CR rate: $P < 0.001$/CR + PR rate: $P = 0.32$.
CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Table 3. Analysis of individual lesions

	Conform to new criteria		
Site	Yes	No	Total
Lung	72	60	132
	54.5%	45.5%	
Soft tissue	30	18	48
	62.5%	37.5%	
Liver	25	11	36
	69.4%	30.6%	
Lymph nodes	18	10	28
	64.3%	35.7%	
Skin	7	7	14
	50.0%	50.0%	
Other		7	7
		100.0%	
Total	152	113	265
	57.4%	42.6%	

Table 4. Lung lesions

Response	Conform to new criteria: Yes	No < 2 cm	No 1 dimension only	Total
CR	16	22		38
	25.4%	40.0%		31.9%
PR	27	10	1	38
	42.9%	18.2%	100.0%	31.9%
NC	18	15		33
	28.6%	27.3%		27.7%
PD	2	8		10
	4.2%	11.3%		8.4%
Unevaluable	9	4		13
Total	72	59	1	132

CR rate: $P = 0.09$/CR + PR rate: $P = 0.66$. For explanation of abbreviations see footnote to Table 2.

Table 5. Soft tissue lesions

Response	Conform to new criteria: Yes	No No CT/US	No 1 dimension only	Total
CR	4	7		11
	14.3%	46.6%		24.4%
PR	09	05	1	15
	32.1%	33.3%	50.0%	33.3%
NC	11	3	1	15
	39.3%	20.0%	50.0%	33.3%
PD	4			4
	14.3%			8.9%
Unevaluable	2	1		3
Total	30	16	2	48

CR rate: $P = 0.03$/CR + PR rate: $P = 0.05$. For explanation of abbreviations see footnote to Table 2. No CT/US, no CT scan on ultrasound.

statistically significant, but the power of the comparison is low because of the limited sample size. Results are shown in Table 6.

Table 6. Liver lesions

Response	Conform to new criteria: Yes	No < 2.5 cm	No ld/CT/US	Total
CR	1	1		2
	4.2%	14.3%		5.9%
PR	6	1		7
	25.0%	14.3%		20.6%
NC	13	3	2	17
	54.2%	42.9%	66.7%	50.0%
PD	4	2	1	7
	16.7%	28.6%	33.3%	20.6%
Unevaluable	1	1		2
Total	25	8	3	36

ld/CT/US = 1 dimension only or no CT scan or ultrasound.

DISCUSSION

According to these results, the EORTC Soft Tissue and Bone Sarcoma Group would lose only 20% of its potential recruitment in phase II studies when adopting the new EORTC recommendations for the selection of target lesions. These criteria mainly exclude patients who present with lesions too small to be used as targets. The trial used to assess the consequences of adopting the new recommendations was a study of first line therapy (this choice was motivated mainly by the observed high response rate). However, in soft tissue sarcomas, phase II trials of new therapeutic agents are usually conducted as second or even third line therapy, because doxorubicin-containing regimens are known to be active. Although this is not reflected in survival, many clinicians consider it to be unethical to treat these patients with an investigational agent before trying a proven regimen. Consequently, patients for whom participation in phase II trials of new drugs is considered are usually in a more advanced stage of disease, and their lesions are probably larger than in the population investigated here. Therefore, the potential loss of patient recruitment will be even less than 20%.

More important was the problem of a possible induction of a selection bias: exclusion of the patients with small lesions (i.e. in a less advantaged stage of disease) could have altered the response rate. The present data show that the overall response rate is similar for large and small lesions: this appears not only from the analysis of the patients, but also from the analysis of the individual lesions; in all sites (and particularly in lung metastases), the overall response rate was similar for small and large lesions.

This might seem inconsistent with prior publications showing that tumour size is a significant prognostic factor in this disease. However, prognostic factor analyses generally have been performed in studies on adjuvant treatment, with survival as the endpoint. Adjuvant treatment is given in a completely different stage of disease, as the presently discussed treatment for metastatic disease and prognostic factors derived from adjuvant studies cannot be compared to those derived from metastatic studies. Moreover, there is no evidence that the factors relating to response are the same as those relating to survival. While it has clearly been shown that the diameter of the tumour at presentation did strongly influence survival in an adjuvant study [12, 13], it has never been proven that small lesions respond better to chemotherapy; presence of a large tumour up-front might be either the consequence of a late diagnosis, with the risk of occult dissemination, or of a rapidly growing tumour type, which would rapidly become metastatic, and compromise patient survival. There is, however, no evidence that those tumours would not regress during chemotherapy, before any clinical manifestation of metastases.

Although the overall response rate does not vary with the size of the lesions, complete responses are more often observed in small tumours. This might be attributed to the biology of cell kill and to methodological problems: for a given number of decades of cell kill, the probability for the tumour to reach subclinical size increases with decreasing initial tumour size, and, for lesions with an initially small diameter, there is a large probability of measuring a false positive complete response. When reporting complete responses in advanced disease, it would be useful to know how many lesions were initially present,

and what was their total size. In the present study, all complete responses were assessed on the basis of only one target lesion, the size of which was inferior to the new requirements for eligibility in 7 out of 10 cases.

Apart from a minimum size of the target lesions, the new recommendations require CT scans or ultrasound measurements for deep lesions. In our study, nearly all liver metastases were assessed by one of those techniques: the method of clinical measurement of liver metastases, described in the WHO guidelines, has apparently been replaced spontaneously by imaging techniques for response assessments in the EORTC Soft Tissue and Bone Sarcoma Group. Soft tissue lesions, however, are only assessed by CT scans or ultrasound in two thirds of cases, resulting in complete (14%) and overall (46%) response rates consistent with the overall results of the trial (respectively, 10% and 45%). For lesions not assessed by those techniques, both rates were significantly higher (respectively, 47% and 80%). This suggests that CT scans and ultrasounds are superior to clinical measurements in the evaluation of soft tissue lesions, and, despite their costs, these techniques are crucial in the evaluation of response for phase II trials.

The present results validate, for soft tissue sarcoma, the recommendations of the EORTC for conducting phase II trials: with a minimal loss in the potential recruitment (less than 20%), measurement errors will be minimised, and overall response rate will not be affected by the patient selection. On these grounds, the EORTC Soft Tissue and Bone Sarcoma Group has now adopted these new rules for conducting phase II trials investigating the activity of new drugs in soft tissue sarcoma.

Recommendations issued by the EORTC are meant to be generally applicable, still realising that more specific criteria (i.e. including the primary tumour, or specific markers as targets) may be developed for specific tumour types [16].

Thus, before adopting these recommendations for other tumour types, their impact should be evaluated on the basis of previous trials conducted in each particular disease: the number, size and site of the metastases does vary from one tumour type to another, and the same criteria may become more restrictive for one tumour type than for another [15]. Moreover, the availability of imaging techniques may differ from country to country, and between centres or departments within one centre.

Whichever criteria are used, it is important to include in all phase II protocols, an exhaustive list of the types of target lesions and to specify for each type if there are particular requirements in terms of method of measurement and of minimal size. This must also be reported in the publication of the results, to enable a comparison with other drugs tested on the same tumour type [5].

The decrease of the potential recruitment was the major objection of some investigators against these recommendations. In the experience of the EORTC, recruitment is rarely a problem in phase II trials, and depends more on the interest of the investigators for the tested drug than on the availability of patients. Practically, the new recommendations imply that a new promising investigational drug might not be available to a large proportion of patients, only because their lesions are not objectively measurable or are too small. However, it should not be forgotten that the aim of a phase II trial is to contribute to the decision to further develop a new agent, and not to treat any patient on a compassionate basis with an agent without proven efficacy.

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Acknowledgements—This work was supported in part by the E.C. D.G. XII Programme "Europe Against Cancer".