Statistical issues on the design and analysis of cancer immunotherapy trials

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Background

The recent introduction of cancer immunotherapies has heralded an era of significant change in the treatment of cancers. The indirect mechanisms of action of cancer immunotherapies stimulate the patient’s own immune system to fight against cancers by targeting antigens expressed on cancer cells and kick starts the antitumor effects. Monoclonal antibodies (mAbs) represent a significant subset of immunotherapy agents that are currently being used to treat cancers. Examples of such agents include ipilimumab, a fully human IgG1 that blocks cytotoxic T lymphocyte-associated protein 4 (CTLA-4), or nivolumab, a fully human IgG4 that selectively blocks the interaction of the PD-1 receptor with its two known programmed death ligands, PD-L1 and PD-L2 (1). These mAbs have shown striking antitumor activities in patients with melanoma or other cancers. The efficacy and safety profiles differ from those of previously characterized cytotoxic and pathway-specific agents. Some of the unique characteristics displayed by the cancer immunotherapies, e.g., immune checkpoint inhibitors, include the promising long-term survival and delayed clinical effects. In addition, the endpoints and the conventional approach of assessing antitumor activity derived from chemotherapeutic agents may not adequately capture extended clinical benefit from immunotherapies. Consistent with the idea that immunotherapies fight cancers by augmenting the immune response, most adverse events are expected to be inflammatory in nature. The introduction of these new therapies warrants a closer look at the endpoints as well as the conventional assessment approaches in efficacy and safety.

Discussion

The phenomena of long-term survival and delayed clinical effect have been observed in multiple phase III clinical trials (2–7). A simulation study conducted by Chen (8) showed that a three-month delayed clinical effect would lead to an absolute 20 percent statistical power reduction in a hypothetical randomized study designed with a constant hazard ratio of 0.75 and a median control of 12 months, whereas a cured fraction of 10 percent in the control arm with the proportional cure rates would result in additional six to seven months in trial duration.

If the separation in the Kaplan-Meier curves occurred at a later time, the study would lose more power. Note that the hazard ratio post-survival curve separation also impacts the statistical power. If the true treatment effect post separation exceeded expectations, the statistical power...
would improve depending on the magnitude of the observed treatment effect. The proportional cure rates were implemented in the simulation in order to maintain the risk ratio at 0.75 so the impact on the trial duration could be independently assessed without inducing the loss of statistical power simultaneously. Another important aspect of the study design due to the presence of delayed clinical effect concerns the necessity and the timing of interim analyses. The inclusion of superiority interim analyses may lead to unnecessary waste of resource, while the futility interim analyses may increase the false negative rate.

As the proportion of patients who enjoy the durable clinical benefit increases due to the introduction of these new therapies, the consideration of alternative endpoints becomes eminent in late-stage drug development in order to mitigate the challenge of accelerating the research and development process when the strength of this class of agents is derived from the long-term follow-up. In the Brookings Conference on Clinical Cancer Research held in Washington, D.C., in November 2013 (9) as well as Cancer Immunotherapy Consortium Workshop held in New York City in October 2014, several alternative clinical endpoints were proposed to better characterize the clinical activity profile in immune checkpoint inhibitors. Some of the key alternative endpoints, including milestone survival (9), disease control rate (10), immune-related response rate (10), (immune-related) progression-free survival (11, 12), are highlighted below:

- **Milestone Survival**: a cross-sectional assessment of the OS data at the prespecified time point using Kaplan-Meier survival probabilities, such as two-year OS rate
- **Disease control rate**: the composite rate of objective response and stable disease
- **Immune-related response rate**: response rate based on criteria accounting for pseudo-progression, including the presence of new target lesions and the confirmation of progression at subsequent scans
- **(Immune-related) progression-free survival**: time from randomization to progression or immune-related progression

In addition, patient-reported outcome measures, such as quality of life, also become increasingly important for long-term survivors. Another important challenge would be to identify the subset of patients who attain durable clinical benefit from different types of treatments.

Consistent with the idea that cancer immunotherapies fight cancer by augmenting the immune response, most adverse events are expected to be inflammatory in nature. Immune-related adverse events (irAE) and immune-mediated adverse reaction (imAR) are two methods frequently used to identify adverse events of immune origin. The former was defined as adverse events of unknown etiology, consistent with an immune phenomenon, considered by the investigator to be related to treatments; the latter was performed retrospectively by taking into account the information such as the use of concomitant medications, and duration of the adverse events. In addition, the adverse events are grouped under several key system organ classes such as enterocolitis, hepatotoxicity, dermatitis, neuropathy, and endocrinopathy.
Future Directions

The emerging evidence and increasing knowledge with new therapies have led the clinical trial researchers to challenge the status quo for the study designs and analyses in cancer research (8, 13). Cancer immunotherapies have demonstrated some unique characteristics that were not seen in cytotoxic and pathway-specific agents. Due to their mechanisms of action, these newly introduced immuno-oncologic agents may not show early benefit. This results in a delayed separation in Kaplan-Meier curves in the time to event analysis. In addition, a proportion of patients may sustain remission and do not require therapy within a reasonable monitoring time window. Failure to account for these phenomena in the study design could potentially impact the process of drug development and resource planning.

Study designs and analyses need to be tailored to the characteristics exhibited by the therapeutic agents under investigation. For agents such as cancer immunotherapies that show delayed clinical effect, the non-proportional hazards assumption needs to be implemented in the sizing of the study to reduce the risk of false negative conclusions. If a subset of patients is expected to be event free, i.e., long-term survivors, sufficient patients need to be randomized to ensure the total number of events is reachable. On the other hand, the sample size also needs to be small enough to ensure sufficient follow-up duration to capture the long-term survival benefit. A delicate balance between the study assumptions, the sample size and the trial duration becomes essential in the success of clinical cancer research.

In addition to the most commonly used statistical methods for time to event analyses such as log-rank test and Cox regression analysis, statistical methodology such as weighted log-rank test (14) should be considered as an appropriate alternative when non-proportional hazards, such as delayed clinical effect, are expected. The long-term survival phenomenon can be captured by presenting the milestone survival rates at given time points, such as one-year or two-year OS rates, provided the minimum follow-up duration is sufficiently long to allow robust estimation of the milestone survival rates.

Alternative clinical endpoints, including milestone overall survival, immune-related response, (immune-related) progression-free survival, disease control rate, tumor growth rate, quality of life, warrant a closer investigation in the efficacy or clinical benefit assessment of cancer immunotherapies, particularly immune checkpoint inhibitors. In addition, the development of biomarkers is critical to identify the subset of patients who benefit from different types of treatments. The refinement of existing safety analyses is also required in order to capture the adverse events of special interest with immune origin. These safety analytical approaches, such as irAE and imAR, should facilitate prompt and effective management of the adverse events, and allow identification of truly immune-related events.

There is no doubt that much work lies ahead for cancer researchers. As the new information starts to emerge, they should be continuously incorporated into the assessment and optimization of the drug development strategies in this growing field.

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