Gene-Modified Cellular Vaccines: Technologic Aspects and Clinical Problems

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ABSTRACT

Activity in the cancer vaccine sector has quadrupled in the last decade. A number of therapeutic cancer vaccines are reaching the market. The huge number of clinical trials in progress is expected to undergo evaluation shortly. Whole cell tumor vaccines or gene-modified whole cells are being intensively tested in clinical trials. However, the specificity of the product makes the drug development process, including clinical trials, a considerable challenge. Their complex nature, standardization of manufacturing, and characterization often pose problems. Accordingly, to develop a well characterized controlled vaccine, more than a few factors need to be established. The final cell vaccine formulation must be characterized for product identity, purity, impurities, sterility, potency, cell viability, and total cell number. Therapeutic cancer vaccines show different clinical characteristics than cytotoxic anticancer agents. Unfortunately, the rules of clinical trial design for active immunotherapy have been adapted from the designs for examination of cancer chemotherapy. Accordingly, many research groups and clinical consortia have postulated modifications and unifications of existing clinical trial designs. A clinical development model has suggested that cancer vaccines be investigated in 2 categories of clinical trials: proof-of- principle and efficacy. Moreover, it is becoming clear that no drug demonstrates anticancer activity in all patients. Thus, intensive studies have been performed to seek specific biomarkers which could help stratify patients who are likely to respond to a particular treatment. This presents a big challenge beyond the analysis of the immune system status necessary to assess the effects of active immunotherapy.

Somatic cell–based pharmaceuticals have been used to prepare active immunotherapeutic products, such as vaccines for infectious diseases. For >2 decades, so-called cellular therapeutic cancer vaccines have been tested in humans. Due to the progress in gene engineering, a next-generation of cellular vaccines have been developed as gene-modified products. However, owing to the complexity of human anticancer immune responses and poorly understood mechanisms governing tumor growth and cancer immunologic escape processes, progress has been inconsistent in this field. The major problems relate to the manufacture of medicinal products fulfilling regulatory requirements and to the conduct of properly designed and executed clinical trials. Errors in these processes which may occur during drug development may result in failure to obtain approval of the drug to authorize marketing. Herein we have discussed technologic and clinical problems based on our 20 years of experience in the development of gene-modified cellular vaccines for melanoma.

CELL-BASED VACCINES

A number of cellular cancer vaccines have been evaluated in clinical trials (Table 1). Cell-based vaccines include cancer cell lysates; whole cell vaccines with adjuvants; gene-modified tumor cells; dendritic cells (DC) pulsed with antigens in the form of RNA, peptides, proteins or cell lysates; DC modified with genes encoding immune stimulators; or cancer cells fused with DC or B lymphocytes.[1]

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