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Commentary

Immune-Related Response Criteria

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DESCRIPTION

The immune-related response criteria (irRC) is a set of published rules that define when tumors in cancer patients improve (respond), stay the same (stabilize), or worsen (progress) during treatment, where the compound being evaluated is an immuno-oncology drug. Immuno-oncology, which is a subset of cancer immunotherapy, includes drugs that use the body's own immune system to combat cancer.

The immune-related response criteria, first published in 2009, were established in response to findings that immuno-oncology drugs would fail in clinical trials using the WHO or RECIST Criteria, since these criteria couldn't account for the time delay in many patients between initial treatment and the immune system's apparent intervention to minimise tumour burden..

The amount of tumour shrinkage that anti-cancer agents can produce is measured as part of the process of evaluating their efficacy in clinical trials. The WHO Criteria, created by the International Union against Cancer and the World Health Organization in the 1970s, were the first widely agreed-upon basic criteria for the codification of tumour response evaluation. These criteria were first published in 1981. The RECIST criteria, first published in 2000, revised the WHO criteria primarily to clarify differences that remained between research groups.

Tumor size was calculated unidimensionally rather than bidimensionally in RECIST, fewer lesions were measured, and the concept of 'progression' was modified so that it no longer relied on a single lesion's isolated increase. For the concepts of tumour response and development, RECIST used a different shrinkage threshold.

The WHO criteria for a Partial Response were >50% tumour shrinkage and >25 percent tumour increase for Progressive Disease. For RECIST, it was a Partial Response shrinkage of >30% and a Progressive Disease increase of >20%. Both of these changes resulted in more patients that would have been classified as "progressors" under the old criteria becoming "responders" or "healthy" under the new criteria.

The discovery that the sought-after Complete and Partial Responses, as well as Stable Disease, in studies of various cancer therapies originating from the immune system, such as cytokines and monoclonal antibodies, only occurred after a rise in tumour burden, which the traditional RECIST Criteria would have called 'Progressive Disease,' was the driving force behind the development of the irRC. RECIST, in essence, refused to account for the time between dosing and an observed anti-tumour T cell response, resulting in the failure of otherwise 'successful' drugs in clinical trials, that is, drugs that eventually prolonged life. This prompted a number of cancer immunotherapy researchers and drug developers, including Axel Hoos of Bristol-Myers Squibb (BMS), to consider whether a new set of response criteria for immuno-oncology drugs should be created. Their proposals, which were first published in the Journal of Immunotherapy in 2007, developed into the immune-related response criteria (irRC), which were published in the journal Clinical Cancer Research in late 2009.

Measurement of tumour burden

Tumor burden is calculated in the irRC by combining 'index' lesions with new lesions. Normally, tumour burden will be calculated using a small number of 'index' lesions (the largest recognisable lesions) at baseline, with new lesions discovered at later timepoints being counted as 'Progressive Disease. New lesions, on the other hand, are simply a shift in tumour burden in the irRC. The irRC kept the bidirectional calculation of lesions that was first established in the WHO Criteria.

Assessment of immune-related response

An immune-related Complete Response (irCR) is defined by the irRC as the removal of all lesions, measured or unmeasured, and the absence of new lesions; an immune-related Partial Response (irPR) is defined by the irRC as a 50% reduction in tumour burden from baseline; and immune-related Progressive Disease (irPD) is defined as a 25% increase in tumour burden from the lowest level reported. The rest is classified as immune-related Stable Disease (irSD). Even if tumour burden is increasing, the immune system is thought to 'kick in' a few months after first dosing, resulting in a decrease in tumour burden for many patients. This apparent delay can be explained thanks to the 25% threshold.

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