ISSUE BRIEF

Conference on Clinical Cancer Research
November 2013

Facilitating the Development of Immunotherapies: Intermediate Endpoints for Immune Checkpoint Modulators

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Introduction

Engaging the immune system to recognize and kill cancer cells holds the potential for long-term, sustained antitumor activity. This approach may be less vulnerable to the development of resistant tumors, since the adaptive immune system has the potential to evolve as the cancer evolves, and may be less toxic than conventional treatment approaches, although significant toxicity risks remain (e.g., cross-reactivity between antigens in tumors and normal tissues). The transformational clinical potential is being increasingly recognized: recent approvals of novel immunotherapeutic agents and promising results from recent clinical trials have generated tremendous excitement within the oncology community. These agents, however, present unique challenges and may require different developmental approaches than conventional chemotherapies or even targeted therapies (1, 2). Because "immunotherapy" is a broad term used to describe several different therapeutic approaches that have been developed with the intent of enabling an anti-tumor immune response, uniform recommendations for all immunotherapies are challenging. However, this panel will review some key challenges related to immunotherapies as previously defined by the Cancer Immunotherapy Consortium (CIC) (3-5), and discuss potential approaches for the development of immunotherapies that modulate antitumor responses through "immune checkpoints".

"Immunotherapies" include cytokines, therapeutic vaccines, cellular therapies, immune-modulating antibodies, oncolytic viruses, and adjuvants, among others (6, 7). Cytokines are hormone-like molecules that interact with immune cells to modulate a particular type of immune response (i.e., an inflammatory immune response vs. a toleragenic immune response). One example is the cytokine interleukin-2 (IL-2), which was initially approved for treatment of metastatic renal cell carcinoma in 1992 (8). Therapeutic vaccines are intended to induce or amplify a host immune response to a specific tumor antigen. Cellular therapies describe the active transfer of live immune cells, such as tumor-infiltrating lymphocytes or peripheral blood T cells engineered to recognize tumor-specific targets. The only approved cellular

therapy is sipuleucel-T (Provenge), a patient-specific dendritic cell-based vaccine, which was approved in 2010 for treatment of minimally symptomatic metastatic castrate-resistant prostate cancer (9). Innovative adoptive cell transfer approaches have been pioneered that have produced dramatic results in a variety of leukemias and lymphomas, as well as in melanoma or sarcoma. In these approaches, patient T-cells are harvested and then genetically engineered to express chimeric antigen receptors directed against malignant cells before being re-infused into the patient (10-13). Immune-modulating antibodies are similar to other targeted therapies, but aim to enhance natural immune responses or overcome tumor-induced immune-tolerance, and are often targeted against T-cell co-receptors associated with T-cell modulatory signaling pathways, rather than oncogenic tumor growth pathways. Some of these agents bind and inhibit negative regulators of T-cell activity that normally serve as "checkpoints" to maintain self-tolerance, while others stimulate positive T-cell co-receptors (14). Because some tumors co-opt these checkpoints to induce immune tolerance to tumor cells, "checkpoint blockade" enables an anti-tumor immune response. The first immune checkpoint modulator to be tested clinically was ipilimumab (Yervoy), which inhibits cytotoxic T-lymphocyte antigen-4 (CTLA-4) and was approved for treatment of metastatic melanoma by the FDA in 2011 (15-17). Promising clinical trial results have emerged from a similar class of checkpoint inhibitors that inhibit the T-cell co-receptor programmed cell death protein-1 (PD1) or its ligand PD-L1, sparking significant interest within the oncology community (4, 18).

While the enthusiasm surrounding immunotherapies is new, the concept of using the immune system to fight cancer is not. In the past, the field has struggled in part due to insufficient understanding of the immune response to cancer as well as the lack of a methodology for clinical development that recognizes the unique features of immunotherapies (1-3, 19). There are many challenges to the development of immunotherapies, depending on the approach chosen. For example, conventional pharmacokinetic approaches may not adequately guide dosing decisions, since pharmacodynamic effects may be prolonged. Preclinical animal models may not adequately mimic the human immune response to cancer. There is a lack of immune-based biomarkers or other predictive markers that correlate with an effective immune response. Another challenge is that because of the dynamic and multi-factorial nature of the immune system, combinatorial approaches may be necessary in many disease settings: to be successful, an immunotherapeutic approach must facilitate recognition of tumor cells by immune effector cells as well as overcome the immunosuppressive tumor microenvironment. Finally, different types of immunotherapies each present their own challenges. Cellular and gene-therapy based approaches may be challenged by cumbersome manufacturing processes, limited scalability, or high cost of goods. For some other immunotherapies, antitumor responses may be delayed and may occur after initial apparent tumor progression, or survival curves may part with a delay. This may therefore require new criteria to assess response rate and progression-free survival or adjusted statistical methods for assessing survival in order to avoid underestimating or misinterpreting clinical efficacy (5, 20).

This panel will explore potential modified and/or surrogate endpoints for clinical trials that account for the possibility of delayed treatment effect. For some adoptive cell transfer therapies, the expectation remains that any response will occur soon after treatment initiation or not at all, and standard response rates may be the best measure. The potential for therapeutic vaccines to have a delayed effect due to the time necessary to generate a specific anti-tumor immune response is formally recognized by the FDA's Center for Biologics Evaluation and Research (CBER) in the 2011 Guidance for Industry: *Clinical Considerations for Therapeutic Cancer Vaccines* (21). This Guidance describes clinical situations in which it might be appropriate to continue the experimental treatment past initial apparent progression,

given that these are provided for in the trial protocol (e.g., no deterioration of patient performance status, no dose-limiting toxicity, no curative salvage therapy exists), and recognizes the need for alternative statistical models to assess survival. This Guidance applies only to therapeutic cancer vaccines. Therefore, the proposals in this document are specific to immune checkpoint modulators, for which the delayed treatment effect remains a potential challenge, and are intended to promote discussion.

Response Kinetics to Checkpoint Modulators and Intermediate Endpoints

Clinical trials of CTLA-4 inhibitors and PD-1 inhibitors have shown unusual response kinetics to these agents (4, 22). In some patients, tumor progression may be observed before tumor regression. Furthermore, some patients may experience "pseudo"-progression, in which there is enlargement of lesions on CT scans due to the presence of immune cell infiltrates and inflammation at tumor sites (23-25). Early clinical trials of nivolumab (anti-PD-1) have indicated that measurement of progression-free survival may underestimate overall survival benefit (26). Another consequence of delayed treatment effect is that a delayed separation of survival curves may be observed with several types of immunotherapies: in the case of ipilimumab, the treatment ultimately provided an overall survival benefit; the Kaplan-Meier curves, however, were indistinguishable for the first four months of therapy (15). The development of a similar CTLA-4 inhibitor, tremelimumab, was hampered when a planned early interim analysis was reported as having crossed the futility boundaries for the overall survival endpoint based on two-thirds of planned events (27). Later follow-up showed a non-statistically significant separation of the survival curves, suggesting that the development of tremelimumab was prematurely terminated (1). While other hypotheses exist for the disappointing results in this trial, including the dosing regimen and the availability of ipilimumab as a salvage therapy, the potential for a delay in the separation of survival curves to lead to an incorrect determination of futility at an interim analysis should be considered. Delayed separation of survival curves may also result in reduced statistical power to assess the overall survival benefit after trial completion, necessitating alternative statistical approaches that can account for non-proportional hazards (5).

In 2009, immune-related response criteria (irRC) were proposed based on the body of phase 2 clinical trial data from ipilimumab development that was available at the time (28). The original irRC criteria were based on the World Health Organization (WHO) two-dimension measurements, and a variation has been proposed using the RECIST one-dimension measurements, which moves it closer to the current standard response criteria evaluation for other agents (29). The irRC capture 4 different potential patterns of response, the latter two of which are not considered responses by standard RECIST criteria: immediate tumor regression with no new lesions, durable stable disease, tumor regression following an initial increase in tumor volume, and regression of the index lesion(s) in the presence of new lesions. The irRC were designed as an additional tool to capture clinical activity for cancer immunotherapies on tumor burden-based endpoints. Other factors, such as growth kinetics, cannot be adequately assessed with irRC and require other methods. Still, the premises leading to irRC may be a useful measure and prospective validation is ongoing to assess the utility of irRC-based responses.

This panel discussed further endpoint adaptations that take the potential for unusual response patterns and delayed treatment effect into account, and could potentially be used as additional tools to characterize the activity of checkpoint modulators or to accelerate their development. These are described below. Overall survival remains the most reliable endpoint of treatment benefit and the "gold standard" for oncology clinical trials; however, this endpoint can be confounded by post-progression active therapies, which is a

significant liability when several active similar agents are in clinical development (i.e., anti-CTLA4, anti-PD-1/PD-L1). Therefore, intermediate and potential "surrogate" trial endpoints may be useful as the basis for accelerated drug approval. As is true for any potential "surrogate" endpoint, substantial evidence supporting the use of the endpoint and prospective validation in randomized trials is necessary for an intermediate endpoint to be considered reasonably likely to predict clinical benefit. Furthermore, the appropriateness of any intermediate endpoint must be considered in the context of what is known about the disease and patients being treated, as well as the existing body of knowledge about the investigational agent and other drugs in its class. For example, the endpoints below may only be appropriate when early clinical trials have indicated that an investigational agent may induce unusual response patterns.

1. Clinical Benefit Rate

In this context, clinical benefit rate (CBR) is defined as the rate of partial responses + complete responses + durable stable disease in patients who were previously progressing. What constitutes "durable" stable disease will be disease-dependent; for example, in metastatic melanoma, this might be stable disease for greater than six months. Because stable disease can sometimes reflect the natural course of the disease, in some cases measurement of stable disease may overestimate the efficacy of an agent by labeling a patient with a more indolent disease as having benefit. For this endpoint, we propose that clinical trials require evidence of measurable progressive disease before initiation of the study drug. Depending on the disease, it may be necessary to pre-specify a rate of progression that defines "progressive disease" or only use the endpoint in the context of a randomized comparison. Tumor growth rate may be an alternative measure to address the role of slowing tumor growth without inducing a response. The utility of this endpoint could first be assessed by analyzing the existing ipilimumab database to determine if there is a correlation with overall survival.

2. "Gated" Progression-free Survival

In this modified approach to measurement of PFS, progression-free survival would be assessed with "T-zero" at two to three months post-treatment initiation, rather than at the time of treatment initiation. The rationale for this approach would be to minimize the impact of early and/or "pseudo" progressions, thus allowing the time to mount a full immunological response. However, this endpoint has some important limitations. This approach would entail designing a protocol where patients are kept on the investigational treatment past initial radiographic progression for some period of time. This may only be ethical or appropriate for patients with refractory disease and no other standard treatment options and for agents for which delayed responses have been previously described. Patients may be unwilling to consent to such a protocol, especially if there is no expectation that the control arm will induce tumor regression or disease stabilization. As with the proposed clinical benefit rate described above, the first step towards evaluating the utility of this endpoint would be an analysis of the existing ipilimumab database to determine if there is a correlation with overall survival. Further, the relative difference between regular PFS and gated PFS would need to be established to understand the incremental value of this endpoint. Overall, this may be a difficult endpoint to interpret from a regulatory standpoint, limiting its value as a primary endpoint for approval decisions, but could be useful for exploratory purposes to characterize the effects of a given agent.

3. "Milestone" Survival Analysis

In this approach, the proportion of survivors based on the Kaplan-Meier estimate at an interim time point is assessed in a fully powered study, and the probability of survival at the interim point is used as the

basis for accelerated approval, with the confirmatory endpoint being final log-rank analysis of overall survival at a later time point in the same trial when the pre-specified number of events is reached. To support this proposal, a retrospective analysis of a phase 3 ipilimumab trial was performed (CA184-024; ipilimumab + dacarbazine vs. dacarbazine alone). This trial enrolled 502 patients with advanced but previously untreated melanoma and demonstrated an overall survival benefit for the ipilimumab combination arm (9.1 vs 11.2 months; HR = 0.716; p-value = 0.0009) (30). To assess "milestone" survival, Kaplan-Meier probability analysis was conducted for the first 300 patients randomized into the trial once those patients had reached a minimum of 2 years of follow-up. The analysis showed that the estimated 2-year overall survival rates among these 300 patients were 14.1% and 24.9% (p-value = 0.021). The timing of the analysis could have been accelerated by a year if this analysis had been incorporated in the original study design.

In addition to potentially serving as a surrogate endpoint for accelerated approval, this milestone analysis approach has several other advantages: it provides greater statistical power to detect a treatment benefit at an interim analysis, it would enable information regarding survival probabilities and long term survival information to be included in the package insert, it entails a predictable timing of analysis, and KM probability is also an OS endpoint. However, there are also some disadvantages to this approach that warrant discussion: there is a challenge in maintaining the integrity of the study post-milestone analysis, this approach does not account for the totality of OS data, and there is risk in pre-specifying a milestone time point since different treatment approaches and different cancer types may have different tumor growth and survival kinetics. Therefore, this endpoint would only be appropriate for a registration trial when prior data has been obtained that enables an understanding of what milestone time point is suitable.

4. Tumor Growth Rate

For some targeted therapies, tumor growth rate constants have been proposed as a potential measure of therapeutic efficacy (31, 32). Capturing the kinetics of tumor growth would enable the analysis of changes in tumor growth rate which may translate into survival improvements. Tumor growth rates can be calculated from the tumor burden data usually collected for response or PFS assessments. This measure may be of particular relevance for therapies that induce low levels of response but may also help to describe therapeutic effects beyond response for treatments such as immune checkpoint modulators. Tumor growth rate would be considered exploratory, but over time could become validated for use as a surrogate measure.

Conclusions and Next Steps

Here we have discussed potential intermediate clinical endpoints that take the potential for a delayed treatment effect into account and could be used to better characterize the clinical activity profile of some cancer immunotherapies. One of the above proposals is supported by retrospective analysis of phase 3 ipilimumab data and similar analyses could be performed to assess the other proposals. Much of the data demonstrating delayed treatment effects for survival and unusual response patterns come from the development of a single agent, ipilimumab. However, trials with therapeutic vaccines and early clinical results from PD-1/PD-L1 inhibitors are showing similar responses, suggesting that this phenomenon might occur generally with checkpoint inhibitors in 5-10% of the treated patient population. Using endpoints such as those discussed above might reduce the chance of prematurely discontinuing clinical development of an effective therapy and increase the probability of accurately characterizing the activity

profile of new immunotherapies. Use of a validated intermediate endpoint could also reduce the time to market by serving as the basis for accelerated approval.

A major challenge that these proposals do not address is the feasibility of performing randomized, controlled trials of immunotherapies that ultimately assess overall survival in an environment where patients and clinicians are aware of the potential for immunotherapies to induce long-term anti-tumor responses and survival. Some prominent experts have argued that randomized trials of highly effective immunotherapies are unnecessary and potentially unethical, particularly when early clinical trials have shown significant and reproducible evidence of efficacy (33); furthermore, traditional randomized trials with survival endpoints may not be feasible in a landscape where multiple drugs within the same class are being developed simultaneously by several pharmaceutical sponsors, as is the case for PD-1/PD-L1 blocking antibodies. While response rates may be appropriate for evaluation of adoptive cell transfer approaches or immunotherapies with high response rates, and therefore might be amenable to single-arm registration trials, it is unclear what endpoints would be appropriate to support registration of other immunotherapies which induce long-term benefit but lower rates of response in single-arm trials. Validated endpoints that reflect the mechanism of immunotherapies are needed in order to expand the toolbox of clinical endpoint from which the most suitable measure can be chosen for characterizing the effects of a given agent. Adequate and complete characterization of clinical effects for new immunotherapies may ultimately reduce the number of patients needed for clinical trials and accelerate the development of these promising agents.

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