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Approaches to improve development methods for therapeutic cancer vaccines

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ABSTRACT

Therapeutic cancer vaccines are an immunotherapy that amplify or induce an active immune response against tumors. Notably, limitations in the methodology for existing anti-cancer drugs may subsist while applying them to cancer vaccine therapy. A retrospective analysis was performed using information obtained from ClinicalTrials.gov, PubMed, and published articles. Our research evaluated the optimal methodologies for therapeutic cancer vaccines based on (1) patient populations, (2) immune monitoring, (3) tumor response evaluation, and (4) supplementary therapies. Failure to optimize these methodologies at an early phase may impact development at later stages; thus, we have proposed some points to be considered during the early phase. Moreover, we compared our proposal with the guidance for industry issued by the US Food and Drug Administration in October 2011 entitled "Clinical Considerations for Therapeutic Cancer Vaccines". Consequently, while our research was aligned with the guidance, we hope it provides further insights in order to predict the risks and benefits and facilitate decisions for a new technology. We identified the following points for consideration: (1) include in the selection criteria the immunological stage with a prognostic value, which is as important as the tumor stage; (2) select immunological assays such as phenotype analysis of lymphocytes, based on their features and standardize assay methods; (3) utilize optimal response criteria for immunotherapy in therapeutic cancer vaccine trials; and (4) consider supplementary therapies, including immune checkpoint inhibitors, for future therapeutic cancer vaccines.

1. Introduction

Therapeutic cancer vaccines amplify or induce an active immune response specific to tumors; immunotherapy can help (1) evade drug resistance caused by signal-transduction pathways in tumor cells, (2) escape unexpected side effects for high specificity, and (3) continue therapeutic efficacy by immune memory [1]. Thus, the potential benefits of therapeutic cancer vaccines stem from their new mechanisms of action. However, the traditional way of developing or evaluating anti-cancer therapeutics is not always applicable for therapeutic cancer vaccines, as their kinetics include cellular immune response and eventually feature changes in tumor burden and survival [2,3].

Regulatory science aims to facilitate innovation by evaluating, predicting, and decision-making for new technologies based on a scientific rationale. The scientific rationale behind therapeutic cancer vaccines is extremely interesting, because their effect is induced by complex interactions in the human body. However, few therapeutic cancer vaccines have been approved by a regulatory agency, despite the many vaccines that have been developed for cancer treatment through Phase II studies. Some researchers suggested that reasons for Phase III failure might include disease burden, which rapidly enhances tumor progression prior to an immune response, and heterogeneity of the disease burden, responses to which occurred differently to therapeutic cancer vaccines [44,45]. To provide further insight into therapeutic cancer vaccine development, we reviewed the study design and developmental trends of therapeutic cancer vaccines in Phase III studies.

Selection of the assays for immune monitoring is also important. Immune monitoring is conducted from the early phase of clinical development. Therefore, we surveyed not only Phase III studies but also Phase I and II studies to clarify the trends in evaluation methods of clinical studies for therapeutic cancer vaccines. Immunological

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factors are often measured for correlation analysis with clinical outcomes to validate their use as predictive factors in investigating the correlation with clinical outcome. Therefore, we surveyed clinical studies to analyze the correlation between clinical outcome and immune response in therapeutic cancer vaccine studies to identify frequently used methods and show the scientific rationale for therapeutic cancer vaccines and their issues.

For cytotoxic agents, tumor measurement is conducted based on the World Health Organization (WHO) criteria or response evaluation criteria in solid tumors (RECIST). However, prolonged survival has been observed in some patients already diagnosed with progressive disease (PD) based on WHO or RECIST criteria. Therefore, immune-related response criteria (irRC) were defined to capture response patterns observed with immune therapy [14]. Wolchok et al. suggested that irRC can identify at least an additional 10% of patients with favorable survival prognosis among those characterized with PD based on WHO criteria [14].

In our retrospective analysis, we evaluated the optimal methodologies for therapeutic cancer vaccines based on the following: (1) patient populations, (2) immune monitoring, (3) tumor response evaluation, and (4) supplementary therapies. Currently, the guidance for industry issued by the US Food and Drug Administration (FDA) in October 2011 entitled "Clinical Considerations for Therapeutic Cancer Vaccines" (hereafter, FDA guidance) is the only guidance specific to the therapeutic cancer vaccines [4]. Therefore, we used this guidance as a benchmark for identifying opportunities for improvement. Discussion is essential for predicting the risks and benefits and making decisions regarding a new technology, and for improving existing evaluation methods; we hope this analysis will serve to initiate such discussion.

2. Patients and methods

2.1. Patient populations and supplementary therapies

A retrospective analysis was performed using information obtained from ClinicalTrials.gov, PubMed, and published articles [21] and [22]. All clinical trials registered on ClinicalTrials.gov as of June 25, 2012, were searched using the following terms: condition, "cancer"; treatment, "vaccine therapy"; and study type, "interventional studies". In addition, clinical trials related to "herpes zoster", "HIV", human papilloma virus "(HPV) vaccine" and "influenza vaccine" were excluded. Completed Phase III trials were selected from the search results and therapeutic cancer vaccine products were verified by manual review. Other Phase III trials were also identified by literature searches via PubMed and company homepages. We selected Phase III trials that had been completed in order to evaluate the results of the studies. Study design details, which include tumor stage, pre-treatment and combination treatment, ITT population for each arm and the results of the completed Phase III trials, are shown in Table 1. The Phase III trials that selected patients based on tumor or immunological stage are summarized in Table 2.

2.2. Immune monitoring and tumor response evaluation

All clinical trials registered on ClinicalTrials.gov as of December 21, 2013, were searched using the following terms: condition, "cancer"; treatment, "vaccine"; and outcome measures, "overall survival", "time to progression", "progression free survival", "disease free survival", "recurrence free survival", immune-related response criteria (irRC) "irRC", "response rate", "tumor infiltrating", "skin infiltrating", "DTH", and "immune response" [5]. Moreover, clinical trials were collated by each evaluation term. Clinical trials identified according to "response rate" were further sorted to exclude "response rate" related to "irRC" and "immune response" to extract only information regarding tumor response based on WHO or RECIST criteria. Furthermore, clinical trials related to "herpes zoster", "HIV", "HPV vaccine" and "influenza vaccine" were excluded. The search results are shown in Table 3. Clinical trials that performed correlation analysis between immune response and clinical outcome were identified through PubMed and the other published articles. Immune monitoring methods and results were collected from each article. Clinical studies that evaluated the correlation with immune response in the use of multiple immune assays are summarized in Table 4.

3. Results

3.1. Patient population

A total of 24 completed Phase III clinical trials with therapeutic cancer vaccines were reported; however, one trial did not evaluate efficacy, as it was a confirmatory trial for immunopharmacological analysis, and was excluded from this study. Therefore, we used 23 Phase III clinical trials to survey patient selection criteria. As shown in Table 1, 14 of the 23 trials (61%) selected patients based on the tumor stage at the time of trial recruitment, as determined by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM classification or relevant criteria. Conversely, none of the trials selected patients based on immunological criteria at the time of trial recruitment to classify the patients' immune condition, which may be representative of the tumor microenvironment. As shown in Table 2, although patients were selected by tumor stage, 12 of the 14 trials failed to demonstrate efficacy in Phase III studies; only two trials that selected patients based on the tumor stage successfully demonstrated efficacy in Phase III studies, and none of the trials selected a patient population based on immunological stage.

Prior to the therapeutic application of cancer vaccines, 14 of the 23 trials conducted pre-treatment, which included surgery (seven trials), anti-cancer drugs (five trials), and chemoradiation (two trials) to ensure a decreased tumor burden; however, only two Phase III trials for BiovaxID® and OncoVAX® successfully met the primary endpoint.

In March 2014, a Phase III (MAGRIT) study with a fusion protein formed by melanoma-associated antigen A3 (MAGE-A3) failed to meet its first or second co-primary endpoints. Co-primary endpoints were disease-free survival (DFS) in the total MAGE-A3 positive population (first co-primary endpoint) or in those MAGE-A3 positive patients who did not receive chemotherapy (second co-primary endpoint). The MAGRIT study included stage IB, II and IIIA patients with non-small cell lung cancer whose tumors expressed MAGE-A3. In September 2013 [46], the other Phase III (DERMA) study with the same MAGE-A3 immunotherapeutic use in patients with melanoma did not meet the first co-primary endpoint of DFS in the MAGE-A3-positive population. The second co-primary endpoint is DFS in the gene signature population, the outcome of which is expected in 2015 [47]. Because the DERMA trial is ongoing, it was not included in Table 1 or 2.

As shown in Table 1, the control arm type was available for 18 studies. A comparator, placebo, or active comparator was used for 14 studies. Four studies did not use a comparator. One Oncophage® study allowed physician choice in the control arm, while three studies used an observation arm as the control arm.

3.2. Immune monitoring

A total of 553 trials were identified, which evaluated immune response by peripheral blood tests, skin-test infiltrating lymphocyte (SKIL) and tumor infiltrating lymphocyte (TIL) measurement,