Adjuvant Immunotherapy of Resected, Intermediate-Thickness, Node-Negative Melanoma With an Allogeneic Tumor Vaccine: Overall Results of a Randomized Trial of the Southwest Oncology Group (SWOG-9035)

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Background

There is no standard adjuvant therapy for completely resected, intermediate thickness, node-negative melanoma patients. Both external beam radiation treatment and cytotoxic chemotherapeutic agents have thus far demonstrated limited efficacy at best, prompting interest for novel adjuvant treatment modalities. Because of multiple case study reports of spontaneous regression of melanoma lesions, the disease was felt to be susceptible to attack by the immune system. To date, both autologous and allogeneic melanoma cancer vaccines have been used in the settings of either documented metastatic disease or in patients at high risk of harboring microscopic residual disease following resection. It stands to reason that vaccination might be more efficacious in the setting of minimal tumor burden due to issues of decreased tumor antigen heterogeneity and less tumor-induced immunosuppression. In 1990, the Southwest Oncology Group initiated development of a phase III clinical trial of allogeneic melanoma cell lysate for use as vaccine therapy in patients with completely resected, node negative melanoma. The vaccine chosen had shown an objective response rate in 7% of 81 patients in multicenter phase I and II trials in advanced melanoma, and was known to contain tumor antigens potentially able to induce a significant immune response.

Methods

- the primary objective of the trial concerned both DFS and OS, and the trial was designed to detect a 50% increase in median DFS
- eligibility requirements included age 18 years or older, pathological diagnosis of completely resected (≥1 cm margin except in head & neck or hands and feet requiring only histologically negative margin) primary cutaneous melanoma (1.5-4.0 mm thickness via Breslow technique or Clark’s level IV if Breslow analysis unavailable) with no gross satellitosis, clinical or pathologic evidence of negative lymph node involvement, absence of metastatic disease by exam or CXR, Zubrod 0 or 1 performance status, satisfactory organ function, and no prior radiation, chemotherapy, or steroid treatment of their melanoma
- stratification factors included gender, tumor thickness (≤ or > 3 mm), and type of nodal staging (clinical versus pathologic)
- patients were randomized to vaccination therapy for two years versus observation
- registration occurred within 8 weeks of either primary resection or surgical lymph node staging
- central review of all pathologic specimens was performed
- the Melacine vaccine consisted of an allogeneic cell lysate harvested biopsy specimens of two different patients with metastatic disease; the vaccine was administered with DETOX adjuvant (Somonella endotoxin and components of mycobacterial cell wall) in order to increase immunologic activity
- patients randomized to the treatment arm received therapy for a two year duration; each treatment consisted of two intramuscular injections of Melacine and Detox; the vaccinations were delivered as four 6-month cycles of ten treatments (weekly X 4, biweekly X 2, monthly X 4) with 3-week intercycle rest periods
Results

- 689 patients were enrolled between 4/92 and 11/96, of which 600 were eligible; most patients who were deemed ineligible failed to meet enrollment criteria following central pathologic review
- median age was 51 years
- 24% of patients underwent surgical staging of nodal regions, of which approximately one-quarter were sentinel node biopsies
- median f/u was 5.6 years with a minimum f/u of 4 years
- the majority of patients on vaccine arm experienced mild to moderate toxicity thought secondary to injection of adjuvant
- 68 patients experienced grade III toxicity including severe local reactions, malaise/fatigue, visual complaints, fever, diarrhea, thrombocytopenia, and skin rash
- there were 107 events (progression or death) on the vaccine arm compared to 114 events on the observation arm
- there was no significant difference in DFS between the two groups (p=0.51) with an estimated 5 yr DFS of 65% in the vaccine arm and 63% in the observation arm (p=0.51)
- OS was not statistically analyzed as the study had not yet reached the predetermined level of maturity for analysis
- two of the three stratification factors (gender and tumor thickness) were found to be statistically significant, while type of nodal staging was of borderline significance

Author's Conclusions

- SWOG 9035 is the largest randomized controlled trial involving therapeutic cancer vaccination to this point
- there was no difference between the two groups with respect to DFS, though the trial was not powered to detect small but clinically meaningful differences
- toxicity data was encouraging, and the vaccine was well-tolerated by the patient population
- surgical staging of lymph nodes in all patients might have improved intended patient selection with regard to node negativity
- OS data will be statistically analyzed in two years

Clinical Implications

Cancer vaccine therapy, while novel, is not a new treatment approach, as significant amounts of pre-clinical and phase I and II trials have been reported. However, the lack of encouraging phase III trials relegates the approach to one of experimental status with poor results to date. Though this trial was the largest of its kind, even larger patient populations will be required in the future should investigators wish to evaluate smaller but clinically significant differences. In addition, an allogeneic vaccine strategy, while much less expensive and time-consuming versus autologous preparations, has shown little activity in phase I and II trials, most probably due to the fact that the majority of effectively immunogenic tumor antigens are as of yet undiscovered. While an autologous vaccine approach seems to make better sense at the level of immune recognition and response, the cost and time implications involved render this largely impractical. Nevertheless, the field of vaccine therapy continues to garner much attention, and hope persists that significant advances will soon be reported.