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Cancer clinical trial outcomes: Any progress in tumour-size assessment?

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ABSTRACT

Cancer for many patients is still a lethal disease, and we are at the edge of the time that it will be the leading cause of death in the western world. One of the hallmarks of cancer is its ability to spread to other organs, turning cancer in essence to a systemic disease. For this reason, systemic therapy plays an important role in our efforts to either obtain cure or to prolong life and palliate symptoms. The ultimate goal in the development of such new treatments is cure or prolongation of life, but the process to ascertain this may be lengthy. This presents a limitation to the rapid assessment of the potential benefit of new cancer treatments, which is why investigators and regulators have been interested in clinical trial measures that could provide early readouts of drug activity or efficacy, in other words for surrogate indicators for the ultimately desired outcome.

1. Introduction

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2. Why do we assess anatomical tumour-size changes?

Theoretically, in cancer patients with disease-related symptoms, the first and the most rapid readout of treatment effect could be the amelioration of these symptoms. This end-point, however, is subjective, and reliable tools to assess symptom palliation are subject of ongoing investigation and debate.

If the patient is without symptoms, it is clear that symptom relief cannot be used as an end-point. For this reason, and because assessment of symptom improvement, even if applicable, is subjective, investigators have concentrated on determining the impact of treatment by following the change in anatomical measurements of tumour, commonly called 'tumour response'. This term may be a confusing misnomer since classifications of response include both increase and decrease in the size of detectable tumour masses.

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The first attempts to objectively describe the anatomical change in tumour burden as response to an anticancer agent date back to the early 1960s.[1,2] In 1979, World Health Organisation (WHO) first defined criteria to assess tumour response, and reported the results of cancer treatment in a consistent manner.[3,4] These were widely disseminated and adopted internationally. Over the years, various discrepancies and interpretive variations of the WHO criteria became evident.

To address this problem, after a long period of validation analyses of actual data and discussions among key users of response assessment in cooperative groups, pharmaceutical industry and regulatory authorities, RECIST was released in 2000.[5] RECIST is the acronym for Response Evaluation Criteria In Solid Tumours. In principle, using the word criteria after the acronym RECIST is duplication, since the word criteria is included in the acronym. Yet, most commonly one has started to speak about 'RECIST criteria'. In this and subsequent papers of this special issue of EJC, we will be consistently using RECIST.

The 2000 version of RECIST retained the four response categories, as originally defined in the WHO Handbook,[3] acknowledging that there remained an important need to continue describing anatomical change in tumour-size in solid tumours, despite the fact that newer agents might work by mechanisms unlikely to cause tumour regression. In this regard, it has to be stressed that end-point assessment options and design of early clinical trials are obviously interrelated.[6–9]

While assessing the four categories of change in anatomical tumour-size is particularly helpful in the early stages of treatment- or drug-development, particularly in screening phase II clinical trials, for later phase III trials it is the assessment of tumour progression that is of greatest importance, since increasingly time to progression or similar end-points are primary end-points in such trials. Proper methods for assessing tumour progression may thus be even more important than the methodology to define tumour shrinkage.[10]

For the individual patient, treatment benefit may to a large extent be based on the medical judgement that results from a synthesis of clinical, imaging and laboratory data. Therefore, it should be stressed that response criteria are primarily designed for use in clinical trials, and may not necessarily be applicable in clinical practice. In addition, it is important to understand that RECIST is a guideline that is unable to cover each and every protocol specific issue. Investigators will have to ensure that their protocol clearly describes specifics on how RECIST will be applied in their study.

3. RECIST revision 1.1

At the time of the publication of RECIST in 2000, the task force indicated that these criteria would be dynamic, and therefore were likely to be the subject to change over the years. Since the release of RECIST, some suggested shortcomings have been discussed in the literature.[11] RECIST is not commonly used, for instance, in the assessment of lymphoma- and mesothelioma studies[11] and many still prefer bi-dimensional or volumetric measurement of brain tumours.[12] In the current special issue of the European Journal of Cancer, the first formal revision of RECIST is published.[13]

The changes in the new version are not as major as those found between the WHO and the original RECIST, and for this reason this revision is called version 1.1 rather than 2.0. With the original RECIST, it was recognised that the major utility of response criteria was not dependent on the precision of individual measurements as it was on finding consistent and easily applied methods to draw reproducible conclusions at the level of the trial. Historically, the definitions for partial response and progression have been based on arbitrary cut-offs, and this was the same approach applied in the original RECIST guidelines; however, in it calculations were made simpler by using the sum of unidimensional measures of tumour lesions rather than bidimensional products. The revised version RECIST 1.1 remains based on this approach. Before being considered for inclusion in RECIST 1.1, important changes regarding the need for confirmation of response, how to measure and incorporate malignant nodal disease, as well as the number of target lesions selected at baseline for longitudinal assessment have been based on intensive analysis of a dataset of over 6000 clinical trial patients with prospectively documented tumour measurements.[14] In RECIST 1.1, confirmation of response has been kept as a requirement only for studies where response rate is the primary end-point, but not for other studies. This is because when response is not the primary end-point, assessment of progression (which in most cases is the primary end-point in such trials) is not affected by response confirmation. The need to measure large numbers of target lesions has also been addressed: Data analysis revealed that study outcomes were not affected when only 5, as opposed to up to 10, lesions were selected as targets.[14]

Based on the data analysed, the guideline reduces the maximum number of target lesions for the assessment of response from 10 to 5, and discusses in detail those trials in which exceptions to the guideline may be appropriate.

Based on extensive analyses and input from imaging experts,[15] now there is a different description on how to measure lymph nodes on CT-scans.

Obviously, there will always be a subset of patients whose response status is on the borderline between stable disease and partial response (PR) given the somewhat arbitrary (albeit historically validated) nature of the criterion for PR, zone along the arbitrary cut-offs, and an ideal system is likely difficult to achieve. When using the option of independent radiology review in cancer trials,[16] a review that could ascertain unbiased assessment of anatomical changes in tumour burden, it is still important to integrate clinical judgement into the overall response assessment. This means that any observer could always be helped by information on the individual patient's clinical situation.

Finally, towards the future it would be desirable to incorporate the use of modern functional imaging techniques in assessing benefit to treatment. Although there are many exciting developments in this field, none of these techniques was considered as ready to substitute for anatomical end-point assessment in clinical trials yet, since their use (and definitions for outcome categorisation) awaits validation in large datasets, and their availability in trial centres is limited. However, because their potential value remains important, a paper proposing some criteria to validate these new

techniques in the context of tumour assessment has been added to this special issue.[17]

As with the preceding version, the guidelines proposed in RECIST 1.1 are not meant to discourage the development of new tools that may provide more reliable surrogate endpoints than objective tumour assessment for predicting a potential therapeutic benefit in cancer patients.

Conflict of interest statement

None declared.

REFERENCES

1. Zubrod CG, Schneiderman SM, Frei III E, et al. Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and thio phosphoamide. *J Chronic Dis* 1960;**11**:7–33.
2. Gehan E, Schneidermann M. Historical and methodological developments in clinical trials at the National Cancer Institute. *Stat Med* 1990;**9**:871–80.
3. WHO handbook for reporting results of cancer treatment. Geneva (Switzerland): World Health Organization Offset Publication No. 48; 1979.
4. Miller AB, Hogestraeten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;**47**:207–14.
5. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer I* 2000;**92**(3):205–16.
6. Booth CM, Calvert AH, Giaccone G, Lobbezoo MW, Seymour LK, Eisenhauer EA. Endpoints and other considerations in phase I studies of targeted anticancer therapy: recommendations from the task force on Methodology for the Development of Innovative Cancer Therapies (MDICT). *Eur J Cancer* 2008;**44**:19–24.
7. Booth CM, Calvert AH, Giaccone G, Lobbezoo MW, Eisenhauer EA, Seymour LK. Design and conduct of phase II studies of targeted anticancer therapy: recommendations from the task force on methodology for the development of innovative cancer therapies (MDICT). *Eur J Cancer* 2008;**44**:25–9.
8. Ratain MJ, Humphrey RW, Gordon GB, et al. Recommended changes to oncology clinical trial design: revolution or evolution? *Eur J Cancer* 2008;**44**:8–11.
9. Ratain MJ, Sargent DJ. Optimizing the design of phase II oncology trials: The importance of randomization. *Eur J Cancer* 2009;**45**:275–80.
10. Dancey JE, Dodd LE, Ford R, et al. Recommendations for the assessment of progression in randomized cancer treatment trials. *Eur J Cancer* 2009;**45**:281–9.
11. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer* 2006;**42**:1031–9.
12. Galanis E, Buckner JC, Maurer MJ, et al. Validation of neuroradiologic response assessment in gliomas: measurement by RECIST, two-dimensional, computer-assisted tumor area, and computer-assisted tumor volume methods. *Neuro Oncol* 2006;**8**:156–65.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**:228–47.
14. Bogaerts J, Ford R, Sargent D, et al. Individual patient data analysis to assess modifications to the RECIST criteria. *Eur J Cancer* 2009;**45**:248–60.
15. Schwartz LH, Bogaerts J, Ford R, et al. Evaluation of lymph nodes with RECIST 1.1. *Eur J Cancer* 2009;**45**:261–7.
16. Ford R, Schwartz L, Dancey J, et al. Lessons learned from independent central review. *Eur J Cancer* 2009;**45**:268–74.
17. Sargent DJ, Rubinstein L, Schwartz L, et al. Validation of novel imaging methodologies for use as cancer clinical trials endpoints. *Eur J Cancer* 2009;**45**:290–9.