Investigating better endpoints for immunotherapy trials

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Cancer immunotherapy calls for revised clinical endpoints that differ from those used for chemotherapy, according to an article published online September 8 in *The Journal of the National Cancer Institute.*

Unlike chemotherapy, which acts directly on tumors, cancer immunotherapies exert their effects on the immune system, which may delay or change response patterns, perhaps owing to the dynamics of the immune system itself. For example, initial tumor burden may increase due to lymphocytic infiltration, because of T-cell proliferation, which is followed by lymphocyte-induced tumor response. These delayed reactions and other novel patterns of anti-tumor response are not part of standard criteria from the World Health Organization (WHO), or the Response Evaluation Criteria in solid Tumors (RECIST).

To study and develop a new paradigm for immunotherapy clinical trials, Axel Hoos, M.D., of the Global Clinical Research division of Bristol-Myers Squibb, looked at design and outcomes of immunotherapy clinical trials, as part of several initiatives undertaken by the Cancer Immunotherapy Consortium of the Cancer Research Institute and partner organizations between 2004 and 2009. The resulting principles for redefining immunotherapy trial endpoints were subsequently tested by Bristol-Myers Squibb (a member of the Consortium) in its immunotherapy clinical trials. In these studies, four response patterns were detected: immediate response, durable stable disease, response after tumor burden increase, and development of new lesions. The latter two are specifically recognized with immunotherapeutic agents. The

results were translated into new response criteria called the immune-related response criteria, or irRC.

Hoos writes, "The irRC are generally based on the WHO and RECIST criteria and do not require a substantial departure from standard oncology practice. The novelty of the irRC lies in the measurement of new lesions, which are included in the overall tumor burden, allowing for it to be described as a continuous variable."

Furthermore, "Considering the time of translation of immunologic responses into clinical activity, the survival of patients may not be affected until some months after treatment started compared with chemotherapy," writes Hoos, adding that the kinetics observed for survival may require new statistical approaches for planning randomized trials.

In an accompanying editorial, Donald A. Berry, M.D., of the University of Texas M.D. Anderson Center, addresses the conundrum of delayed responses often induced by immunotherapies: "Any delayed effect of therapy makes product development harder and more expensive than developing a drug that works by attacking the tumor directly."

Moreover, Berry worries about another potential problem in developing immunotherapies: "To fully investigate the potential of an immunotherapy, clinicians may have to stick with it beyond a patient's progression and thereby delay switching to potentially more effective therapy," he writes.

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