Safety and Long-Term Maintenance of Anti-HER2 Immunity Following Booster Inoculations of the E75 Breast Cancer Vaccine

Raethsa S. Dabney, Diane F. Hale, Timothy J. Vreeland, Guy T. Clifton, Alan K. Sears, Ritesh Patil, Sathibalan Ponniah, Nathan M. Shumway, Elizabeth A. Mittendorf, George E. Peoples

Background

We have completed accrual and are in the final follow-up portion of phase III clinical trials evaluating the E75 vaccine, an HLA-A2/ A3 restricted HER2/neu (HER2) peptide mixed with GM-CSF. E75 has been proven safe, capable of stimulating HER2 immunity, and appears effective in decreasing breast cancer recurrence rates. During the conduct of this trial, it was noted that E75-specific immunity waned after the Primary Vaccine Series (PVS) which corresponded with late recurrences. To maintain long-term immunity, a voluntary booster program was started. Here we present analyses of the booster inoculations.

Methods

The trial enrolled node-positive or high-risk, node-negative breast cancer patients with tumors expressing any level of HER2 (IHC 1–3+). HLA-A2/A3+ patients comprised the vaccine group (VG), HLA-A2/A3- patients were followed prospectively as the control group (CG). The VG received 4-6 monthly inoculations as the PVS, followed with one inoculation every 6 months as the booster vaccine series. Patients were monitored for toxicities, in vivo responses by local reactions and DTH, and in vitro responses measured by enumeration of E75-specific cytotoxic T lymphocytes using HLA A2:E75 dimers.

Vaccinations were well tolerated with primarily Grade 1 and Grade 2 toxicity (Local toxicity: 24% no toxicity, 73% had Grade 1, and 3% had Grade 2; Systemic toxicity: 74% no toxicity, 35% had Grade 1, 1% had Grade 2) (Figure 1).

To date 53 patients received at least one booster, 34 received two, 24 received three, 20 received four, 12 received five, and 8 received at least six. Overall, vaccinated and control patients only has the number of ER/PR negative status. When looking at boosted, not boosted and control patients, the only additional difference is the number of patients receiving Trastuzumab. This is likely due to the fact that these patients enrolled later in the trial.

Conclusions

Booster inoculations are well-tolerated and appear to assist in the maintenance of long-term peptide-specific immunity. Boosted patients have improved recurrence rates. Based on the success of this program, we have incorporated the practice of booster inoculations in our current cancer vaccine trials, to include the recently initiated PRESENT Phase III Trial of E75 + GM-CSF.

Disclosures

This research was supported by grants from the Department of the Army, Department of Defense or the U.S. Government. No disclosures.

Results

Local reactions increased significantly from the initial vaccine (R1) during PVS to each booster (B) (R1: 59.5±3.1 vs B1: 89.2±3.3, p<0.001; vs B2: 95.1±5.4, p<0.001; vs B3: 86.3±5.5, p<0.001; vs B4: 83.2±6.6, p<0.001; vs B5: 80.6±6.7, p<0.006; vs B6: 78.7±5.4, p=0.04) (Figure 2).

At a median of 60 months, the disease free survival for the booster group was 96.2% vs 80.5% in the control group (p=0.037) (Figure 4). The recurrence rate for the booster group was 3.8% vs 18.9% in the control group (p=0.01).

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Figure 1: Toxicity

E75 Booster Demographics

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Age (median) 58 vs 54 0.37
Node Positive 67.2% 72.7% 0.04
Tumor Size (T2-4) 28.5% 39.2% 0.20
ER/PR negative 75.0% 78.2% 0.97
HER2/neu overexpression 34.0% 17.7% 0.03
HER2/neu underexpression 32.1% 21.4% 0.33
Hormonal Therapy 52.5% 73.0% 0.09
Chemotherapy 74.5% 72.2% 0.57
Trastuzumab Therapy 73.0% 81.0% 0.33

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Figure 3: E75-specific CD8 T cells

Figure 4: Disease Free Survival

At a median of 60 months, the disease free survival for the booster group was 96.2% vs 80.5% in the control group (p=0.037) (Figure 4). The recurrence rate for the booster group was 3.8% vs 18.9% in the control group (p=0.01).