EDITORIAL

Special Focus: Viral-immunotherapies and vaccines in melanoma

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Current clinical trials for melanoma vaccines: where do we stand?

“Despite such a huge incremental growth in our understanding, it was also a trying time to convince the research community of the proof-of-principle that tumor immunotherapy could be a viable treatment for patients with metastatic melanoma.”

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Many of us can reflect upon our past educational clinical and research experiences, acknowledging the incredible number of advances that have been made in our understanding and treatment of melanoma. Indeed, the last few decades have resulted in a period of learning, clinical experience and research knowledge gained in tumor biology, molecular and cellular immunology, genomics, immunology and immunotherapy of cancer, especially for melanoma. At the National Cancer Institute, in Bethesda, Maryland, the surgical oncology fellowship consisted of active participation in cutting-edge clinical trials that were often unique and at the leading edge of advancements that arose only months earlier from the research laboratory. The large group of clinicians and research scientists was comprised all of the different research labs within the surgery branch, still led by the Chief of Surgery, Dr. Steven Rosenberg, some four decades later. We would examine in great detail the data obtained fresh from a set of experiments, such as the identification of a newly identified set of peptides and melanoma

associated tumor antigens, uniquely identified by CD4⁺ and CD8⁺ T cells. Such new findings were often quickly translated into the first-in-human clinical trials in melanoma patients, usually in combination with high-dose IL-2. These were considered, by many, as the basis and foundation for many of the ‘vaccine’ trials to subsequently be tested in patients with metastatic melanoma.

It also provided for the basis of our current understanding of the host immune system and its complex interactions with the tumor microenvironment. Despite such a huge incremental growth in our understanding, it was also a trying time to convince the research community of the proof-of-principle that tumor immunotherapy could be a viable treatment option for patients with metastatic melanoma. Such unconventional ideas were viewed by many with an eye of nihilistic skepticism, suspicion and, sometimes, even outright anger. It was simply not generally accepted at this time that the human body had the capacity to not only mount a robust immune response to its own growing cancer, but the

Melanoma Management

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ability to destroy it completely. The proper activation of the immune system against a patient's own melanoma had the capacity to convert a stage 4 melanoma patient with limited long-term survival, into a long-term cancer survivor.

It is beyond the scope of this editorial to succinctly summarize the history and development of melanoma vaccines. However, I would refer the readers to an excellent review on this topic by Dr. Jim Yang, senior member of the Surgery Branch, Tumor Immunology Section, NIH/NCI [1]. In 2002, Rosenberg *et al.* published their results of 440 patients who participated in a cancer vaccine trial at the NCI, Surgery Branch between 1995 and 2004 [2]. They reported a resoundingly low objective response rate of 2.6%, comparable to the results of cancer vaccine trials published by others. This greatly dampened any remaining excitement or enthusiasm for cancer immunotherapy up to that point in time. Skeptics continued to pan the dismal results as evidence of such futility with immunotherapy, while few others viewed these disappointing results as an opportunity to take up the challenge in order to learn more about the interactions of the host immune system in response to cancer [3].

Indeed, we have come a long way since this time, with novel immunotherapies being approved for patients with advanced melanoma at an astounding rate. Researchers worldwide have further examined the clinical efficacy of melanoma vaccines utilizing a variety of agents, either alone or in combination, often with some type of immunoadjuvant [4–11]. Although each study is somewhat unique in their approach to melanoma vaccine development and administration, there is a clear commonality among each of them at trying to elicit a specific T-cell response that will selectively eliminate viable and growing tumor completely. However, we still have much work to do in our continued efforts to identify effective treatment options centered upon stimulating and activating the immune system to destroy melanoma wherever it may grow.

We recently published our results utilizing a novel combinatorial immunotherapy vaccine approach for high-risk, resected and metastatic melanoma patients [12]. This Phase II trial of 25 patients examined the combination of pegylated interferon with a melanoma vaccine comprised three allogeneic human melanoma cell lines genetically altered to express the α -(1,3) galactosyltransferase (α -GT) epitopes. These

epitopes are not present in human tissues, resulting in the immune system reacting with a potent antibody-mediated immune response against the α -GT epitopes, now expressed by the melanoma cells. Although small in total number, we found that such an approach clearly activated the host immune system in a select few, with an astounding response in a patient with metastatic melanoma becoming a complete responder to treatment after 8 years. I saw this happy patient back in my office just a few months ago, still without evidence of disease and seemingly the only lasting sequelae from this vaccine being some patchy areas of vitiligo on her skin and at her injection sites.

On 27 October 2015, the US FDA approved talimogene laherparepvec (IMLYGIC®, T-VEC, Amgen, CA), for the treatment of melanoma lesions in the skin and lymph nodes that are not deemed surgically resectable [13]. This is the first-of-its-kind therapy utilizing a herpes simplex virus type-1-derived oncolytic immunotherapy designed to selectively replicate within tumors and produce GM-CSF to enhance systemic antitumor immune responses. Andtbacka *et al.* showed in their Phase III clinical trial an overall response rate of 26.4% with T-VEC versus 5.7% with GM-CSF alone, with a median survival of 23.3 months versus 18.9 months [14]. Of note, there was a complete response rate of 10.8%, which is quite impressive for an intralesional therapy, when compared with other single agent immunotherapies. Ongoing trials are now looking at T-VEC in the neoadjuvant setting for resectable stage IIIB, IIIC and IV (M1a) melanomas and in combination with ipilimumab for unresectable melanoma.

In conclusion, questions remain as to the overall effectiveness and optimal utilization of cancer vaccines for patients with advanced melanoma. We need to continue our commitment to further our efforts at identifying unique combinations of agents that can be utilized as effective melanoma vaccines. This may require combining targeted therapies, such as PD-1 inhibitors, with vaccines that may result in some degree of synergism via the activation of different cellular pathways of the host immune system. Currently, there are many promising studies examining the future immunotherapies with a focus upon targeted therapies and melanoma vaccines. We have entered a truly exciting era in our ability to successfully treat patients with melanoma. We must remain steadfast in the pursuit of both

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clinical and research efforts that are aimed at improving the lives of patients with melanoma and other cancers.

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