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Use of standard criteria for assessment of cancer vaccines

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Excitement in the immunotherapy of cancer has never been greater. Objective clinical responses are now seen in about 50% of patients treated with the adoptive transfer of anti-tumour T cells after non-myeloablative chemotherapy.¹ Objective and often complete regressions of large, established, highly vascularised tumours are also seen in mice treated with a current adoptive immunotherapy regimen, when used in conjunction with appropriate antigen stimulation and cytokines.^{2,3}

Much progress has been made in the immunotherapy of cancer. Although the development of cancer vaccines is a promising area of experimental work, no current cancer vaccine used alone has induced significant objective clinical responses in patients.⁴ There remains some confusion about this point because many reports on the clinical status of cancer vaccines do not use standard criteria for the assessment of clinical responses. Mocellin and colleagues' recent *Review* on vaccines for solid tumours in the November, 2004, issue of *The Lancet Oncology* is an example of a report that fails to use rigorously standard, agreed criteria.⁵ These sorts of errors are most evident in webtable 1 of their review.

It is important that standard oncological criteria are used so that researchers can compare results and so that practicing physicians can make enlightened choices about how best to treat their patients. In oncology, the most commonly used criteria are those set forth by the International Union Against Cancer and WHO, which define an objective clinical response as a reduction of at least 50% in the sum of the product of perpendicular diameters of all tumours, without the growth of any tumour by more than 25% and without the appearance of any new tumours.⁶ Another set of criteria, designated response evaluation criteria in solid tumours (RECIST), is in many ways similar to the WHO criteria and designates that an objective response can be declared if there is at least a 30% reduction in the longest diameters of all target lesions. In the RECIST criteria, no target lesion can grow by 20% or more and no new lesions can appear.⁷

It is obvious that a clear-eyed perspective on cancer vaccines is needed if we are to make real progress. It is important with use of these standard criteria that responses cannot automatically be attributed to the effect of a cancer vaccine when patients are treated simultaneously with other known and effective therapies such as surgery, chemotherapy, interleukin 2, or radiotherapy. Evidence of the effectiveness of a response to a cancer vaccine (or any other experimental treatment) cannot be proved in patients unless the appropriate controls are included.

Investigators sometimes use non-standard criteria that can lead to confusion for their scientific and clinical colleagues. These non-objective claims of response to a treatment create the impression that a negative study is actually positive. Examples of non-objective criteria can be identified when investigators claim tumour necrosis, lymphocyte infiltration, antigen loss, or shrinkage of some lesions. These types of changes are often seen in the natural history of tumours even in the absence of treatment.

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Claims of benefit to patients that include improvement of symptoms and longer-than-expected survival are subjective and generally uncontrolled.⁴ Finally, use of surrogate endpoints such as the generation of anti-tumour T cells in vivo is of interest, but is not a substitute for tumour regression in assessment of the clinical effect of an experimental treatment.

We think that progress will be made to improve cancer vaccines by the definition of ligands for toll-like receptors and of the way in which the innate and adaptive immune systems interact, as well as by the inhibition of negative regulatory signals, such as those provided by CTLA4 and regulatory T cells. These and many other experimental approaches are being tested in preclinical and clinical trials. But perhaps cancer vaccines will be most effective when they are used in combination with adoptive cell-transfer-based immunotherapeutic regimens.

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