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Review

Therapeutic vaccines in solid tumours: Can they be harmful?

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ABSTRACT

Rosenberg and coworkers caused an uproar in the immunotherapy community when they stated in a position paper that despite great advances in the field of tumour immunology, optimism about the clinical application of therapeutic vaccines lacked justification. They argued that such optimism was based more on surrogate end-points, which lacked robustness, than on proof of anti-tumour effects [Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. Nat Med 2004; 10:909–15]. They pointed out that cancer vaccine trials in 440 patients, conducted at the NCI Surgery Branch, had an overall objective response rate of only 2.6%. This was comparable to the 4.0% response rate reported in 40 studies that involved 756 patients. They concluded that surrogate end-points with such low response rates lack robustness. The situation may be even more problematic. Results of a number of larger trials in the past few years have indicated that vaccination therapy can also have a detrimental effect and be associated with worse outcome. These findings need to be looked at seriously and should lead to a critical appraisal of how well we understand these outcomes, how vaccine trials should be designed, monitored and conducted and which opportunities should be considered to be implemented in vaccine trial designs to improve the rationale and chances for a positive outcome.

1. The problem

Rosenberg and coworkers caused an uproar in the immunotherapy community when they stated in a position paper that despite great advances in the field of tumour immunology, optimism about the clinical application of therapeutic vaccines lacked justification. They argued that such optimism was based more on surrogate end-points, which lacked robustness, than on proof of anti-tumour effects.[1] They pointed out that cancer vaccine trials in 440 patients, conducted at the NCI Surgery Branch, had an overall objective response rate of only 2.6%. This was comparable to the 4.0% response rate reported in 40 studies that involved 756 patients. Surrogate end-points with such low response rates lack robustness they concluded.

The situation may be even more problematic. Results of a number of larger trials in the past few years have indicated that vaccination therapy can also have a detrimental effect and be associated with worse outcome. These findings need to be looked at seriously and should lead to a critical appraisal of how well we understand these outcomes, how vaccine trials should be designed, monitored and conducted and which opportunities should be considered to be implemented in vaccine trial designs to improve the rationale and chances for a positive outcome.

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2. Experience in melanoma patients

The development of therapeutic vaccines for solid tumours remains the 'holy grail' pursued by many researchers. It would combine a non-toxic approach with longlasting anti-tumour effects, based on the immunity of the host. Moreover the anti-tumour effects could theoretically be re-activated by renewed vaccinations. In spite of significant progress made in the understanding of basic immunologic mechanisms involved in various animal models over the last decades, there has been a notable lack of successful translation into the clinical setting.

Many, if not most vaccine trials, have been conducted in melanoma patients. Melanoma has for a long time been considered the best candidate solid tumour because of its immunogenic characteristics such as spontaneous remissions, the prognostic importance of lymphocytic infiltration in primary melanomas and the expression of a wide variety of antigens. Moreover it is one of the few tumours that respond to a variety of cytokine-based therapies and immunemodulatory antibodies.[2] In addition to strong induction of a T-helper cell and cytotoxic T-cell response, preventing the induction of immune tolerance and overcoming immunosuppressive conditions at the tumour site are key requirements for success. Therefore cytokines, antibodies, adoptive transfer of effector cells, immunologic preconditioning of the patient and various vaccine approaches are all of interest in the development of immuno-therapeutic regimens.

3. Lack of efficacy of vaccines in advanced melanoma

No effective therapy for advanced metastatic melanoma is currently available. In spite of a response rate of only about 10% and no formal proof that prolongs survival, DTIC is still the comparator drug to beat in most pivotal phase III trials.[3]

Often in medicine big expectations are based on initial observations in small number of patients. Also in the vaccine development field early reports of efficacy have often been based on observations in small series, only to be followed by negative large trials. Two striking examples that received great publicity were the report by Nestle et al. on the efficacy of peptide-pulsed dendritic cells (DCs) in combination with IL-2 in 16 patients.[4] A response rate of 30% was claimed, and this phase II experience was followed by a phase III randomised trial comparing this vaccination approach to DTIC. This trial was stopped early, at the 2nd interim analysis, because of futility, with the survival curve of the DC-arm clearly below the DTIC arm.[5]

Similarly, in the same issue of Nature Medicine, Rosenberg and colleagues reported a 41% response rate observed in a phase II study in 31 melanoma patients after treatment with high dose IL-2 in combination with the immunogenic peptide gp100:209-217(210M).[6] Ten years later, Smith and colleagues reported that in 305 patients in whom peptide vaccines were combined with high dose IL-2, the results were almost identical to those obtained in 379 patients treated with IL-2 alone.[7] Only combination of IL-2 with the immunogenic peptide gp100:209-217(210M) was associated with an increased response rate in their experience. Sosman et al. however, did not observe such an increase for this peptide in three phase II trials consisting of 131 patients, and could only confirm the activity of high dose IL-2.[8] In a recent systematic review Lens concluded that no vaccines with proven clinical efficacy are available.[9]

4. Detrimental outcome in adjuvant vaccine trials in melanoma

Immunosuppression in advanced metastatic melanoma patients is often identified by the investigators and authors as the reason for failure of vaccines in this stage of the disease. Development of vaccines, so it is argued, should be done in the adjuvant setting in high risk patients with an intact immune status, who have only micrometastatic disease.[10] At least at the systemic level these patients usually do not have an immunecompromised status. Of note here is that nobody knows the immune status at the site of micrometastases. The literature on the immune status of sentinel nodes containing micrometastases indicates that severe local immunosuppressive mechanisms may already be in play at this stage.[11,12]

Thus a number of large adjuvant vaccine trials have been conducted. However, it is precisely in this setting that in large adjuvant trials in resected stage II–III–IV patients results with adjuvant vaccines have failed, or even worse, have given an indication of being potentially detrimental. An allogeneic cancer vaccine (Canvaxin™) developed from three cell lines has been used in clinical trials. In large-randomised trials involving 1166 patients with stage III melanoma and 496 patients with resected stage IV melanoma patients were randomised to Canvaxin™ plus BCG or placebo plus BCG after surgery. Matched pair analyses on patients who had received this vaccine after melanoma metastasis resection suggested efficacy and important survival benefit.[13] The randomised trials would tell a very different story however. Morton reported at the ASCO annual meeting on these trials that were closed prematurely on the advice of the Independent Data Monitoring Committee (IDMC).[14] There was a survival disadvantage in patients receiving Canvaxin™ treatment in both the studies. The median survival in the stage III study had not been reached, but the 5-year survival was 59% for those receiving Canvaxin™ and 68% for the untreated patients. In the stage IV study, the median survival was 32 months for the patients treated with Canvaxin™ and was 39 months for patients receiving placebo, with respective 5-year survival rates of 40% and 45%. Eggermont reported, at the 2008 ASCO annual meeting, the results of the large phase III EORTC 18961 trial of adjuvant ganglioside vaccine GMK in 1314 patients with stage II melanoma.[15] This trial was stopped earlier by the IDMC because of inferior survival in the vaccine arm. This difference in survival at the second interim analysis is quite similar to that observed in the second interim analysis of the ECOG1694 trial, in which 880 stage IIB–III patients were randomised between high-dose interferon (IFN) therapy and the GMK-vaccine.[16] This trial is difficult to interpret with respect to the potential detrimental impact observed. It is clear that the results of these large adjuvant trials are a significant set-

back to the development of a vaccination strategy in melanoma.

5. How to turn the tide

5.1. *Methods for patient selection*

The adjuvant trial of the Melacine vaccine in stage II patients showed no benefit for the total study population.[17] Interestingly a strong benefit was demonstrated in patients with HLA-A2 and/or HLA-C.[18] Unfortunately a prospective study of the vaccine in patients with the relevant HLA-types has never been conducted. This observation demonstrates that patient selection remains an important opportunity to identify which vaccine could be effective in which patient population.

Another way to identify patients who may respond well to a particular vaccine is by identification of a geneprofile that correlates with response: A recombinant MAGE-A3 fusion protein combined with different immunological adjuvants – AS02B or AS15 – has been assessed in the EORTC 16032-18031-randomised phase II trial as a first-line treatment to 68 patients with unresectable stage III or stage IV M1a melanoma. The combination with AS15 yielded higher anti-MAGE-3 antibody titres, stronger T cell induction and some long-lasting clinical responses.[19] A gene signature derived from pre-treatment tumour biopsies has been developed and shown to predict clinical benefit.[20]

6. How to turn the tide

6.1. *Conditioning of the patient by lymphodepletion?*

Rosenberg's group recently reported on the very impressive response rates in 93 metastatic melanoma patients that received adoptive T-Infiltrating tumour-lymphocyte therapy in combination with high dose IL-2 after myeloablative conditioning therapy with fludarabine and cyclophosphamide with or without total body irradiation.[21] Lymphodepletion is one of the hallmarks of this innovative approach and seems to play a crucial role in its success. Immunosuppressive lymphocyte populations in patients with advanced metastatic melanoma, lymphocytes that also compete for IL-2, need to be eliminated to allow for an effective adoptive transfer of tumour-infiltrating T-cells, that now can thrive on the concomittantly administered IL-2. Competition for IL-2 by other lymphocyte populations has been reported to be able to abrogate efficacy of adoptive immune therapy.[22] The current approach that reported 50–72% response rates, with complete response rates of 9–16% depending on the combination with degree of total body irradiation, is of great importance. It does not only demonstrate that immunotherapy has a future, but also demonstrates that concepts such as lymphodepletion may also be quite important for vaccine development strategies.[23]

7. How to turn the tide

7.1. *Immunemodulatory antibodies?*

The induction of cytotoxic T cell activity goes hand in hand with the induction of T-regulatory cell activity. In other words immune activation is always followed by immune suppression. Immune-suppressive mechanisms at the tumour site and the critically important role of the tumour microenvironment are now better understood. A crucial theme in immunotherapy is the maintenance of T-cell activation and prevention of immune suppression or tolerance and breaking of tolerance. T-cell activation will only take place when an antigen is presented by a major histocompatibility complex molecule and a co-stimulatory molecule, B7.1 or B7.2. Binding of B7 molecules to CD28 then leads to T-cell activation. This leads to upregulation of CTLA4 and thus to increased competition for binding to B7, resulting in inhibition of T-cell receptor (TCR) signalling, *IL-2* gene transcription and T-cell proliferation. CTLA4 thus has a critical inhibitory role in T-cell control and blocking this function can be a crucial step in augmenting and maintaining cytotoxic T-cell responses, so this is desperately needed in immunotherapy of cancer.

The two monoclonal antibodies to CTLA4, ipilimumab and tremelimumab, can break self tolerance, and thus mediate anti-tumour effects, but at the same time result in autoimmunity in some tissues, also called immune-related adverse events.[24–26] The antitumour effect of anti-CTLA4 antibody administration seems to be due to increased T-cell activation, rather than inhibition or depletion of T-regulatory cells.[27] Strikingly, in various stage IV patients slowly developing, long-lasting complete remissions have now been observed. These observations have been made in both melanoma patients with extensive metastatic disease and patients that have failed various prior treatments.

Another monoclonal antibody that has been developed acts against the programmed death-1 receptor (PD-1R), the ligand of which (PD-1L) can be directly expressed on melanoma cells. PD-1R is a part of the B7:CD28 family of co-stimulatory molecules that regulate T-cell activation and tolerance and thus anti-PD-1R can play a role in breaking tolerance.[28,29] The antibodies anti-OX44 and anti-1-4BB have an agonistic action on T-cell activation and the anti-CD25 antibody that targets vmx T-regulatory cells that constitutionally overexpress CD25, are examples of other potential candidates to be combined with vaccines. It has been demonstrated that combinations of these antibodies can significantly optimise T-cell responses; thus, we are witnessing an emerging field of immunemodulation that holds great promise.[30,31] These antibodies may be crucial to successful development of vaccines in the future.

8. Conclusions

The development of therapeutic vaccines is extremely complex. The recent experience of melanoma vaccines exemplifies this and demonstrates that 'simply vaccinating the patient' does not work. The potentially detrimental effects that have been observed in adjuvant trials should lead to a very cautious approach and to the development of better immune monitoring methodology. Moreover, new elements such as patient selection, preconditioning of the patient and the use of immunomodulatory antibodies may all be necessary to make progress in this field. The holy grail is not yet within reach.

Conflict of interest statement

Alexander M.M, Eggermont – consultant (BMS, compenstated); (GSK-Bio, compensated); Sanofi-Pasteur, compensated).

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