Melanoma Vaccines
Mixed Past, Promising Future

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KEYWORDS

• Melanoma • Vaccine • Immunomodulator • Adjuvant • Immunotherapy

KEY POINTS

- Numerous vaccine antigen sources have been evaluated, and each has advantages and disadvantages.
- Most phase 3 vaccine trials have not shown clinical benefit, although there have been a few successes and suggestions of activity.
- Novel vaccine strategies using the tumor in vivo as an antigen source bypass the need to define tumor antigens; allow simple, yet personalized therapy; and are perhaps the most interesting current method of vaccination.
- Numerous immunomodulators are now available or in development that could enhance vaccination.
- Adequate immune monitoring with clinically meaningful surrogate end points are critical for additional vaccine development.

INTRODUCTION

Vaccination is the earliest form of immunotherapy, corresponding to the discovery of the immune system itself, and infectious disease vaccinations are perhaps the greatest advance in the history of medicine. Vaccination for cancer has been more difficult, although it had auspicious and early beginnings. The first attempt predates our knowledge of the specific mechanisms involved in vaccination. In the late nineteenth century, William B. Coley, a surgeon in New York at the time, was deeply saddened by the death of a 17-year-old patient with metastatic Ewing sarcoma, spurring him to

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begin to look for novel therapies to treat cancer.[1,2] He was struck by the case of a patient who had tumor regression after developing erysipelas.[3] He wondered if this phenomenon was caused by the infection and then took it on himself to begin inoculating patients with streptococcal organisms in 1891. He reported tumor regression in numerous patients. Coley continued to refine his therapy by using a heat-killed *Streptococcus* and *Serratia* combination, which became known as Coley toxin.[1] This administration of an immune adjuvant to the site of a superficial tumor is perhaps the first example of cancer vaccination, albeit using the existing tumor as antigen source. This strategy has interesting echoes in melanoma immunotherapy, as is discussed later.

More than a century later, Coley's vision of therapeutic immunology is a reality, with the approval of several immune agents in melanoma, and additional promising therapies moving through the development pipeline. However, vaccines continue to present difficulties, showing consistent benefit. Although several negative vaccine trials have led many to discount the possibility of effective cancer vaccination, there are hopeful signs that continued research efforts are not only justified but important components of the overall effort to develop effective therapies for melanoma and other cancers. After several decades of failed attempts at developing potent therapeutic vaccines, the first proof-of-concept cancer vaccine Sipeucel-T was approved for use in patients who have prostate cancer by the US Food and Drug Administration in 2010,[4,5] and as discussed later, a trial of peptide vaccination in melanoma[6] showed a significant survival advantage in the vaccine group.

Increased knowledge of the immune system and its interaction with tumors, along with a widening array of clinically available immunomodulators, make the prospect of effective vaccines increasingly likely. Over several decades, breakthroughs in basic science and an increased knowledge about the role of antibodies in infection have made many surmise that vaccination and the establishment of antitumor antibodies may be a possible strategy to cure cancer.[7] Many cancers have been studied extensively with respect to vaccine treatment but, perhaps, no cancer as extensively as melanoma.

Vaccine strategies are highly varied and may be characterized by the antigen source and the adjuvants or immune modulators given with the antigen. Much of the early period of vaccine development was characterized by substantial debate regarding the ideal antigen. Options vary from the simplest peptide vaccines to the most complex autologous whole-tumor cells. Each approach has advantages and disadvantages (**Fig. 1**, **Table 1**). Generally, simple peptide vaccines are easier to prepare, store, administer, and monitor, but they offer the narrowest spectrum of tumor targets and are potentially relevant to fewer patients. More complex vaccines are the most likely to offer antigens that are relevant to any given patient, but are more difficult to produce and administer. They also present substantial difficulties in monitoring immune responses, because those responses may be varied among different individuals. It is becoming increasingly apparent that the nature of the antigen is only a part of the story, perhaps a small part. What may be more significant is the context of the immune stimulation in terms of both patient characteristics and immunologic adjuvants or other immunomodulators. Modification of these factors could prove more important than the specific source of antigen for a vaccine.

Autologous Melanoma Vaccines

In autologous vaccines, the patient's own tumor is used as the antigen source. There are several significant advantages to autologous vaccines. First, because the source of antigen is the patient's own tumor, there is, by definition, an HLA-type match,