Understanding Immuno-oncology Trials

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The immune system is a very finely tuned system and is designed to protect the body against attack from pathogens, including viruses, bacteria, and parasites, by targeting and destroying them. Its role also involves targeting and destroying cancer cells, and immuno-oncology therapeutics are designed to augment the immune response, helping the immune system to recognize the malignancy as foreign and therefore to attack it.

Immuno-oncology: A Brief Introduction

The very beginnings of recruiting the immune system in an attempt to treat cancer goes back to William Coley's studies in 1891, when he tried to trigger sarcoma remissions using intratumoral injections of live or inactivated Streptococcus pyogenes and Serratia marcescens, with mixed and sporadic results [1]. Since then, there have been a number of much more successful approaches to immunotherapy of cancer, from the non-specific cytokines, to the newer cancer vaccines and monoclonal antibodies.

The non-specific cytokines, which include interleukins, interferons, and granulocyte-macrophage colony-stimulating factor (GM-CSF), act by stimulating the body's immune cells to attack the foreign cancer cells. As an example, interleukin-2 (IL-2, Aldesleukin) is used in melanoma and renal cancer, but the response rates are only around 15%, and patients can develop a systemic inflammatory reaction. Interferon-α has also been widely used for these cancers, and responses are high and durable in a subset of patients, but these individuals can be hard to identify [1]. The cytokines may also have potential in combination regimens with standard and emerging therapeutics.

The newer immunotherapeutic approaches are targeted and include cancer vaccines, as well as monoclonal antibodies targeted against specific molecules on the cancer cell's surface. Cancer vaccines can be prophylactic (preventive); these protect against viruses that can trigger cancer, such as hepatitis B virus (HBV) and human papillomavirus (HPV) [1]. The therapeutic cancer vaccines in development trigger an immune response against cancer cells specifically, without affecting healthy cells. These include "off-the-shelf" vaccines, as well as autologous cell-based therapeutics created for an individual patient.

Finding The Endpoints: Challenges in Clinical Trial Design

With the traditional cytotoxic chemotherapies, especially those with a narrow therapeutic window, higher doses are generally the most effective. Therefore, the phase I clinical trial sets out to find out what is the maximum tolerated dose (MTD), which will then be used to select the dose for the next stage of clinical trials [2].

The majority of phase I dose-finding studies in cancer therapy use the 3+3 design, in which three patients are treated at a low dose that is expected to be tolerated, and the next three are treated at a higher dose, which increases until the MTD is found [3] (see Figure 1).

Because immunotherapeutics do not necessarily work by directly killing cancer cells, their efficacy is not always directly related to their toxicity, pharmacokinetics, or MTD, which means that the standard approach to trial design is not as effective for immuno-oncology studies. This makes designing early-stage dose-finding and safety studies much more challenging.

Designing the later stage efficacy studies can also be a challenge, as the differences in responses to immunotherapeutics make it difficult to select appropriate endpoints. As an example, in standard chemotherapy trials, response is generally measured by looking for shrinkage of the tumor, measured by area or volume. The RECIST (response evaluation criteria in solid tumors) guidelines were created as objective, uniform, and reliable criteria to define

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responses, stable disease, and progression in solid tumors [4, 5]. Immunotherapeutics may act by stopping cancer growth and metastasis rather than shrinking the primary tumors. Immunotherapeutics may also trigger what is known as the "tumor flare reaction." This inflammatory response can make the cancer appear larger, and therefore look as if the disease is progressing, when it is actually the start of a response [6]. The outcomes can also depend on the stage that patients present; for example, whether they are treatment-naïve or heavily pretreated, or whether the disease is at an early or late stage.

Because these "non-standard" responses do not fit in with the RECIST guidelines, a number of researchers worked to create new criteria that were immune response-specific, resulting in the immune-related Response Criteria (irRC), published in 2009 [7]. These are based on the WHO and RECIST guidelines but take into account the response kinetics seen with immunotherapeutics (see Figure 1).

Biomarkers are increasingly being used as surrogate endpoints in clinical trials and to predict clinical efficacy. If these are to be applied to immuno-oncology clinicals (as with any other clinical trials), it is vital that their use is planned from the beginning and that their detection and measurement is standardized and consistent across all sites.

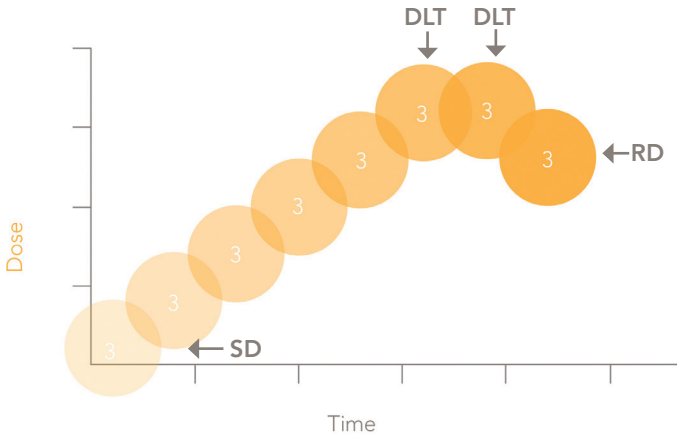
Getting the Timing Right

Scheduling clinical trials can be a challenge in immuno-oncology, as some of the therapeutics are manufactured individually for a specific patient, and therefore the timing of dosing may have to be determined by the time it takes to create the vaccine.

An example of this is Provenge® (sipuleucel-T), developed by Dendreon and approved in April 2010 by the FDA for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. Creating the cell-based immunotherapy involves collecting peripheral blood mononuclear cells (PBMCs) from the patient at 0, 2 and 4 weeks and transporting them to a central facility where they are cultured with a fusion protein of prostatic acid phosphatase (PAP), which is expressed in prostate cancer tissue, and GM-CSF, an activator for immune cells. Then, each patient-specific dose is returned to the clinic where it is infused back into the patient. At each step, the live cells need to be maintained at the correct temperature and protected from contamination. The logistics with trials involving these types of vaccines can be more complex and involve more steps if the study products have to cross international boundaries.

Figure 1: Traditional 3+3 Design

Source: Le Tourneau, Lee, Siu [3]



Source: Le Tourneau, Lee, Siu [3]
DLT=dose-limiting toxicity; SD=starting dose; RD=recommended dose

Another challenge with immune-oncology trials is the length of trial required. Chemotherapeutics tend to induce a quicker response, whereas because immunotherapeutics are dependent on the immune system, the tumors may take longer to respond.

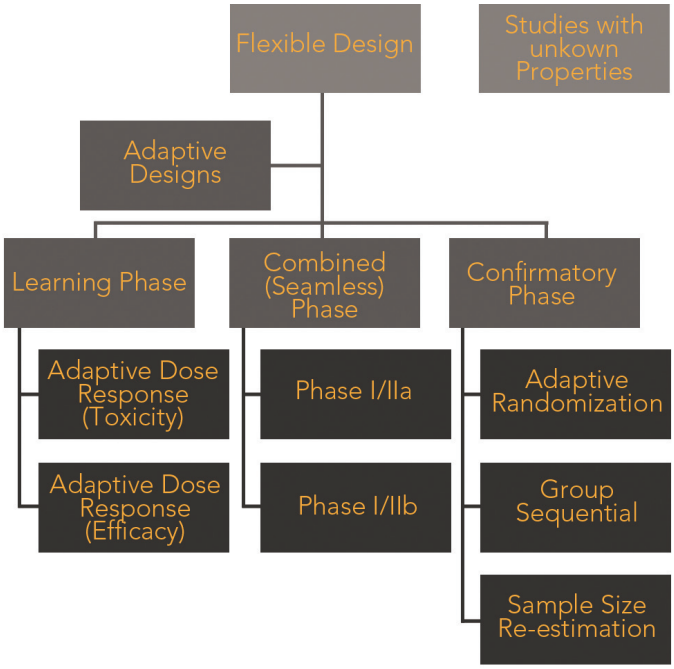
Improving Trial Design

Using an adaptive clinical trial approach [8], in which the treatment assigned and trial characteristics may be modified based on the outcomes from previously-treated patients, can make the clinical trial process more efficient. This is particularly true for studies where information gained from early trial participants can be used to modify one or more criteria for later trial participants, such as in dosing or recruitment criteria (see Figure 2).

The Role of Combination Therapies

Tumor cells have evolved a number of escape mechanisms that allow them to "hide" from the immune system by suppressing the immune response, and the use of immunotherapeutics can select these cells, creating resistant tumors and metastases [9]. The use of combination therapies, including immunotherapeutics that tackle different targets and pathways, should reduce the risk of resistance development. However, before the therapies can be studied in combination, the safety of each component has to be assessed, which makes the overall development of combination treatment approaches longer and more complex. This generally requires the recruitment of more patients with the appropriate cancer types or subtypes.

Figure 2: Summary of different types of adaptive designs for clinical trials



Source: Kairalla et al. [5] [

Feasibility Studies: Looking at the Practicalities

As shown, developing clinical trials for immunotherapeutics for the treatment of cancer is a complex process. Once the study has been designed and the endpoints selected, it is important to look at the feasibility of conducting the clinical trial at a given site. This includes developing an understanding of the regulatory environment for immuno-oncology investigational products and the epidemiologic characteristics of the patient population, and becoming familiar with the standard therapies and practice patterns used in the region.

Later-stage clinical trials are generally conducted in a multinational setting, in order to collect enough data for regulatory approval across regions. Regulatory authorities frequently look for local or regional data to ensure the study population enrolled in the trial is representative of the potential patients who would receive the product, if marketed.

Oncology clinical trials generally compare the candidate drug with standard-of-care. However, different countries may use different standards of care, because of variations in local guidelines, because only certain drugs are available in the target country, or because of physician preferences. In addition, new therapies may be introduced into the market and/or the standard of care may change in a region before the existing trial completes enrollment. All of these factors should be carefully considered in planning trials, their location, the number of sites needed and the estimated enrollment rate.

Despite careful planning, recruitment may encounter challenges, and risk mitigation strategies should be considered early, if needed. Clinical trials of targeted agents and immunotherapeutics require patients who express the right target, or who have the right subtype or stage of cancer, and this can mean that recruitment takes longer, particularly in regions where the cancer is less common overall, unless additional sites are activated. In addition, immuno-oncology studies may involve trial procedures that may be unfamiliar to both patients and physicians, requiring training to be a key consideration. For patients, this will include making sure that they understand what is involved, the potential risks and benefits, so that they can have complete information to provide informed consent. Finally, oncology is the most active therapeutic area of research today, and patients may have multiple options available for trial participation.

Understanding Immuno-oncology Trials

Studies of immunotherapeutics in development for the treatment of cancer may be longer and more complex than small molecule chemotherapeutics, creating treatments that are likely to be more expensive when they reach the market. However, the immunotherapeutic approach creates products that have potential to be safer and more effective, improving patients' outcomes and quality of life, and reducing the impact and sequelae (and the cost of the management) of the adverse drug events associated with traditional chemotherapeutic approaches.

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