Vaccination with the HER2-derived E75 Peptide Vaccine in Breast Cancer Patients May Confer Greater Benefit to Patients with Less Aggressive Disease

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BACKGROUND

We have conducted phase II trials of the HER2-derived E75 peptide vaccine given to breast cancer patients in the adjuvant setting. E75 (HER2: 369-377) is an immunogenic HLA-A2/A3-restricted peptide from the extracellular domain of the HER2 protein. When combined with the immunoadjuvant GM-CSF as a vaccine, E75 may reduce breast cancer recurrences. In combined clinical trial results, patients vaccinated with E75 had a 5.6% recurrence rate compared to 14.2% in controls at 20 months median follow-up (p=0.04).[1] However, the immunological benefit of vaccination was not durable, as the recurrence rates at 26 months median follow-up were 8.3% vs. 14.8% (p=0.15). This finding has initiated the use of booster vaccines, which appear to prolong clinical benefit.[2]

The E75 vaccine appears to have efficacy and has recently moved forward to phase III clinical trials. One remaining challenge lies in determining the ideal patient population to derive the greatest benefit from vaccination.

Use of the HER2 monoclonal antibody trastuzumab in the adjuvant setting has been shown to reduce breast cancer recurrence by 50% in HER2-overexpressing breast cancer.[3,4,5] In contrast, further analyses of the E75 vaccine suggest that this peptide vaccine may have greater clinical benefit in patients with low levels of HER2 expression.[6] With this observation, we hypothesized that breast cancer patients with less aggressive disease features vaccinated with the E75 peptide vaccine may derive more clinical benefit.

Adjuvant! for Breast Cancer is an on-line evidence-based tool used to estimate breast cancer-related mortality based on a patient's age, comorbidities, ER status, histological grade, tumor size, and nodal status.

In this analysis, we evaluate the clinical response in vaccinated patients with varying risk of recurrence based on individual clinicopathologic factors as well as the Adjuvant! for Breast Cancer 10 year mortality score.

METHODS

Our trials enrolled node positive or high-risk node negative breast cancer patients with any level of HER2 expression (IHC 1+, 2+, or 3+), rendered disease-free after standard adjuvant therapies. HLA-A2/A3$^+$ patients were vaccinated with E75 + GM-CSF while HLA-A2/A3$^-$ patients served as controls. The vaccine was given as 4-6 monthly intradermal inoculations. The primary endpoint was disease-free survival.

Recurrence rates were compared between vaccinated and control patients based on nodal status (node positive or node negative), HER2 expression (overexpression or low expression), histological grade (high grade or low-intermediate grade), and hormone receptor status (positive for either ER or PR or negative for both ER and PR).

Clinicopathologic factors for each enrolled patient were used to calculate the Adjuvant! Online 10 year mortality score (Adjuvant! for Breast Cancer, Version 8.0). Recurrence rates were compared between vaccine and control patients based on the Adjuvant! for Breast Cancer 10 year mortality score.

p-values were calculated using log-rank and chi-square tests.

RESULTS

187 patients have enrolled (vaccine=108, control=79). Vaccine and control patients were well-matched except vaccine patients had a greater percentage of patients negative for both estrogen and progesterone receptors (Table 1).

With 60 months median follow-up, the vaccine group experienced a 10.6% recurrence rate compared to 20.3% in the control group (48% risk reduction, p=0.098).

Recurrence rates for vaccine and control patients with different disease features (nodal status, HER2 expression, histological tumor grade, and hormone receptor status) are shown (Table 2).

Vaccinated patients had a mean Adjuvant! for Breast Cancer mortality score of 23.9 (SE ± 2.1) compared to 28.0 (SE ± 2.9) for control patients (p=0.26). Vaccine patients with mortality scores ≤55 had a 6.2% recurrence rate (6/97) compared to a 15.6% (10/64) in controls (p=0.05) (Table 3). In patients with Adjuvant! for Breast Cancer scores above 55, vaccine patients had a 45.5% recurrence rate (5/11) compared to 35.7% (5/14) for controls (p=0.70)

Table 1: Clinicopathologic features

	Vaccine	Control	p-value
	108	79	
Age (median)	57	53	0.26
Node Positive	49.1%	55.7%	0.38
Tumor Size (T2-T4)	34.3%	46.2%	0.13
Histological Grade 3	40.0%	39.5%	1.00
ER and PR negative	31.1%	17.7%	*0.04*
HER2 overexpression	31.7%	26.8%	0.50

Table 2: Recurrence Rates for Different Disease Features

		Control Patients		Vaccine Patients			
	Disease Feature	n	Recurrence Rate	n	Recurrence Rate	Risk Reduction	p
	All Patients	79	20.3%	108	10.6%	48%	0.098
Less Aggressive	Node Negative	35	18.4%	55	5.5%	70%	0.19
	HER2 Low Expression	52	25.1%	69	10.6%	58%	0.06
	Low or Intermediate Grade	46	21.2%	63	4.8%	77%	0.01
	ER or PR positive	65	19.7%	74	8.6%	56%	0.07
More Aggressive	Node Positive	53	22.9%	44	15.8%	31%	0.31
	HER2 Overexpression	19	15.8%	32	12.6%	20%	0.68
	High Grade	20	20.8%	42	20.6%	1%	0.96
	ER and PR negative	14	25.0%	33	15.2%	39%	0.65

Table 3: Recurrence based on Adjuvant! for Breast Cancer Mortality Score ≤ 55

	Recurrence	No Recurrence	%
Vaccine	6	91	6.2%
Control	10	54	15.6%

DISCUSSION

Breast cancers with more aggressive features or presenting at more advanced stages are more likely to evade the immune system and have more pronounced immunosuppressive effects. In contrast, less advanced disease may be better suited for active immunotherapy given a smaller volume of less aggressive disease.

The disease features evaluated in this study taken individually or in combination (e.g. Adjuvant! Online mortality score) appear to support the same conclusion—that peptide vaccines may confer greater clinical benefit in breast cancer patients with less aggressive disease. These findings may help define the ideal patient for adjuvant breast cancer peptide vaccines.

In the context of HER2 expression, these findings may suggest a future treatment paradigm of passive immunization (e.g. trastuzumab) in patients with HER2 overexpression and active immunization (e.g. peptide vaccine) in patients with lower levels of HER2 expression, offering an adjuvant immunotherapy option for all HER2-expressing breast cancer tumors.

CONCLUSIONS

In a phase II trial evaluating the HER2-derived E75 peptide vaccine in breast cancer patients in the adjuvant setting, vaccinated patients with node negative disease, lower levels of HER2 expression, lower grade tumors, hormone receptor positivity, or lower Adjuvant! Online scores appear to have lower rates of breast cancer recurrence. These findings suggest that patients with less aggressive disease features may derive greater clinical benefit from vaccination compared to patients with more aggressive disease features.

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DISCLOSURE

Dr. Peoples has inventor rights to E75. This vaccine has been licensed for commercial development based on clinical trial results. He is entitled to financial proceeds associated with this license per Federal policy. Dr. Peoples also consults in the development of the vaccine.

All other authors have no relevant financial disclosures