Is vaccine research still relevant for metastatic melanoma?

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There are several assumptions that might lead one to question whether research into therapeutic vaccines for recurrent stage III and stage IV metastatic melanoma (MM) is still relevant. These suppositions include: all melanoma vaccines have been proven to be ineffective; sufficiently effective melanoma vaccines already exist; or therapeutic melanoma vaccines are unnecessary because newer therapies are so effective. None of these assumptions is correct. In fact, one can make the case that melanoma vaccine research was never more relevant.

Erroneous assumption 1: all melanoma vaccines have proven to be ineffective

It is true that most melanoma vaccines that have been tested in randomized trials have failed to demonstrate a survival advantage for various antigen sources [1]. These antigens have included gangliosides detected by monoclonal antibodies [2], proteins recognized by cytotoxic T lymphocytes (CTLs) [3] and cells or lysates from allogeneic tumor cell lines [1,4]. In one trial, compared with the control arm, gp100 peptide was associated with a higher objective response rate (ORR), longer progression-free survival (PFS) and a trend towards

longer overall survival (OS), but this study was limited to patients who also received high-dose IL-2 [5]. Particularly concerning is that two trials were stopped early because of inferior survival in a vaccine arm [2,5].

On the other hand, complete durable responses have been observed in some patients after immunosuppressive therapy followed by the infusion of billions of antigen-specific CTLs [6]. After it was shown that CTLs recognized specific melanoma tumor associated antigens (TAAs), investigators began using single and combinations of well-characterized TAAs as immunogens. These studies established that antigen-specific immune responses could be induced or enhanced in cancer patients whose melanomas express such antigens, but clinical benefit was uncommon. This is not surprising because the endogenous immune system mobilizes numerous B- and T-cell clones to effect humoral and cellular immunity against hundreds to thousands of antigens. However, there are numerous combinations and permutations of antigens and inflammatory adjuvants or other costimulatory agents; thus, the number of theoretically active vaccine products is by no means exhausted [1]. It is also noteworthy

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that none of the vaccines has been associated with significant toxicity [1].

Immunizing with cells from allogeneic melanoma cell lines has the advantage of presenting multiple antigens that are commonly expressed on melanoma cells from numerous patients. Furthermore, as a cell line, these cells may express antigens associated with tumor-initiating cells, which may not be expressed on more differentiated tumor cells that make up most of a depot of MM. The major drawback to allogeneic cell lines is that they contain many irrelevant allogeneic antigens that may interfere with the response to TAAs. One explanation for the inferior outcomes associated with single-antigen and allogeneic products is that such immunization may detract from ongoing host-mediated anti-tumor immune effects, similar to the immune distraction that occurs with a viral or bacterial infection, which may lead to the recurrence of latent herpes virus infection.

The most important components of any vaccine are its TAAs. Because of cancer heterogeneity, many feel that autologous tumor cells are the best source of antigens for any given patient. Fresh whole tumors are a potential source of relevant TAAs, but they also contain numerous normal cells in a milieu that is often immunosuppressive, and limited quantities of tumor cells in fresh specimens can make it difficult to obtain adequate quantities of TAAs and to standardize therapeutic products [7]. The identification of tumor stem cells and the recognition of their role in causing metastases and the recurrence of cancer suggests that self-renewing autologous tumor cell lines may be a better source of TAAs [8,9]. This allows for immunization with TAAs derived from a known quantity of tumor cells that not only have the characteristics of being self-renewing, tumor-initiating cells, but also contain the relevant TAAs for that individual patient's cancer, including unique neoantigens. That such unique antigens exist and are potential immune targets has recently been shown using CTLs directed against such TAAs resulting from nonsynonymous mutations [10]. Melanomas are known to have some of the highest numbers of nonsynonymous mutations among cancers [11].

Few investigators have tried to test autologous tumor cell lines as patient-specific antigen sources because of the need to establish a cell line for each patient, the time needed to establish such a cell line and the cost and expertise needed to produce a separate product for each patient.

However, the long-term survival results associated with this approach are quite encouraging in melanoma [12,13]. Recent improvements in manufacturing have made it possible to proceed with a randomized Phase III trial designed for the regulatory approval of such a product.

Erroneous assumption 2: effective melanoma vaccines already exist

To date, no melanoma vaccine has been approved by the US FDA. However, it is anticipated that the genetically engineered product talimogene laherparepvec (OncoVEX™; Amgen, Inc., CA, USA), which contains herpes simplex virus expressing GM-CSF, will receive regulatory approval for intralesional injections based on a 2:1, randomized, nonblinded trial of approximately 435 patients with unresectable stage IIIB, IIIC and IV MM who had received at least one prior therapy [14]. This trial has been criticized because intralesional injections of talimogene laherparepvec were compared with subcutaneous injections of GM-CSF rather than to intralesional injections of GM-CSF, which would have been a more relevant control treatment and would have enabled a double-blind design. End points related to ORR and PFS were met, but median OS was less than 2 years and not clearly different between the two arms. In 2013, it was announced that a related vaccine product for intralesional injection (HLA-B7 β 2-microglobulin; velimogene aliplasmid; Allovectin™; Vical, Inc., CA, USA) had failed to reach its objectives compared with chemotherapy in a randomized Phase III trial.

Erroneous assumption 3: therapeutic melanoma vaccines are unnecessary because newer targeted therapies are so effective

Recently, there have been exciting additions to our therapeutic armamentarium. This list includes agents such as vemurafinib, dabrafenib and trametinib, which target aberrant kinases that affect signal transduction [15]. The list also includes monoclonal antibodies that interfere with T-lymphocyte checkpoint molecules, including ipilimumab that blocks CTLA-4 [3], nivolumab and pembrolizumab that block T-lymphocyte PD-1 [16,17] and MPDL3280A and BMS-936559 that block PD-L1 [18].

The kinase inhibitors are associated with high response rates, but only for the 45–50% of patients whose tumors harbor the relevant

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mutations. Unfortunately, they are also associated with some unique toxicities, and resistance tends to develop within a matter of months. Therapies that target signal transduction in tumor cells do not totally eliminate the cancer. They stop the proliferation and enhance apoptosis so that a tumor shrinks, but they do not effectively eliminate the tumor stem cells; therefore, continuous therapy is required. Toxicity is inevitable over time, and the cost of continuous treatment can be substantial. However, the responses and intervals of disease control provide an opportunity for consolidating the response by inducing and/or enhancing an endogenous immune response that might persist indefinitely.

The checkpoint inhibitors have response rates (15–40%) that are lower than those reported for the signal transduction inhibitors, but they appear to be associated with longer survival. They work by unleashing existing immune effects that have been repressed, including some potential autoimmune activity that can be deleterious because of inflammation in normal tissues. These products are associated with less acute toxicity than IL-2 and appear to be associated with 5-year survival rates that will be greater than the 15% 5-year survival rates associated with IL-2 [5]. The 5-year survival rates for ipilimumab are approximately 20%, and it appears that survival will be even longer for the PD-1 and PD-L1 inhibitors [19] or combinations of these with ipilimumab [20]. The increased survival associated with these treatments confirms that immunotherapy is effective for treating melanoma and that long-term OS is a more important end point than ORR or PFS.

It appears that a limiting factor for IL-2 and the anticheckpoint antibodies is whether the immune system already recognizes the full repertoire of an individual patient's TAAs. IL-2 stimulates existing immune responses

to TAAs while the anticheckpoint antibodies release repressed immune responses to TAAs. An effective antimelanoma vaccine that induces or enhances an endogenous immune response against all possible TAAs could increase the number of melanoma antigens recognized by the host immune system, which could make these checkpoint inhibitors even more efficacious.

Conclusion

There are several reasons why research into melanoma vaccines is still relevant. First, melanoma is steadily increasing in incidence and prevalence, and as a cause of cancer death. Second, we now have several new agents that are overcoming mechanisms of self-tolerance and immune suppression, thus allowing existing immune effector responses to TAAs to take effect. However, these responses may be limited by the repertoire of TAAs that is recognized. Third, vaccines are typically less toxic than other systemic therapy approaches. Fourth, because there are so many different combinations and permutations of antigens and antigen delivery systems, as well as adjuvants, it is premature to conclude that vaccines cannot work. The best source of TAAs may be self-renewing, autologous tumor cells with the characteristics of tumor-initiating cells.

Financial & competing interests disclosure

RO Dillman is now an employee of NeoStem Oncology and has stock equity in that company. In the past year, he has served as a consultant to Genentech and Prometheus. His immediate family owns stock in Bristol-Myers Squibb and GlaxoSmithKline. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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References

- Dillman RO. Melanoma vaccines: trials and tribulations. *Vaccine Dev. Ther.* 3, 57–78 (2013).
- Kirkwood JM, Ibrahim JG, Sosman JA *et al.* High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB–III melanoma: results of intergroup trial E1694/S9512/C509801. *J. Clin. Oncol.* 19(9), 2370–2380 (2001).
- Hodi FS, O'Day SJ, McDermott DF *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* 363(8), 711–723 (2010).
- Morton DL, Mozzillo N, Thompson JF *et al.* An international, randomized, Phase III trial of bacillus Calmette–Guerin (BCG) plus allogeneic melanoma vaccine (MCV) or placebo after complete resection of melanoma metastatic to regional or distant sites. Presented at: *43rd Annual Meeting of the American Society of Clinical Oncology*. Chicago, IL, USA, 1–5 June 2007.
- Schwartzentruber DJ, Lawson DH, Richards JM *et al.* Gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. *N. Engl. J. Med.* 364(22), 2119–2127 (2011).
- Rosenberg SA, Yang JC, Sherry RM *et al.* Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clin. Cancer Res.* 17(13), 4550–4557 (2011).
- Berd D. A tale of two pities: autologous melanoma vaccines on the brink. *Hum. Vaccin. Immunother.* 8(8), 1146–1151 (2012).

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- 8 Dillman RO, Nayak SK, Beutel L. Establishing *in vitro* cultures of autologous tumor cells for use in active specific immunotherapy. *J. Immunother. Emphasis Tumor Immunol.* 14(1), 65–69 (1993).
- 9 Dillman RO, Cornforth AN, Nistor G. Cancer stem cell antigen-based vaccines: the preferred strategy for active specific immunotherapy of metastatic melanoma? *Expert Opin. Biol. Ther.* 13(5), 643–656 (2013).
- 10 Robbins PF, Lu Y-C, El-Gamil M *et al.* Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. *Nat. Med.* 19(6), 747–752 (2013).
- 11 Lawrence MS, Stojanov P, Polak P *et al.* Mutational heterogeneity in cancer and the search for new cancer genes. *Nature* 499(7457), 214–218 (2013).
- 12 Dillman RO, Selvan SR, Schiltz PM *et al.* Phase II trial of dendritic cells loaded with antigens from self-renewing, proliferating autologous tumor cells as patient-specific anti-tumor vaccines in patients with metastatic melanoma: final report. *Cancer Biother. Radiopharm.* 24(3), 311–319 (2009).
- 13 Dillman RO, Cornforth AN, DePriest C *et al.* Tumor stem cell antigens as consolidative active specific immunotherapy: a randomized Phase II trial of dendritic cells versus tumor cells in patients with metastatic melanoma. *J. Immunother.* 35(8), 641–649 (2012).
- 14 Andtbacka RHI, Collichio FA, Amatruda T *et al.* OPTiM: a randomized Phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte–macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma. Presented at: *49th Annual Meeting of the American Society of Clinical Oncology*. Chicago, IL, USA, 31 May–4 June 2013.
- 15 Flaherty KT, Infante JR, Daud A *et al.* Combined BRAF and MEK inhibition in melanoma with *BRAF* V600 mutations. *N. Engl. J. Med.* 367(18), 1694–1703 (2012).
- 16 Topalian SL, Hodi FS, Brahmer JR *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* 366(26), 2443–2454 (2012).
- 17 Hamid O, Robert C, Daud A *et al.* Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N. Engl. J. Med.* 369(2), 134–144 (2013).
- 18 Brahmer JR, Tykodi SS, Chow LQ *et al.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N. Engl. J. Med.* 366(26), 2455–2465 (2012).
- 19 Topalian SL, Sznol M, McDermott DF *et al.* Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J. Clin. Oncol.* 32(10), 1020–1030 (2014).
- 20 Wolchok JD, Kluger H, Callahan MK *et al.* Nivolumab plus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 369(2), 122–133 (2013).