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International criteria for measurement of tumour response

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Efficacy of anti-cancer agents in clinical trials is mainly determined on the basis of objective response rate. The response evaluation criteria introduced by the World Health Organization (WHO) have been reviewed, and a new set of response criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Group. These simplified guidelines are still based on the change of the tumour size under treatment, but introduce the use of unidimensional measurement, and of new methods of assessing tumour lesions.

Introduction

Overall survival and objective response rates are the usual parameters used to assess response to treatment in cancer patients. Overall survival is the gold standard but the delay necessary to obtain this parameter is too long: physicians need to determine rapidly whether the agent demonstrates encouraging results or not, in order to adjust therapy. In contrast to survival, objective response is more difficult to assess because it is highly dependent on the quality of radiological tumour measurements. Because of the cost and toxicity of treatments, a rigorous evaluation of their efficacy is necessary, as well as evaluation of the toxicity. Many factors interfere with response evaluation, such as the quality and reproducibility of the imaging examinations, the choice of targets and the investigator's objectivity. International rules for measurement of therapeutic response were progressively established during the 1970s. The WHO (World Health Organization) criteria[1] published by Miller in 1981[2] have been widely adopted and remain the standard method of reporting tumour response to treatment. Recently, members of the National Cancer Institute (NCI), of the National Cancer Institute Canada (NCI Canada) and of the European Organization for Research and Treatment of Cancer (EORTC) have proposed a new set of tumour response criteria (Response Evaluation Criteria in Solid Tumours : RECIST) designed to replace existing WHO criteria[3].

WHO criteria

Tumour size is determined by measurement of the 'tumour area' by multiplication of the largest diameter of the tumour by the greatest perpendicular diameter and, when multiple lesions are present, by the sum of the products of the perpendicular diameters. Complete response is defined as the disappearance of all known disease, determined by two observations not less than 4 weeks apart. Partial response is defined as a decrease of 50% or more in the size of the lesions and progressive disease as a 25% or more increase in the size of one or more measurable lesions, or the appearance of new lesions.

Reasons for response rate variability

A French group (the Research Group in Clinical Evaluation: GREC) studied the impact of an evaluation committee on patients' overall response status in a large multicentre trial in oncology[4]. It identified reasons for disagreements between investigators and the evaluation committee. Overall tumour responses were reduced by 23% by the review evaluation committee. Reasons for major disagreements included errors in tumour measurements, errors in selection of measurable targets. Pitfalls such as tumour necrosis, intercurrent diseases, and radiologic technical problems were highlighted. The

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group recommended that an independent evaluation committee should review all therapeutic trial results.

RECIST

These new criteria support the simplification of response evaluation through the use of unidimensional measurements and the sum of the longest diameters instead of the conventional method using two measurements and the sum of the products.

It is important to note that the RECIST criteria still rely on size change of lesions to make response assessment. The guidelines introduce the use of computed tomography (CT) and magnetic resonance imaging (MRI). Technical recommendations are provided for the use of CT, concerning the slice thickness, the use of contrast media, image filming, etc. Ultrasound should not be used to measure tumour lesions or as a possible alternative to clinical measurements for superficial palpable lesions. RECIST response criteria are linked to the WHO criteria by the relationship between change in diameter, product and volume. Partial response which was defined as a 50% decrease using WHO criteria (tumour area) becomes 30% with the new criteria (diameter) and the disease progression becomes a 20% increase (tumour diameter) instead of 25% (tumour area). This relationship was chosen partially to allow comparison with response rates obtained using WHO criteria, particularly in historical trials. For the moment, the RECIST guidelines are based on retrospective statistical evaluation of measurements obtained in clinical trials.

Assessment of tumour response

Objective tumour shrinkage is widely used in everyday clinical practice to estimate the benefit of anti-cancer treatments. According to the RECIST criteria, a percentage change in tumour size of about 20% or 30% from baseline is necessary to determine a progression or a partial response while measurements on CT images with electronic calipers provide a precision of more than 1 mm. Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions that are not superficial and palpable. However, high frequency probes allow extremely accurate measurements of cutaneous or sub-cutaneous lesions closer to the histological than the clinical measurements[5]. Cross-sectional imaging permits 3-dimensional measurements (3-D) and 3-D image display and each technique provides information about tumour volume. While state-of-the-art imaging machines can acquire such information these techniques are not yet widely available. Furthermore, standardization and simplification of methodology are desirable and it is not sure that increased precision of measurement of tumour volume is an important goal in clinical trials.

Decreasing tumour size is recognized as the major indicator of tumour response, but other factors may reflect the activity of anti-cancer agents. Metabolic and physiological changes antecede size changes, some tumours show little change in volume and may also enlarge under treatment[6]. Modern imaging technologies, particularly positron emission tomography (PET)[7] allow functional assessment of tumour metabolism. Tumour neovascularity can be precisely assessed using Doppler ultrasound with contrast agent, enhanced dynamic CT and dynamic MRI[8,9]. However, these techniques are not yet validated and cannot be widely used for tumour response assessment in clinical trials.

Conclusion

The end-points of phase II drug trials remain objective tumour response. Oncological radiologists must continue to describe objective changes in tumour size, using simple, standardized international guidelines but have to develop new tools that may provide additional indicators not only reflecting changes in tumour volume, but also demonstrating changes in tumour metabolism.

Key points

(1) Guidelines for tumour response evaluation unidimensional measurements.
(2) Methods of assessing tumour size.

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