Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: informahealthcare.com/journals/ierv20

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To cite this article: Andreas Draube, Nela Klein-González & Michael von Bergwelt-Baildon (2011) Proving the principle: dendritic cell-based vaccines in urogenital cancers, Expert Review of Vaccines, 10:10, 1355-1357, DOI: 10.1586/erv.11.125

To link to this article: https://doi.org/10.1586/erv.11.125

Published online: 09 Jan 2014.

Proving the principle: dendritic cell-based vaccines in urogenital cancers

Expert Rev. Vaccines 10(10), 1355–1357 (2011)

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"…'negative' results of many former trials might be, in part, explained by inadequate clinical end points."

Convincing clinical success of active immunotherapy has been awaited for more than 20 years now and a large number of clinical trials have been performed to achieve this goal (e.g., more than 250 in dendritic cell [DC]-based tumor vaccinations). Meanwhile, low clinical response rates contributed to substantial skepticism at least about tumor vaccines [1]. However, in recent years a growing body of knowledge about cancer immunosurveillance – and loss thereof – has led to a refinement of cancer immunotherapy [2]. Finally, the first cellular immunotherapy has been approved by the US FDA – sipuleucel-T. This consists of DCs pulsed with a prostatic acid phosphatase–granulocyte–macrophage colony-stimulating factor fusion protein and is applied for patients with advanced prostate cancer [3]. In addition to this important step in active immunotherapy, ipilimumab, an anti-CTLA-4 antibody addressing T-cell functions, was recently approved for metastatic melanoma [4]. PSA-TRICOM for prostate cancer and vitespen for renal cell cancer (RCC) are two examples of immunotherapeutics in late stages of clinical research. Among the valuable lessons learned from the trials leading to the approval of sipuleucel-T and ipilimumab, one is that active immunotherapy needs time to translate immune responses into clinical benefit. Although these therapies induce low rates of clinical responses at the beginning, both achieve a sustained overall survival benefit that does not become evident until some months after initiating the treatment. The discrepancy between the low number of objective responses and delayed disease stabilization has led to a 'paradigm shift' for clinical end points in cancer immunotherapy in general [5]: augmenting overall survival should be the ultimate end point for active immunotherapy, rather than objective response rates measured by conventional WHO/Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Therefore, 'negative' results of many former trials might be, in part, explained by inadequate clinical end points. Thus, if the clinical end point of overall survival is not applicable (e.g., in nonrandomized trials), terms such as 'clinical benefit rate' or 'tumor control rate', in which the status of stable disease (SD) is added to the objective response rate, might indeed help to evaluate therapeutic success.

DC-based tumor vaccination in prostate cancer & RCC

The urogenital tumors prostate cancer and RCC appear to be good candidates to address the aforementioned issue. They are regularly infiltrated by antigen-specific immune cells and, thus, considered to be susceptible to immunotherapy. Recently, different immunotherapies in both entities have been reviewed in *Expert Review of Vaccines* [6,7]. The success of ipilimumab as a key reference of the targeted manipulation of the immune system raises the question as to whether 'old-fashioned' cellular adjuvants such as DCs are less suitable. However, active immunotherapy aims not only to induce tumor-specific cytotoxicity, but also long-lasting immunological memory to the patient. Therefore, using

Keywords: dendritic cell • prostate cancer • renal cell cancer • tumor vaccination

 10.1586/ERV.11.125 ISSN 1476-0584

DCs as professional antigen-presenting cells (APCs) with the ability to activate specific antigen-experienced and naive T cells for the induction of cellular cytotoxicity, as well as the ability to induce long-lasting Th1 responses, still appears attractive [8].

Prostate cancer and RCC differ in some important aspects: in prostate cancer, relevant tumor-associated antigens (TAAs) have been identified, whereas in RCC they remain elusive. This issue is reflected in different DC-based vaccination strategies: for prostate cancer trials, DCs have been mainly pulsed with well-defined peptides or proteins, whereas in RCC trials, whole tumor-cell lysates or RNA have been preferred. Clinical end points used also differ in these tumor entities: conventional RECIST/WHO criteria in RCC, and a combination of radiographic criteria and biochemical markers in prostate cancer (as defined by the NIH Prostate-Specific Antigen Working Group). Owing to these complementary hallmarks, we identified them as optimal candidates for a comparative meta-analysis to revisit the following two fundamental questions surrounding DC-based tumor vaccinations [9].

Is there a link between immunological & clinical response?

Thus far, an association between immunological and clinical response has only been reported within single Phase I/II trials (e.g., for prostate cancer see [10] and RCC see [11]). There are no data from randomized trials supporting this key issue. In the aforementioned systematic review, prostate cancer and RCC trials using DC-based tumor vaccination and published within the past 10 years were analyzed. Available individual-patient data was used for a meta-analysis. In total, 29 publications (17 prostate cancer and 12 RCC trials) with a total of 906 patients were eligible. The reported objective response rates were 7.7% in prostate cancer and 12.7% in RCC trials, and were within the range found for other tumor entities [1]. Adding SD – after having documented progressive disease at study entry – amounted to a clinical benefit rate (CBR) of 54% in prostate cancer and 48% in RCC. The main objective of the meta-analysis was to address the key question about whether there is a link between the cellular immune and clinical response, which is assumed for DC vaccines. Indeed, a statistically significant effect of DC-mediated cellular immune responses on CBR could be verified in both tumor entities, which was primarily independent from the chosen vaccination protocols (e.g., DC subtype, vaccination route or different strategies of antigen delivery). Thus, this finding provides a 'proof of concept' for DC-based immunotherapy.

Does a dose–response relationship exist?

The second relevant finding of the meta-analysis was the positive correlation between higher numbers of total vaccinated DCs and the clinical outcome. Nowadays, it is assumed that repeated vaccinations are necessary to boost and maintain a tumor-specific immune response. However, there is little information about the optimal number of vaccinations, number of DCs per vaccination or about vaccination schedules. The fact that DCs can interact with up to 5000 T cells per hour [12], the phenomenon of determinant spreading [13], as well as the observation that T cells activated by the vaccine themselves enable the activation of both pre-existing and new antitumor T cells [14], led to the theory that successful vaccination is less dependent on the number of induced tumor-specific T cells than on qualitative aspects of the vaccine [8]. On the other hand, a correlation between vaccinated DC dose and clinical response has been suggested in murine models [15]. For prostate cancer, this has been observed in one clinical trial but without statistical significance [16]. Indeed, one possible explanation for the efficacy of sipuleucel-T might be the high number of DCs used, which can be generated by the density-enrichment process established for this cellular vaccine (e.g., at least 40×10^6 per vaccination in [3]). Therefore, we believe that both qualitative and quantitative aspects of the DC vaccination are important for the induction of a potent cellular immune response.

Future directions

After a long period of disappointment, recent success of active tumor immunotherapy encourages further research in the laboratory as well as in the clinic. We believe that the urogenital tumors, prostate cancer and RCC are good candidates to develop immunotherapeutic strategies and that sipuleucel-T represents the beginning of a shift toward clinical practice. Thanks to the lessons learned about the time course of the induction of immunological tumor control, patients with slowly progressive disease should be enrolled in clinical trials preferentially. Furthermore, results from studies addressing the adjuvant setting or patients at minimal residual disease will be extremely exciting. Rather than adherence to conventional trial designs conceived for cytotoxic drugs as conducted in the past 15 years, we strongly encourage the two-phase clinical research model for active immunotherapy, which has been postulated in recent years [17]. In the first phase, early 'proof-of-principle' trials should provide evidence of immunological and/or clinical responses, establish feasibility of dose/schedule, and address safety issues. Successful trials should be followed by randomized 'efficacy trials' determining clinical benefit, ideally by end points such as overall survival or time to progression. Beside other strategies, DC-based tumor vaccinations are evolving [8] and the future might not be the demonstration of superiority of one strategy but rather the combination of different approaches [18]. Furthermore, combination of chemotherapy with active immunotherapy is no longer taboo. In fact, quite the contrary has now been shown for the combination of ipilimumab with chemotherapy in melanoma [19]. Whether *ex vivo*-generated DCs as cellular adjuvants can be complemented or even replaced by alternative, technically less challenging APCs [20] or by targeting DCs *in vivo* more effectively [8], the future will show.

Financial & competing interests disclosure

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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