Persistent Immunity and Survival after Immunization with a HER-2/neu (HER2) Vaccine

L.G. Salazar1, V. Goodell1, M. O’Meara1, K. L. Knutson1,2, Y. Dang1, C. dela Rosa1, K. A. Guthrie3, and Mary L. Diis1

1University of Washington, Seattle, WA, 2Mayo Clinic College of Medicine, Rochester, MN, 3Fred Hutchinson Cancer Research Center, Seattle, WA

INTRODUCTION

- Our initial studies demonstrated that breast cancer patients can develop significant levels of HER2 specific T cell immunity with active immunization.[1]
- HER2 breast cancer patients were immunized with HER2 peptide-based vaccines containing putative T helper epitopes.[1]
- HER2 vaccine-induced T helper responses resulted in development of o Persistent immunity at 1 year post-vaccination.
  - Intramolecular epitope spreading (ES) which may provide survival benefit.
- Few studies have evaluated the persistence of antigen-specific immunity at time points distant from completed vaccination.
- The goal of this study was to determine if patients previously immunized with HER2 peptide-based vaccines had persistent immunity years after active immunization and to assess their clinical outcome in terms of overall survival.

PATIENTS AND METHODS

Study population. This Long Term Follow-up (LTFU) study was approved by the University of Washington Human Subjects Division. The primary objective of the study was to obtain breast cancer patients previously enrolled in a placebo controlled trial of HER2 vaccine (n=38) and a placebo controlled trial of GM-CSF (n=18) to evaluate immunity, survival, and overall survival (OS). Patients eligible for the study must (1) have completed vaccine enrollment at least 1 year prior to vaccine enrollment and 1 year of follow-up, and (2) have at least 1 year of data on survival. Patients who were followed for <12 months were not included in the analysis. The study was conducted at the Fred Hutchinson Cancer Research Center. All study patients had persistent immunity years after vaccination, may be a critical parameter to monitor as a potential indicator of beneficial response.

RESULTS

- HER2 specific T cell immunity, including intramolecular ES within HER2 domains, persists years after the end of vaccination.
- Survival was significantly associated with the development of ES following vaccination.
- Median OS for study subjects (n=33) who developed ES was 84 months vs 25 months for subjects (n=16) not developing ES (p=0.036)(Figure 4).
- Multivariate analysis indicated that epitope spreading was an independent variable (p=0.05, HR=0.34) for prediction of overall survival in this population (Table 2).

CONCLUSIONS

- In multivariate analysis, epitope spreading elicited with active immunization was the only immune marker which was an independent predictor of overall survival.
- These data suggest that ES elicited with vaccination may be a marker associated with clinical outcome.
- Thus, development of ES following vaccination may be a critical parameter to monitor as a potential indicator of beneficial response.
- Vaccine development should focus on strategies designed to induce epitope spreading.
- HER2 specific T cell immunity, including intramolecular ES spreading within HER2 domains, persists years after the end of vaccination.

REFERENCES


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Table 1. Patient characteristics.

Table 2. Univariate and multivariate Cox proportional hazard models

Figure 1. HER2 specific T cell immunity including intramolecular epitope spreading within HER2 protein domains persists years after vaccination. T cell responses to HER2 peptide domains and their (control antigen) are shown. Each circle represents individual patient responses to either immunizing (o) or non-immunizing (x) antigens. Bold bars indicate the median. T cell responses to non-immunizing HER2 peptide domains were greater than T cell responses to immunizing HER2 peptide domains (p=0.16).

Figure 2. HER2 specific T cell immunity including epitope spreading within HER2 domains persists years after the end of vaccination. Long-term post-immunization ELISPOT responses (frequency of IFN-γ secreting cells in 10^6 PBMC) for HER2 peptide domains and it (control antigen) are shown. Each circle represents individual patient responses to either immunizing (o) or non-immunizing (x) antigens. Bold bars indicate the median. T cell responses to non-immunizing peptide epitopes were not significantly greater than maximal response to non-immunizing peptide epitopes (p=0.8).

Figure 3. Patients vaccinated with HER2 vaccines have improved overall survival. Kaplan-Meier curves comparing overall survival between all 52 study patients (solid line) and matched SEER stage matched historical controls from the SEER Database (dotted line) are shown. Vaccine study patients had significantly improved median overall survival of 49 months compared to a median overall survival of 40 months for the 16 study subjects who did not develop ES and was statistically significant (p=0.036).

Figure 4. Patients who develop intramolecular epitope spreading after vaccination have improved overall survival. Kaplan-Meier curves comparing OS between study patients who developed epitope spreading following HER2 vaccine vaccination (solid line) and study patients who did not ES (dotted line) are shown. Median OS for 35 study subjects who developed ES was 84 months compared to 25 months for the 16 study subjects who did not develop ES and was statistically significant (p=0.036).

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