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Critical issues in cancer vaccine trial design

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ABSTRACT

As the clinical experience with cancer vaccines and cancer immunotherapy increases, there are important lessons that can be learned from the successes and failures of past trials. Many lessons affect the design and conduct of clinical trials themselves. Appropriate patient selection, clinical trial design, immunologic monitoring, and appropriate endpoints are all essential to the efficiency and success of bringing cancer vaccines from conception to clinical use.

1. Introduction

Cancer vaccines have garnered the attention and interest of researchers for decades. The idea that vaccines could prevent or ameliorate the burden of cancer as they have for infectious diseases and without the toxicity that has long been associated to cancer treatment has proven too appealing to resist. However, tantalizing preclinical and early phase clinical trial results repeatedly led to disappointment in later phase trials. With the FDA approval of the first cancer vaccine, sipuleucel-T, this approach has gained increased interest. However, active immunotherapy for cancer has certainly not reached its full potential. As we move forward, it is important to be mindful of the lessons learned through previous work.

In the past, cancer vaccines have fallen short of the mark for multiple reasons. First, the complexity of the immune system and complex interplay of malignancy was not fully appreciated. Along with this, the depth of immune suppression and evasion that malignancies possess was underestimated. New approaches to avoid or counter the immune suppression and evasion of cancer may make cancer vaccines more effective and broadly applicable. Along with biological factors, clinical trial design and conduct may share some of the blame, both in terms of effectiveness and efficiency of the trials being performed.

Even as the shortcomings of previous trials are becoming more apparent, it is not hard to understand why they occurred. Cancer vaccine trials have largely followed the model of chemotherapeutic drug trials. However, just as chemotherapy and immunotherapy attack cancer through different mechanisms of action, the malignancies respond differently in the face of these treatments. It is conceivable that effective cancer vaccines have been discarded because they were used on wrong patients, given at the wrong dose, assessed with the wrong immunologic assays, or evaluated for the wrong endpoint. Certainly there is more clarity to be had in these areas as we attempt to move forward in understanding the immune system and bringing these therapies to patients in a meaningful way. Understanding the subtleties of cancer vaccine trial design may lead to more effective trials and therapies in the future.

2. Patient selection

Historically, cancer vaccine trials, like initial chemotherapy trials, were tested on patients with incurable tumors and minimal remaining treatment options [1]. Many also focused on aggressive cancer types, where the need for new therapies is often greatest. The use of heavily pre-treated patients with high volume of disease may be at least partially responsible for the generally disappointing results. More recent data suggests that cancer vaccines may be more effective in less aggressive cancer types and patients with a lower disease burden [2]. Care should be taken to select the appropriate cancer type or subtype and the appropriate clinical situation to test novel cancer vaccines. For many cancer types, vaccines may work best when patients have minimal residual disease or, ultimately, for prevention of developing cancer.

In light of this, it is not surprising that Sipuleucel-T (Provenge), the only FDA approved cancer vaccine, has shown a survival benefit in patients with metastatic castrate-resistant prostate cancer (mCRPC), a disease that tends to progress slowly and with an

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extended survival time, although the prognosis is variable. Other supportive evidence of this effect comes from examining cancer vaccination effectiveness between different trials using similar vaccines. Follicular lymphoma patients who had a complete response to chemotherapy and were vaccinated with a hybridoma-derived autologous tumor immunoglobulin conjugated to keyhole limpet hemocyanin had a significant improvement in disease-free survival compared to randomized control patients; whereas, similar vaccination failed to show effect in patients with more advanced disease [3,4]. Similarly, patients with metastatic colorectal cancer rendered disease-free after metastectomy who were vaccinated with PANVAC, a viral vector encoding CEA, MUC-1, and TRI-COM, or were given autologous dendritic cells stimulated with PANVAC had better survival than a contemporary control group. This contrasts with patients with metastatic colon cancer who were vaccinated with PANVAC, where a more modest effect was seen and primarily in patients who were not pretreated and with lower disease volume [5,6].

There is also evidence from within individual trials that patients with less aggressive disease appear to respond better to vaccination. PROSTVAC-VF, a vaccine formulation consisting of recombinant vaccinia expressing prostate specific antigen (PSA) and TRICOM prime followed boosters with recombinant fowlpox also expressing PSA and TRICOM, has been used in trials to treat men with mCRPC. In a phase II trial, men treated with PROSTVAC-VF had a median survival that was 9.2 months longer than predicted by the Halabi model, a well-validated nomogram to predict survival in mCRPC. Interestingly, for patients with a Halabi model predicted survival of <18 months, there was no difference between actual and predicted survival, while those with a predicted survival $\geq$18 months had an actual survival of >37.3 months (median not reached at the time of the report) compared to a predicted survival of 20.9 months ($p = 0.035$) [7]. Additional analysis of this trial has also shown that patients with smaller tumor burden derived a greater benefit from vaccination [8]. Another example comes from the use of the HER2/*neu* peptide vaccine, E75, in breast cancer. In a phase II trial, E75 with GM-CSF immunoadjuvant was given to women with node positive or high-risk node negative breast cancer after surgery and standard adjuvant therapy to prevent recurrences. In the final analysis, the vaccinated patients had a trend toward increased five-year disease free survival (89.7% vs 80.2%, $p = 0.08$) [9]. Patients with HER2/*neu* low expression (IHC 1+, 2+; 89.4% vs 74.9%, $p = 0.06$) and low or intermediate grade histology (95.2% vs 78.8%, $p = 0.01$) derived the greatest benefit [2].

The reasons that less aggressive disease types appear to respond better to vaccination are likely multiple. High disease burden may lead to greater tolerance to cancer antigens as well as a better established and more immune suppressive tumor microenvironment. Furthermore, more aggressive cancer types and subtypes may progress substantially before the full benefit of vaccination, which can take several months, is achieved. Finally, rapidly dividing cancer cells may, through selection under immunologic pressure, may develop resistance to immunotherapy through down-regulation of tumor antigens, necessary costimulatory molecules, MHC-complexes or through expression of co-inhibitory signals [10–13].

3. Cancer vaccine development paradigm

In 2007 the Cancer Vaccine Clinical Trial Working Group published a clinical development paradigm for cancer vaccines that was the work of a collaborative effort between academic researches, pharmaceutical industry and US Food and Drug Administration (FDA) representatives [14]. The resulting work suggested that the traditional three phase clinical trial design was, in many cases, unnecessary in cancer vaccine development and instead suggested a two trial design. A subsequent guidance publication by the FDA further endorsed the use of a two step trial design for cancer vaccine development [15]. The change in trial organization comes from the recognition that cancer vaccines are typically less toxic and do not need the same dose escalation model or pharmokinetic monitoring necessary for safe monitoring of chemotherapeutic drugs. The appropriate endpoint for early phase trial should instead be based on immunologic response and observed clinical benefit. If this is achieved in early phase trials, the cancer vaccine can then transition into a late phase trials with a goal of proving efficacy.

4. Adaptive clinical trials

Adaptive trials allow for modification of the trial methods during the conduct of the trial without affecting the validity of the trial or its findings [16]. Often, unanticipated modifications need to be made during the conduct of the trial based on new information that becomes available, unanticipated circumstances, or the progress of the trial itself in order complete the trial successfully. As long as these modifications are performed in a blinded fashion and made in coordination with review boards and regulators, they should not be viewed in a negative light. From a trial design standpoint, criteria triggering modifications and modifications themselves can identified prior to the start of the trial and written into the protocol [17]. Planned modifications can include eligibility criteria, eliminating treatment arms, randomization procedures, study size, and primary or secondary endpoints. Adaptive trial designs can often answer trial hypotheses more quickly and with fewer patients than more traditional designs. As in more conventional drug development, cancer vaccines are well suited for adaptive designs. Design modifications are can be triggered by initial immunologic or clinical responses to the vaccination [17]. However, the response triggering the design modification, whether immunologic or clinical, need to be observed within a reasonable time period and be expected to correlate with the ultimate trial endpoint in order to make modifying the trial worthwhile.

5. Early phase trial design

The primary goal of early phase trials is to determine the safety and appropriate dosage and schedule for administering a new drug. Historically, phase I trials in cancer have been performed with chemotherapeutic drugs with the assumption that higher doses lead to greater tumor-specific cytotoxicity. Therefore, phase I trials were designed to determine the maximum tolerated dose (MTD). The traditional 3 + 3 dose escalation phase I trial is designed around the assumption that dose limiting toxicity (DLT) of less than 33% is acceptable. In as such, an initial cohort of three patients received a dose below the expected MDT based on preclinical and animal data. Increasing doses were given to subsequent cohorts of three patients until DLT was observed. If DLT was observed in one of the three patients, three additional patients were added to this dosing cohort. If DLT was seen in any two patients at this cohort, the previous (lower) dose was selected at the MTD. If not, a new, higher dosing cohort is enrolled until the MDT is determined. The traditional 3 + 3 trial design is safe and easy to implement; however, it requires relatively large number of patients to determine the MTD, many of whom will receive a suboptimal dose. Alternative designs have been proposed and used, albeit infrequently, in traditional pharmaceutical development [18].

As clinical experience with cancer vaccines grows, it is increasingly clear that traditional dose escalation trials, with relatively large numbers of patients required and slow dose escalation, are not always necessary. Cancer vaccines, for the most part, has been marked by extremely well tolerated treatments with low toxicity.

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