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LETTERS TO THE EDITOR

Radiological assessment of tumour response to anti-cancer drugs: Time to reappraise

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To the Editor,

Ever since the earliest observations over 50 years ago of tumour volume reduction following treatment with alkylating drugs, the paradigm in medical anti-cancer treatment has been to find drugs with the property to kill as many cancer cells as possible while sparing a sufficient number of normal cells for the patient to recover. Most models used in anti-cancer drug development comply with this paradigm by using a measurement of tumour cell kill, either *in vitro* in cell lines or in tumour bearing animals, as their key endpoint.

With this background and with the development of cross sectional diagnostic imaging techniques, it has been logical in clinical trials on the effect of anti-cancer drugs, to measure tumour volume changes in advanced solid tumours. Such measurements are now included as an important trial objective in most anti-cancer drug clinical trials, including those in the late efficacy confirmatory phase, and are considered to provide pivotal information on stop-go decisions in drug development and use. The importance of recording response rate is underlined by the fact that this putative surrogate marker for therapeutic efficacy has formed the basis for drug approval in rare cases, such as the recent approval of the tyrosine kinase inhibitor, sunitinib [1]. Furthermore, tumour volume assessments form the basis on which tumour progression is defined and progression-free survival seems to be a relevant endpoint in clinical trials, as demonstrated at least in the case of colorectal cancer [2].

The status of tumour volume assessments has led to efforts to harmonise the principles and performance of these measurements to safeguard comparisons in tumour response over time and between study centres and different trials. In consideration of these efforts, but also to simplify tumour response assessment, the WHO evaluation criteria were proposed to be changed to "Response Evaluation Criteria In Solid Tumours" (RECIST) [3]. Since the publication of this report, tumour assessment according to RECIST has rapidly become the dominating principle for response evaluation and reporting in clinical trials [4].

Discussions on tumour response evaluation have mostly focused on the correspondence between RECIST and the previous WHO criteria, variability in assessment between observers, variability in technical platforms and on the unrealised potential of functional tumour imaging [4–7]. There has also been focus on the difficulties in applying RECIST criteria in specific clinical settings, e.g. in lung cancer, mesothelioma, gastro-intestinal stromal tumour (GIST), prostate cancer, breast cancer with bone metastasis only, lymph nodes and cystic lesions. Based on such discussions a revision of RECIST is ongoing [4,8].

We should like to draw attention to some other aspects of radiological tumour assessments. We agree that correct tumour volume measurement and response reporting, e.g. according to RECIST, should be included in phase 1 and phase 2 trials on new drugs, as this is part of the basic characterisation of

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the pharmacodynamic properties of anti-cancer drugs. However, in efficacy confirmatory phase 3 trials, standard use of response evaluation along the lines of RECIST for all types of drugs is questionable. Rather, clinical experience and/or knowledge from the preclinical and the early clinical phases of drug development should be called upon in order to support a decision on whether or not detailed tumour volume assessment in the confirmatory phase of drug development is justified.

We are frequently involved in industry sponsored multi-centre phase 3 trials on new drugs or new combinations of existing drugs in patients with advanced solid tumours. The protocols almost always include tumour measurements, now mostly according to RECIST. These measurements increase the workload on the study teams, notably on the radiologists involved, but also on study nurses and investigators. According to our experience, radiological tumour response assessment based on current pharmaceutical industry standards may consume up to a third of the total trial budget for the team at the clinic. The costs for the pharmaceutical companies are unknown to us but are probably not negligible.

These tumour measurements would be justified if the efforts and money spent resulted in pivotal information that could be used in the assessment of the new treatment. However, this is seldom the case. It is acknowledged that tumour volume reduction is strongly correlated to survival, at least for cytotoxic drugs in some major solid tumour types, but only very large differences in tumour response rate will transmit into a statistically and clinically significant survival benefit [9–12].

Accordingly, response rate is not considered by medical authorities involved in new anti-cancer drug approval to be a fully justified surrogate endpoint for clinical benefit. For this reason, the European Medicines Agency (EMEA) recommends overall or progression-free survival as the primary endpoint in therapeutic confirmatory trials [13,14]. However, according to its own guidelines on the evaluation of anti-cancer medicinal products in man, the EMEA nevertheless states that tumour response rate should be reported as a secondary endpoint [13].

The EMEA guidelines, together with a record of approval by the US Food and Drug Administration of anti-cancer drugs based on the effects on surrogate endpoints, have probably had a strong impact on the pharmaceutical industry's standard operating procedures for phase 3 clinical trials. Moreover, due to efforts to maintain this seemingly high standard, confirmatory trials initiated by academic groups almost always include costly radiological tumour assessments according to RECIST.

Where health care resources are unlimited, meticulous tumour volume assessments according to current or revised, and probably even more detailed, guidelines would not present any problem. However, in light of the low relevance of the response rate in the judgement of clinical efficacy and with the great number new drugs under development [15] there is a need to focus on the efficacy and costs of the performance of the trials and consider if certain steps may be rationalised [16,17].

Tumour control rate, i.e. the proportion of patients with at least stable disease, may be a more clinically relevant endpoint than response rate [11,12,17]. This would seem to be even more justified in light of the fact that many new drugs may be cytostatic rather than cytotoxic.

Assessments of tumour control, of course, also require radiological evaluation. However, such assessments could be made simpler than response rate assessments defined in RECIST. According to the experience of the Karolinska University Hospital, Solna, Sweden, tumour progression in a majority of cases of metastatic colorectal and breast cancer is due to development of new lesions or the unequivocal progression of non-target lesions, (Suzuki et al., submitted for publication). In these cases detailed tumour measurements would not be necessary. In the remaining cases, tumour measurements would be necessary only at tumour volume nadir and when progressive disease is suspected. Increased use of the proportion of patients who are progression-free at a fixed time-point as an endpoint would also decrease the tumour assessment workload in late phase clinical trials [13].

The ongoing revision of RECIST seems justified to further improve and standardize tumour assessments in early clinical drug development. However, research and development in this area for later phase clinical trials in the advanced setting should focus on the finding of simple and robust yet clinically relevant radiological changes in patient tumour burden during treatment. This could be achieved by investigating, e.g. the relationships between complete response rate, occurrence of new tumour lesion(s) and change in diameter of only one index lesion on the one hand and response and tumour control rate according to RECIST on the other.

These parameters should then be compared with respect to clinical relevance in terms of progression free and overall survival and changes in tumour related symptoms, as recently reported in the radiological evaluation of imatinib-treated GIST [7]. This type of research would be comparatively easy to pursue since a great deal of data from the many phase 3 clinical trials of anti-cancer drugs is available in the archives. Speculatively, the most drug-resistant

tumour cell clone is decisive for the clinical course of the patient and significant progression of only one of several lesions would then be clinically more relevant than a summary measurement.

While it is normal that improved principles and methods are first introduced in research and are only later applied in routine care, the contrary seems to apply to radiological tumour assessments. At least in our institutions a basis for stop-go decisions for the treatment of patients outside clinical trials is tumour control rather than response. Isn't it high-time that phase 3 clinical trials also adopt such standard?

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Unusual intensification of skin reactions by chloroquine use during breast radiotherapy

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To the Editor

A 57 year old postmenopausal female was diagnosed as a case of locally advanced carcinoma right breast (T4bN1M0). After anthracycline based neoadjuvant chemotherapy, she achieved a clinical partial response and underwent breast conservation surgery. Histopathology revealed infiltrating duct carcinoma grade III with a pathological tumor size of $2 \times 2 \times 1.5$ cm. Four of 15 axillary nodes were involved. She

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