BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

FAQs for BMT CTN PROTOCOL 1401

Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell /Myeloma Fusions

1. Why run a vaccine study in multiple myeloma?

The development of biologically-based therapies for patients with multiple myeloma (MM) has significantly improved disease response and survival. High-dose chemotherapy with stem cell rescue followed by lenalidomide maintenance is associated with further prolongation of disease response. MM, however, remains a lethal malignancy due to the ultimate emergence of resistant disease. Immunotherapy has emerged as a leading area of cancer therapeutics due to its potential to recruit multiple effectors that broadly target malignant cells, thus capturing clonal diversity and overcoming resistance to cytotoxic therapy. MM is characterized by progressive immune dysregulation with the loss of myeloma-specific T cells and an immunologic milieu that fosters disease progression. Tumor vaccines offer the potential to reverse myeloma-induced immune suppression, expand myeloma-specific effector cells, and produce durable disease response. We have developed a potent myeloma vaccine in which patient-derived tumor cells are fused with autologous dendritic cells (DCs), allowing for the presentation of a broad array of myeloma antigens in the context of DC-mediated costimulation. In a phase I study, vaccination with DC/MM fusions was well-tolerated, induced the expansion of myeloma-specific T cells, and resulted in disease stabilization in patients with advanced disease.

While not curative, high-dose chemotherapy with stem cell rescue offers a unique platform for immune therapy. The period of post-transplant lymphopoietic reconstitution is associated with the depletion of immunosuppressive regulatory T cells and the transient partial reversal of tumor tolerance. We postulated that the post-transplant period would offer an enhanced platform for DC/MM fusion vaccination that would result in greater expansion of tumor-specific lymphocytes and the potential targeting of residual disease responsible for subsequent relapse. In a recently completed trial, we demonstrated that the post-transplant period is characterized by a statistically significant rise in myeloma-specific T cells that is further boosted by DC-based vaccination. The induction of myeloma-specific immunity was associated with a near doubling of the complete response rate between 100 days and 1 year post-transplant[1].

Lenalidomide is an immunomodulatory agent with potent anti-myeloma activity[2,3]. Lenalidomide maintenance following high-dose chemotherapy with stem cell rescue is associated with statistically significant improvement in progression-free and overall survival in the post-transplant setting, potentially through diverse effects on T cell and NK cell-mediated immunity[4]. We demonstrated that vaccine efficacy is further augmented by lenalidomide, which creates an enhanced platform for vaccination by biasing toward Th1 as compared to Th2 responses, limiting the expansion of regulatory T cells, and enhancing CTL-mediated killing of myeloma targets by fusion-stimulated T cells[5].

Based on the promising results demonstrated in phase I and II clinical trials evaluating the DC/MM fusion vaccine and its synergy with lenalidomide, in this clinical trial, patients with MM undergoing autologous stem cell transplantation will be randomized to receive (i) post-transplant vaccination with lenalidomide maintenance, or (ii) lenalidomide maintenance alone. The primary study endpoint will be to compare the effect of post-transplant therapy on the percent of patients in CR at 1 year post-transplant. The conversion from partial to complete response, time to progression, and effect on measures of minimal residual disease will be assessed. In correlative science studies, we will evaluate immunologic parameters reflecting myeloma-specific T cell, NK cell, and humoral immunity.

2. Why apply the study interventions as upfront treatment strategy in myeloma?

Autologous stem cell transplantation for MM offers a unique platform to explore the role of tumor vaccines. High-dose chemotherapy results in tumor cytoreduction, which limits tumor-mediated immune suppression and offers the potential to eradicate post-transplant minimal residual disease with vaccination. Both animal models and clinical studies demonstrate that the period of lymphopoietic reconstitution following high-dose chemotherapy is associated with the depletion of regulatory T cells, skewing of recovering lymphocytes toward tumor-reactive T cells, and enhanced responsiveness towards tumor vaccines. In a phase II study, we demonstrated that vaccination with DC/MM fusions following autologous stem cell transplantation significantly boosted anti-myeloma immunity in the post-transplant period and was associated with the conversion of partial to complete responses in a subset of patients.

3. Patients are referred to the transplant centers after initiation of therapy, how is this barrier to accrual being addressed?

Because MM cells are required for vaccine production, a minimum of 20% plasma cells is required at time of study entry. The protocol allows for patients to receive up to two cycles of MM-directed therapy prior to enrollment, provided there is 20% marrow involvement with plasma cells at the time of enrollment. We successfully completed a recent phase II study with similar eligibility criteria. For this multicenter trial we plan to distribute educational materials to centers to be shared with referring doctors and work with patient support groups for trial promotion.

4. Collection of 30 mL of marrow is far more than what patients undergo for diagnosis, how is this volume defined and what modifications in the aspirate technique are required?

The volume of marrow has been defined based on experience from phase 1 and 2 trials in MM, as the amount of marrow aspirated in order to yield a sufficient number of plasma cells for vaccine generation. An SOP for tumor collection has been generated, detailing the process of marrow aspiration for tumor collection.

5. The primary endpoint of the study is conversion to CR, how are you addressing patients who achieve CR after the autologous transplantation?

The primary endpoint of the study is to compare the percentage of patients in CR at 1 year in each of the treatment arms. As a secondary endpoint, the percentage of patients who convert from PR

to CR will be determined. Patients are randomized in the post-transplant period, in order to allow for stratification of patients according to staging (CR vs. not in CR). As such, each arm will contain an equal number of patients who achieve a CR prior to the initiation of vaccination. Correlative science studies will be assessed in all patients, including those in a CR in the early post-transplant period prior to the onset of vaccination, as these patients may have a unique capacity for immune response to vaccination.

6. Among patients who are randomized to vaccine, are there any expected hurdles for collection of dendritic cells for tumor manufacturing?

In prior phase 1 and phase 2 studies evaluating DC/MM fusion cell vaccination, there were no hurdles to DC collection for vaccine generation. Vaccine generation was successful in greater than 95% of patients. In the present study, patients undergo leukapheresis for DC generation in the post-transplant period, which takes place after blood count recovery. In prior studies, including a phase 1 trial in patients with advanced and heavily pre-treated MM, a peripheral WBC of 2 or greater at the time of leukapheresis was sufficient for DC generation. As such, we do not anticipate hurdles for generation of DCs**.**

7. What are the safeguards in this protocol in case there is excess toxicity with the vaccine plus lenalidomide?

The key safety endpoint for this study is treatment-limiting toxicity (TLT) within the first month of combined therapy, defined as grade IV hematologic (lasting greater than 7 days) and grade III-IV non-hematologic toxicity, including development of secondary autoimmune diseases, judged to be related to combined therapy. At least three events must be observed in order to trigger review. The rate of TLT within the first month is expected to be no higher than 25%. Each month, the null hypothesis that the 1-month TLT rate is 25% will be tested. This outcome will be monitored using a truncated Sequential Probability Ratio Test (SPRT) for binary data as described below. The SPRT conserves type I error at 5% across all of the monthly examinations.

8. Why are patients being randomized after transplant?

Patients are randomized in the post-transplant period, in order to allow for stratification of patients in CR post-transplant. The primary endpoint of the study is to compare the percentage of patients in CR at 1 year in each of the treatment arms. As such, patients will be randomized post-transplant to ensure that each arm contains an equal number of patients achieving a CR prior to the initiation of vaccination.

9. Why was complete responseselected as the primary endpoint of this study?

In a previous trial, we showed that the induction of myeloma-specific immunity induced by DC/MM fusion vaccination was associated with a near doubling of the CR rate between 100 days and 1 year post-transplant(1). The hypothesis of this study is that post-transplant lenalidomide will further potentiate the effect of the vaccine, thus augmenting immune-mediated tumor cell clearance. Achievement of CR therefore represents the best clinical assessment of tumor cell clearance. CR is also associated with prolonged progression-free and overall survival. This

primary endpoint will be complemented by the evaluation of minimal residual disease and by the extensive immune correlate assessments included in this study.

10. There are a number of immune correlative studies included in this protocol, what are the steps taken to minimize the collection of blood and marrow at a single time point?

This clinical trial offers a unique opportunity to elucidate the effects of post-transplant lenalidomide on immune reconstitution in the setting of active DC-based vaccination. The immune correlative endpoints are an integral component of the trial and are not considered ancillary studies. A thorough assessment of anti-myeloma specific T-cells and NK cells, immune reconstitution, antigenic reactivity, and humoral responses will provide critical insights into the underlying mechanisms of tumor immunology. Consequently, the comprehensive scope of the proposed studies necessitates more frequent sample collections. To limit the amount of blood or marrow obtained at any given time point, we have minimized the amount of sample required for each assay and have also staggered sample collections. The volumes are the same as were successfully collected in the earlier clinical trials at Beth Israel Deaconess Medical Center.

11. Accrual Estimates: ***please see separate document***

References:

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