Editorial

Further clinical advancement of dendritic cell vaccination against ovarian cancer

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Since the discovery of dendritic cells (DC) as potent stimulators of immune responses by Zanvil Cohn and Ralph Steinman in the 1970s, the idea that DC could be used as adjuvants for activation of antitumor immunity steadily gained traction, culminating in the first published clinical trial of DC vaccination (for treatment of B cell lymphoma) (1). Other clinical trials sometimes showed exciting results, notably for melanoma (2), but the early promise of first generation DC vaccines was not fulfilled in terms of clinical efficacy. There may be multiple reasons for the lack of efficacy, including a tendency for early phase clinical trials to enroll patients with advanced, metastatic disease and associated comorbidities, including immune suppression, which has only recently been recognized as a major barrier to the efficacy of tumor vaccines in general, the lack of optimal maturation and immunogenicity of early DC vaccine formulations and the lack of definition of immunogenic neoantigens. In spite of these problems, DC vaccines continued to engage interest, culminating in the approval of Sipuleucel-T as a DC vaccine for treatment of prostate cancer in 2010. Sipuleucel-T was derived by treatment of peripheral blood leukocytes with a fusion protein consisting of prostatic acid phosphatase combined with GM-CSF. The manufacturing process did not use a defined maturation cocktail, and the end product consisted of the total population of leukapheresis-derived mononuclear cells, of which DC comprised only a small percentage. Perhaps not surprisingly, the clinical benefit from treatment with Sipuleucel-T was limited, with a gain of 4.1 months in overall survival amongst men with metastatic castration-resistant prostate cancer, but no impact on the time to disease progression (3).

Enthusiasm for DC vaccination has recently enjoyed a renaissance, in part due to increasing sophistication in DC preparation and maturation for optimal stimulation of antitumor immunity (4,5), new methods to promote DC migration to draining lymph nodes (6), and most crucially, the recognition that the efficacy of DC vaccination is likely to gain from biomarker-driven adjuvant treatments that target and abrogate mechanisms of tumor-associated immune suppression (7). Indeed, a significant proportion of completed or current clinical trials of DC vaccination for cancer incorporate one or more adjuvant treatments, rather than pursuing an earlier generation monotherapy approach (8).

The recognition that DC vaccination, in common with other tumor vaccines or immunotherapies, may be more effective when combined with other immunomodulatory agents is exemplified by a recently reported clinical trial of DC vaccination in patients with recurrent ovarian cancer (9). In this study, three sequential cohorts of patients were treated with DC vaccination alone (n=5), DC vaccine plus bevacizumab (n=10), or DC vaccine combined with bevacizumab and low-dose cyclophosphamide (200 mg/m^2), given the day before DC vaccination. Bevacizumab is widely used for treatment of ovarian cancer, and there is a strong rationale for the addition

of cyclophosphamide as an immune adjuvant, given its recognized ability to abrogate Treg activity. This latter point is a key consideration, as Treg are known to mediate immune suppression in the ovarian tumor microenvironment, and Treg infiltration is associated with increased morbidity and mortality in ovarian cancer (10). The DC vaccine was prepared from peripheral blood monocytes, and DC loaded with an oxidized autologous tumor lysate to provide broad tumor antigen coverage. Patients received five doses of DC vaccine, delivered intranodally under ultrasound guidance every 3 weeks. Further maintenance doses of DC vaccine were given monthly until disease progression or exhaustion of vaccine supply. The choice of intranodal delivery is intended to circumvent the limited ability of DC injected by other routes to migrate to draining lymph nodes, a handicap that may reduce the immunogenicity and efficacy of DC vaccination.

This Phase I study established that intranodal DC vaccination was feasible and well tolerated in ovarian cancer patients, either as monotherapy or in combination with bevacizumab and cyclophosphamide. Intranodal DC vaccinations were completed without complications, and most vaccine-related reactions were grade 1, with no toxicities greater than grade 2 observed throughout the study. DC vaccination was immunogenic in a proportion of patients, with IFN-secreting T cells detected in response to tumor antigen in 11 of 22 evaluable patients, and T cells capable of directly responding to autologous tumor cells detected in 9 of 13 patients from whom short-term tumor cell lines could be established. Although the overall rate of DC vaccine responsiveness may be viewed as disappointing, it should be borne in mind that these patients had recurrent, measureable disease following surgery and one or more cycles of chemotherapy, and may suffer from both disease and treatment-related morbidities that could compromise immune responsiveness. Encouragingly, a significantly higher proportion of patients receiving DC vaccination combined with cyclophosphamide showed T cell immune responses to tumor antigen (8 of 10), compared with evaluable patients who were not treated with cyclophosphamide (3 of 12). Importantly, though, those patients who showed T cell responses to DC-presented tumor antigen or autologous tumor cells benefited from significantly longer progression-free survival (PFS) than those patients who failed to respond to DC vaccination. One patient who had suffered recurrent disease twice remained in remission for five years following completion of DC vaccination in cohort 1 (i.e., she received DC vaccination only), and T cells recovered post-vaccination showed anti-tumor efficacy in an autologous patient-derived xenograft mouse model, relative to T cells recovered pre-vaccination. Collectively, these observations directly relate immune response to clinical response, and argue for the determination of pre-treatment immune signatures that may enable prediction of immune response linked to clinical benefit. To this end, the investigators asked whether gene signatures associated with T cell infiltration were associated with longer PFS. Unfortunately, immune signatures pre-treatment did not correlate with immune response or clinical response post-DC vaccination. This should not be taken to imply that such efforts are futile, or that predictive gene signatures cannot be identified, rather that the approaches taken to such studies should be further refined, possibly in terms of cell subsets under analysis (e.g., dissection of tumor cell and tumor-infiltrating cell populations from primary disease or recurrent disease biopsies, as available). Overall clinical responses, based on disease assessment by RECIST, showed that 2 patients experienced a partial response and 13 patients enjoyed stable disease periods with a median of 14 months (range, 4–96 months). Of particular note, patients on the cohort that received combinatorial treatment of DC vaccination, bevacizumab and cyclophosphamide benefited from significantly higher overall survival rates than those who were not treated with cyclophosphamide. This observation lends further support to the notion that adjuvant treatments designed to alleviate tumor-associated immunosuppression (in this case, targeted at Treg inhibition) may markedly improve the immunogenicity and clinical efficacy of DC vaccination and potentially other tumor vaccine strategies.

Analysis of tumor lysate-loaded DC vaccine responses in a subset of patients (n=6) revealed $CD8^+$ T cell responses to multiple epitopes, some of which were new responses that were undetectable prior to DC vaccination, and some of which indicated amplification of preexisting responses detectable prior to DC vaccination. However, detailed investigation of T cell responses from two patients revealed a marked increase in the avidity of post-vaccination T cell responses versus pre-vaccination T cell responses to the same neoepitopes. TCR sequencing did not find commonality between pre-vaccination and post-vaccination samples, indicating that the stronger responses were the result of DC vaccine priming of novel high avidity clones. From these observations, the authors drew the reasonable conclusion that peripheral tolerance may suppress the emergence of T cells with high affinity TCR, whereas tumor lysate-loaded

DC may be capable of activating and expanding these T cells. With this in mind, it is worth noting that both subjects in this component of the study received the triple combination treatment including cyclophosphamide, leading to the thought that cyclophosphamide abrogation of Treg activity may have impacted peripheral tolerance mechanisms that limit expansion of tumor antigen-specific T cells with higher affinity TCR.

In conclusion, this report shows that DC vaccination for advanced, recurrent ovarian cancer is feasible and safe, and is immunogenic in at least a proportion of patients. The overall survival data for the cohort that received the full combination of DC vaccination, bevacizumab and cyclophosphamide are also encouraging, and support the prevailing opinion that tumor vaccination is more likely to yield clinical benefit when combined with adjuvants that target immune suppression in the tumor microenvironment. In this respect, it is worth noting that, apart from Treg, other mechanisms of immune suppression in ovarian cancer may also influence morbidity and mortality, including indoleamine 2,3-dioxygenase (11,12) and expression of PD-L1 checkpoint molecules (13), both of which are associated with poor clinical outcomes. Paradoxically, checkpoint inhibitors such as nivolumab and pembrolizumab (which block PD-1 interaction with PD-L1) have shown limited clinical efficacy (14), but checkpoint inhibitors may yet show improved benefit when combined with active immunotherapy such as DC vaccination.

A final consideration is that DC vaccination of ovarian cancer patients post-surgery and chemotherapy, with the goal of preventing disease recurrence, may show greater immunogenicity and clinical benefit than DC vaccination of patients with recurrent and progressive disease. Patients with minimal residual disease following optimal surgical debulking and chemotherapy may enjoy better health and immune function and may present lower barriers of tumor-associated immune suppression, thus allowing generation of stronger antitumor immunity post-vaccination. A practical drawback of this approach is that it takes longer to determine clinical response to DC vaccination in terms of recurrence-free survival in patients with minimal residual disease than it does to determine clinical response by RECIST for those patients with measurable disease. Nevertheless, maintenance and of prolonged recurrence-free interval and overall survival would be highly favorable.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Hsu FJ, Benike C, Fagnoni F, et al. Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells. Nat Med 1996;2:52-8.
2. Nestle FO, Alijagic S, Gilliet M, et al. Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells. Nat Med 1998;4:328-32.
3. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22.
4. Kalinski P, Okada H. Polarized dendritic cells as cancer vaccines: directing effector-type T cells to tumors. Semin Immunol 2010;22:173-82.
5. Hansen M, Hjortø GM, Donia M, et al. Comparison of clinical grade type 1 polarized and standard matured dendritic cells for cancer immunotherapy. Vaccine 2013;31:639-46.
6. Mitchell DA, Batich KA, Gunn MD, et al. Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients. Nature 2015;519:366-9.
7. Garg AD, Coulie PG, Van den Eynde BJ, et al. Integrating Next-Generation Dendritic Cell Vaccines into the Current Cancer Immunotherapy Landscape. Trends Immunol 2017;38:577-93.
8. Saxena M, Bhardwaj N. Re-Emergence of Dendritic Cell Vaccines for Cancer Treatment. Trends Cancer 2018;4:119-37.
9. Tanyi JL, Bobisse S, Ophir E, et al. Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. Sci Transl Med 2018;10. doi: 10.1126/scitranslmed.aao5931.
10. Curiel TJ, Coukos G, Zou L, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 2004;10:942-9.
11. Okamoto A, Nikaido T, Ochiai K, et al. Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. Clin

Cancer Res 2005;11:6030-9.
12. Inaba T, Ino K, Kajiyama H, et al. Role of the immunosuppressive enzyme indoleamine 2,3-dioxygenase in the progression of ovarian carcinoma. Gynecol Oncol 2009;115:185-92.
13. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci U S A 2007;104:3360-5.
14. Hamanishi J, Mandai M, Ikeda T, et al. Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. J Clin Oncol 2015;33:4015-22.

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