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Commentary: Randomized Phase II Trial of Autologous Dendritic Cell Vaccines Versus Autologous Tumor Cell Vaccines in Metastatic Melanoma: 5-year Follow Up and Additional Analyses

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A recent publication described the final results of a randomized phase II clinical trial testing patient-specific autologous dendritic cell vaccines (DCV) and autologous tumor cell vaccines (TCV) in patients with metastatic melanoma[1]. For both products the sources of antigen were autologous tumor cells that were self-renewing in short-term tissue culture. Such cells share characteristics with tumor initiating cells (cancer stem cells and early progenitors) including self-renewal in cell culture, the ability to form tumors in immune-compromised rodents, and the expression of certain phenotypic markers[2]. The results confirmed the survival benefit associated with DCV that was described in an interim report[3], as well as additional details regarding delayed type hypersensitivity (DTH) reactions to intradermal injections of tumor cells, and safety.

The most important observation was the superior survival associated with DCV including a median overall survival of 43.4 vs 20.5 months, a 3-year overall survival rate of 61% vs 25% (p=0.018), and a 70% decrease in the risk of death (HR=0.304, p=0.0035)[1]. This is the only trial in cancer patients that has addressed the question of whether injection of DC loaded with antigen *ex vivo* is associated with better clinical outcome compared to injecting irradiated TC and relying on endogenous loading of DC. The recent publication also confirmed that a patient with progressive, measurable, metastatic melanoma that had been refractory to all therapies available at the time, who had achieved a delayed complete remission[4], was still in complete remission more than five years after study entry. This commentary addresses a number of questions that have been raised about this study.

One obvious concern is the small number of patients enrolled in this trial. The trial was originally designed to enroll 200 patients with 90% power to detect a 50% reduction in the risk of death between the two arms, and an 80% power to detect a 40% difference. Unfortunately, for financial and strategic reasons, the trial was terminated prematurely by the hospital that was providing financial support for it. At the time of closure 42 patients had been randomized. Fortunately, all patients were treated as randomized; so there were no discrepancies for "intent-to-treat" versus actual treatment. The survival difference between the two arms was striking, and consistent with the differences seen when comparing survival for 54 metastatic melanoma patients treated with DCV during 2001-2007[5], to 74 patients treated with TCV during 1990-2001[6]. All three protocols had similar eligibility criteria.

Another concern raised is the numerical imbalance in the treatment arms at the time the study was halted: TCV (n=24) and DCV (n=18). This imbalance was a consequence of the early termination. Because the study was being conducted at one clinical site with one research coordination team, blocking during randomization, which would have assured equal or near equal randomization to either arm at any time point, was not used. Had the study continued as planned, there would have been a 1:1 balance in the arms in terms of assignment for intent-to-treat.

Because of the small numbers and imbalance in the numbers of patients between the two arms, there was concern that an imbalance in prognostic factors might explain the clinical results. Had the study not been terminated early, these variables would have evened out with the randomization assignments. Fortunately, multivariate analyses alleviated these concerns[1]. The two strongest variables associated with better outcome were DCV treatment and non-measurable disease at the time of treatment. In fact, negative prognostic factors were more frequent in the DCV arm. These included imbalances in the two stratification factors used in the randomization, namely highest stage of disease (3 vs 4) and measurable disease (yes or no).

Another issue raised was whether the differences in survival were actually due to previous or subsequent therapies. All therapies received by these patients were documented at the time of enrollment and during long-term follow up. As shown in the paper, there was no evidence other treatments influenced outcome[1]. In particular, at the time this study was conducted, BRAF/MEK and immune checkpoint inhibitors were not widely available, and only a handful of patients eventually received such treatments.

Another criticism of the study is that the final patient population was more heterogeneous compared to populations enrolled in clinical trials that had more restrictive eligibility criteria; and therefore, it is difficult to compare these results to those from other phase II trials. DCV is not an “off-the-shelf” product like the agents being tested in most clinical trials; therefore, it is not surprising that there is no other published clinical trial that has a comparable patient population. All patients enrolled in this trial had experienced either recurrent stage 3 disease or stage 4 metastatic melanoma, and all had undergone surgical resection of a tumor mass as the source for the short-term cell culture. Patients with stage 4 disease were more likely to undergo surgery if they had a single distant metastasis, or oligometastatic disease. Because of the passage of time between tumor acquisition and production of a cell line, and eventual referral for randomization and treatment, many patients had experienced recurrence or progression of disease. It was felt that the perceived advantages of using antigens from self-renewing autologous tumor cells for such patient-specific vaccines outweighed the possible advantages of utilizing allogeneic cell lines or limiting treatment with specific HLA-restricted peptides for such therapeutic vaccines[1,2,11]. Patients could only be treated if they were referred by their managing physician, and there was no certainty that patients for whom a cell line was established would ever be referred for treatment. At the time of enrollment for randomization and treatment, there were three distinct patient cohorts: (1) those who had experienced recurrent stage 3, but had not progressed to stage 4 and had no evidence of disease, (2) those who had experienced stage 4 but lacked measurable disease either because they had not recurred or because they had not recurred after surgery and/or responded to some other therapy, and (3) those with measurable stage 4 disease. If one pools the DCV-treated patients from both phase II trials (n=72)[1,5], the 5-year overall survival rate was 72% for 18 with surgically resected recurrent stage III, 53% for 30 with stage 4 but no measurable disease at the time of treatment, and 2-year survival of 46% for 24 with stage 4 measurable disease, which is actually similar to the 43% reported for anti-PD-1 in similar heavily pretreated patients[7].

Some critics said that the data was provocative, but they would like to see evidence of differential immune effects associated with DCV. As described in the paper, the trial failed to support the use of the tumor DTH test as either a prognostic or predictive marker[1]. However, serologic tests for various markers showed a very different pattern after DCV than after TCV[1]. There is no data available regarding altered targeting of any specific tumor antigens by cytotoxic T lymphocytes, especially to those that might be predicted by exomic analysis, messenger RNA sequencing, and computer-based predictions of antigenicity based on HLA type[8,9]. Such correlative work is important for a better understanding of the mechanism of action and patient selection, but does not change the observation that DCV was associated with a better overall survival than observed in a contemporary control population, who were also treated with a putative vaccine. However, it should be noted that it is not clear whether there actually are useful immune assays that correlate with patient clinical responses.

Another question is whether this DCV approach that relies on short-term autologous cell cultures as the source for tumor antigens is really practical for commercial development. Historically it took over three months for a cell line success rate of under 50%[1,5,6]. So far current methodology has been associated with a cell culture success rate of 100% within four weeks in various cancers including ovary, glioblastoma, hepatoma, colon cancer, cholangiocarcinoma, soft tissue sarcomas, and squamous cell cancers of the head and neck and vulva. Current cost of

goods and services to manufacture the current DCV product and provide it as a treatment is under $25,000, and that includes acquisition of raw materials, all manufacturing costs including personnel, and shipping. Furthermore, there are no hidden costs related to toxicity or immunodepleting pre-therapy, or required concurrent therapy. Thus, the product compares quite favorably to other patient-specific cellular immunotherapies. For example, sipuleucel-T is associated with charges of about $100,000 for therapy.

Another issue is whether such a vaccine approach is even relevant given recent advances in the treatment of metastatic melanoma[10-13]. When this trial was in progress, there were no therapies that improved survival in metastatic melanoma. Now there are, including the highly successful anti-BRAF/MEK combination[14-16], and the monoclonal antibody inhibitors of immune checkpoint molecules such as programmed death molecule-1 (PD-1)[17-21] with or without an antibody inhibitor of cytotoxic T lymphocyte antigen-4 (CTLA-4)[22-23]. However, only about one half of melanoma patients have mutations targeted by BRAF/MEK, and the only patients who benefit from anti-PD-1 (or anti-PDL-1) are those who have an existing immune response to autologous neoantigens that has been suppressed by the PD-1/PDL-1 interaction. A vaccine that induces new immune responses or enhances weak ones could be complementary to anti-checkpoint therapy.

Another issue is whether it is worth the effort to try to establish tumor cell lines rather than using a lysate of whole tumor, or pulsing autologous DC with HLA-specific peptide antigens[11]. From the initiation of trials with TCV in 1990, we have felt that proliferating autologous tumor cell cultures might be the best source of tumor antigens for therapeutic cancer vaccine[24]. This bias has only been strengthened by recent findings regarding neoantigens that are only expressed on autologous tumor[25], and the potential advantages associated with targeting tumor initiating cells, including cancer stem cells[2].

Conclusions

This is the first and only trial that has tested DCV and TCV in a randomized trial. The apparent superiority of DCV confirms observations from previous trials of each vaccine. Detailed analyses have failed to identify any unintentional bias that might account for the differences. Efficacy and safety of the approach are established. Recent changes in manufacturing have made this a more practical approach for commercialization. There is a strong rationale for integrating the product into a combination approach with antibodies that inhibit immune checkpoints.

Conflict of Interest Statement

Since 2016, the author has been the Chief Medical Officer for AIVITA Biomedical, Inc.

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