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European Journal of Cancer 41 (2005) 1426–1430

European Journal of Cancer

www.ejconline.com

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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Received 30 March 2005; accepted 3 April 2005
Available online 24 May 2005

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.

Keywords: RECIST; WHO; Prospective validation; Clinical trials

1. 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 [2–4]. On the basis of previous studies [3,5], 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

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doi:10.1016/j.ejca.2005.04.005

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 [5,6]. 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.

2. 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.

3. 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 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).

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

Table 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 4
Organ/system involved

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

[a] Patients may have more than one site involved.

Table 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.

Table 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)

Table 2
Number of target lesions per patients

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

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.

4. 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 [8–15]. 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 [8,11,13,14], one involves metastatic colorectal cancer [9], and one lung and liver lesions from breast cancer [10], and finally two involve mesothelioma [12,15]. 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 [9,10,13] 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 [9,10], 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.

Conflict of interest statement

None declared.

Acknowledgments

The authors thank all contributors from the EORTC Soft Tissue Sarcoma Group who have contributed to the study and accepted to duplicate their efforts in monitoring their patients to facilitate this study. This publication was supported by the Grant No. 5U10 CA11488-34 from the National Cancer Institute (Bethesda, Maryland, USA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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