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Brief Communications

Cancer Immunotherapy Trials Underutilize Immune Response Monitoring

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Immune-related radiological and biomarker monitoring in cancer immunotherapy trials permits interrogation of efficacy and reasons for therapeutic failure. We report the results from a cross-sectional analysis of response monitoring in 685 T-cell checkpoint-targeted cancer immunotherapy trials in solid malignancies, as registered on the U.S. National Institutes of Health trial registry by October 2016. Immune-related radiological response criteria were registered for only 25% of clinical trials. Only 38% of trials registered an exploratory immunological biomarker, and registration of immunological biomarkers has decreased over the last 15 years. We suggest that increasing the utilization of immune-related response monitoring across cancer immunotherapy trials will improve analysis of outcomes and facilitate translational efforts to extend the benefit of immunotherapy to a greater proportion of patients with cancer. ***The Oncologist*** 2018;23:116–117

T-cell checkpoint-targeted cancer immunotherapies are making an increasing impact on clinical practice, and their investigation in clinical trials has risen exponentially [1]. Effective and efficient response evaluation is essential, but presents challenges due to idiosyncratic radiological responses and lack of early response biomarkers. Concerted efforts to overcome these challenges have included the generation of immune-related response criteria (irRC) [2, 3] to better accommodate immunotherapy-associated response kinetics, and recommendations for immunological monitoring throughout all phases of clinical trial design to help identify predictive/prognostic biomarkers of response and mechanistic insight into patterns of resistance [3, 4].

We assessed quantitatively the inclusion of irRC and immunological biomarker primary response monitoring in the registration details of T-cell checkpoint-targeted cancer immunotherapy trials in solid malignancies registered on the NIH trial registry (clinicaltrials.gov) by October 7, 2016. To overcome potential limitations from incomplete registrations, data were analyzed across three consecutive 5-year periods.

During the completed years, 2001–2015, 91% (622/685) of immunotherapy trials registered use of a radiological endpoint. Analyzing the trend of utilization, we found a significantly increasing ($p = .014$) proportion of these trials specified use of the World Health Organization/Response Evaluation Criteria in Solid Tumors, reaching 56% (307/551) in the last 5 years. Use of the irRC (established in 2009) also increased, but only reached 25% (135/551) of trials. A total of 38% (234/622) of

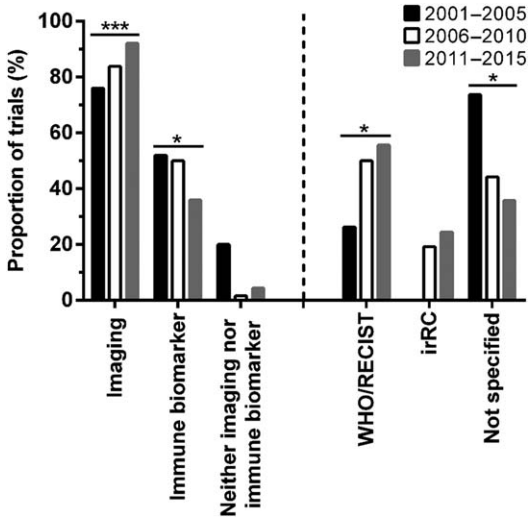

Figure 1. Radiological and immune biomarker monitoring in T-cell checkpoint-targeted cancer immunotherapy trials. All 685 T-cell checkpoint-targeted cancer immunotherapy trials registered on the U.S. NIH trial registry between 2001 and 2015 were categorized according to year of registration and registered imaging and immune biomarker outcome measures (left) and radiological response criteria (right). Six trials used the Response Assessment in Neuro-Oncology criteria (not shown). Immune biomarkers included monitoring of any immune-related parameter, including via immunohistochemistry, immune cell counts, cytokine analysis, and humoral/cellular immune responses. Univariate analysis for data presented was performed using the Cochran-Armitage test for trend. *, $p < .05$; ***, $p < .001$.

Abbreviations: irRC, immune-related response criteria; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

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trials registered use of an imaging endpoint without specifying imaging criteria. Overall, only 38% (259/685) of trials included immunological biomarker monitoring, and this proportion decreased significantly ($p = .011$) over three consecutive 5-year periods (Figure 1).

These findings highlight three areas of concern. Firstly, underutilization of the irRC may be associated with an underestimation of treatment response [2, 5]. This impact may be dependent on tumor type or checkpoint-targeted agent [6]. However, prospective inclusion of radiological criteria that accommodate unconventional response kinetics is essential in order to avoid future misclassification of response and inappropriate cessation of effective therapy. Secondly, the failure to incorporate immunological, and emerging host-centric [7], biomarker monitoring presents a missed opportunity to establish surrogate markers of response and/or resistance [3, 4]. Thirdly, specification and/or metrics of imaging outcome measures were found wanting in 234 trials, an omission that should be addressed, particularly in view of recent regulations [8].

The underutilization of recommended radiographic and immunological monitoring identified by these data, together with suboptimal dose finding identified by others [9], may limit the interpretation of clinical trial results and thereby the development of effective cancer immunotherapies and consensus guidelines for their use. Increasing the incorporation of these measures will help answer the call for greater accountability in the design of clinical trials to optimize the value of data generated [4, 8]. This will improve our knowledge, and application, of immunotherapy for the benefit of patients with cancer.

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