Commentary (Berd)—Melanoma Vaccines: What We Know So Far
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There have been an astounding number of published reviews on human cancer vaccines, and I take responsibility for my share. Apparently the interest of the medical community in cancer vaccines remains intense, despite the modest progress that has been made in our field and the paucity of convincing, positive clinical results. Somehow the idea of treating a cancer by inducing an antitumor immune response or strengthening the existing one is strongly appealing both to physicians and to patients. Whether this enthusiasm is justified by the science is a question that should trouble the sleep of all of us who call ourselves tumor immunologists.

In this review, Bystryn and Reynolds make an honest attempt to define the critical issues and to summarize the results of published clinical trials. Like most previous writers of cancer vaccine reviews, they do not hide their interest in promoting their own technology—partially purified supernatants of cultured melanoma cells[1], an approach that is reasonable, albeit unproven. Consequently, I do not hold this review to the demanding standard of ideologic balance, but it does seem fair to criticize its lack of internal consistency.

Autologous Vaccines

The authors make a convincing argument that single-epitope cancer vaccines (eg, single peptides) are unlikely to induce effective antitumor immune responses in most patients. They clearly describe the Sisyphean task of identifying epitopes, testing their ability to immunize patients, and then returning to the laboratory to identify new epitopes after the clinical trials fail. However, they summarily dismiss the obvious alternative to this approach—immunizing patients with autologous tumor cells or extracts of autologous tumor cells that include all of the antigenic material made by the cells.

The authors' arguments against autologous vaccines seem contrived. For example, they are concerned that "tumor antigens constitute only a small fraction of the material in the [autologous] vaccine." This dilution of relevant antigens has not been an impediment to the success of crude vaccines against infectious diseases such as polio, pertussis, and yellow fever, so why should it be a problem for cancer vaccines? Moreover, Bystryn and Reynolds worry that "nonantigenic material may decrease effectiveness due to the presence of suppressive or immunoinhibitory factors or to ... competitive immune responses. . . ."

It is difficult to reconcile this hypothesis with the myriad of papers, going back 50 years,[2] showing that mice can be effectively immunized against tumor challenge by vaccinating with syngeneic tumor cells. In fact, one could argue from the literature that syngeneic cells or extracted material make the best vaccines, even in the molecular age.

Hapten-Modified Vaccine

There are practical difficulties with the preparation of autologous human cancer vaccines, but Bystryn and Reynolds exaggerate them. Contrary to their assertion, it is not true that "autologous vaccines can only be used in patients with advanced disease. . . ." We have performed clinical trials of an autologous, hapten-modified vaccine in patients with melanoma, ovarian carcinoma, and renal
cell carcinoma who were clinically tumorfree at the time of immunization.[3] There is no technical reason why the same approach cannot be extended to other human cancers. As to the authors’ concern about the cost of autologous vaccines, they must be aware of the aggressive pricing of purified biologic products that have received marketing approval over the past few years. Autologous cancer vaccines may prove to be cheap in comparison.

Bystryn and Reynolds were kind enough to cite one of our publications describing the autologous, haptenmodified vaccine approach. For readers of ONCOLOGY who wish to know more about the technology, I impose upon your patience and provide this brief summary: The vaccine consists of irradiated, autologous tumor cells modified with the hapten dinitrophenyl (DNP); the rationale is that hapten-modified antigens can induce a cell-mediated immune response in situations in which the native antigen fails to immunize.[3]

Phase I/II clinical trials of this preparation have been conducted in 447 patients, 407 with melanoma and 40 with ovarian and renal cell carcinoma. The DNP-vaccine induces inflammation in metastatic sites that is mediated by novel clones of T lymphocytes.[4] Clinical results include regression of metastases in a small proportion of patients with stage IV melanoma and an apparent increase in 5-year survival in patients with clinically evident stage III melanoma.[5] Virtually all patients have developed delayed hypersensitivity responses to autologous, DNP-modified tumor cells, and about half have also responded to autologous, unmodified cells. The development of delayed hypersensitivity to unmodified tumor cells has proven to be a highly significant determinant of clinical outcome. Finally, a biotechnology company (AVAX Technologies) is committed to commercial development of this vaccine.

When read in the proper light, the review by Bystryn and Reynolds supports our technology, and a "thank you"—perhaps unanticipated—is in order.

**Financial Disclosure:** The author, previously a full-time faculty member at Thomas Jefferson University, is currently working for AVAX Technologies and has a financial interest in this company.

**References:**


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