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Journal of Surgery & Transplantation Science

Research Article

Outcomes with Combination Neo-adjuvant Chemotherapy for HER2Neu Over-Expressed Breast Cancer

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Submitted: 02 March 2017

Accepted: 10 May 2017

Published: 13 May 2017

ISSN: 2379-0911

Keywords

- Breast cancer
- HER2Neu
- Estrogen receptor
- Neo-adjuvant

Abstract

Certain breast cancers that over-express HER2Neu (H2N) are now considered for neo-adjuvant chemotherapy using dual anti-H2N targeted drugs. Since January of 2013, 14 women with H2N over-expressed breast cancer were treated with a regimen including trastuzumab (Herceptin) and pertuzumab (Perjeta) prior to definitive surgery in our institution. 7 of 14 (50%) were estrogen receptor negative (ER-/H2N+) while the other 50% were ER+/H2N+. 9 of 14 (64%) had six cycles of chemotherapy prior to surgery while the remaining had four or five cycles prior to surgery. 9 of 14 (64%) had a mastectomy while 5 of 14 (36%) had breast conserving therapy. Final pathology showed that 50% had a complete pathologic response (pCR), while the remaining patients all had a significant partial response. Patients who received all six neo-adjuvant cycles had a higher rate of pCR. 6 of 14 (43%) patients had full axillary lymph node dissections (ALND); only 2 of the 6 (33%) contained residual tumor. 7 of 14 (50%) patients had sentinel lymph node biopsies (SLNB) done during definitive surgery. No SLNB specimens contained tumor. We observed a very low rate of residual axillary nodal disease suggesting that ALND may not always be necessary in these cases.

ABBREVIATIONS

ER: Estrogen Receptor; H2N: HER2Neu; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Biopsy; pCR: Complete Pathologic Response; IHC: Immno-Histochemistry; FISH: Fluorescence in situ Hybridization

INTRODUCTION

In 2014, the American Cancer Society reported 805,000 women newly diagnosed with cancer; breast cancer being the most common type representing 29% of new cancer cases [1]. Breast cancer also represents the second leading cause of cancer related death amongst women in the US [1]. Over the years, we have come to understand breast cancer as a heterogeneous group of disease which requires different approaches based on specific molecular signatures [2]. H2N is a proto-oncogene detected by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) and has prognostic and therapeutic value when treating breast cancer. Invasive breast cancers over-expressing H2N account for up to 15%-25% of all breast cancers [3,4]. These tumors tend to be more aggressive in terms of morphology, proliferation, and metastasis [3]. H2N over-expression does, however, offer a target for monoclonal antibody based therapy which can be used to augment chemotherapy treatment [4,5]. Advances in translational science have led to the development of a large spectrum of H2N directed therapies.

Studies have shown that targeting H2N receptors combined with chemotherapy offers benefits to patients with metastatic H2N+ breast cancer compared with chemotherapy alone [4,6]. This finding led to the use of chemotherapy and anti-H2N targeted therapies in the neo-adjuvant setting with promising outcomes. Over the last several years, studies have explored using dual anti-H2N targeted therapy paired with cytotoxic agents to augment treatment effects. Several large clinical trials have shown outstanding results with the use of dual anti-H2N receptor targeting combined with cytotoxic chemotherapy in the neo-adjuvant setting [4,7,8].

Complete pathological response (pCR) has been used as the primary endpoint in most studies as this is directly correlated with improved survival [4]. The preferred definition of pCR is the absence of residual invasive disease in both the breast and lymph nodes after pathological analysis. Some studies count residual in-situ disease as pCR while others do not. Using pCR as a primary endpoint allows for accelerated studies in neo-adjuvant

treatment as pCR predicts long-term survival benefit in multiple previous studies in various settings.

Previous trials for dual anti-H2N therapy in the neo-adjuvant setting suggest that patients with pCR are more likely to have longer overall survival than patients without pCR [7]. Most studies now accept pCR as a surrogate for long term outcomes [7]. The pCR rate is increased from 20-30% with cytotoxic chemotherapy and single anti-H2N therapy to around 45% with cytotoxic chemotherapy and dual anti-H2N therapy [4]. The cytotoxic chemotherapy component is also important; however, as dual anti-H2N blockade alone affords only a 17% pCR in the Neo SPHERE trial [4]. The TRYPHAENA trial augmented the neo-adjuvant therapy with cytotoxic chemotherapy and dual anti-H2N therapy for a full six cycles with minimal cardiac toxicity and produced a 66% pCR [5]. The cytotoxic chemotherapy component appears to be essential, as dual anti-H2N blockade alone without a concurrent taxane or platinum agent affords only a 17% pCR [4].

Traditionally, county hospital serve as 'safety-nets' which treat patients who present at a later stage of disease. In such patient populations, the efficacy of neo-adjuvant therapy may be pivotal to good outcomes. In our institution, approximately 40% of breast cancer patients present with stage II or III disease. Nearly 40% of patients undergoing SLNB in our institution have positive axillary disease. These figures demonstrate that our facility cares for a high-risk population of patients, who may derive significant benefit from new therapeutic approaches. For this reason we chose to study the impact of neo-adjuvant dual anti-H2N chemotherapy on surgical outcomes in our county hospital breast cancer patients.

MATERIALS AND METHODS

After institutional IRB approval was obtained, we used our prospectively maintained database to retrospectively identify women who were treated with neo-adjuvant dual anti-H2N targeted therapy and underwent definitive surgery in our institution. Pre-treatment imaging consisted of ultrasound, MRI, and/or mammogram. H2N over-expression was determined initially by IHC. Negative (1+) IHC was confirmed with FISH at the physician's discretion. Equivocal (2+) IHC was always confirmed with FISH. Positive (3+) IHC was rarely confirmed by FISH. On the basis of previously published studies, patients with clinical Stage II or III disease and H2N over-expressed tumors were considered for neo-adjuvant dual anti-H2N therapy. Some patients with bone-only limited metastatic disease were included for this analysis as they frequently underwent excision of the primary breast tumor. All patients were treated in a neo-adjuvant fashion with trastuzumab (Herceptin) and pertuzumab (Perjeta) dual anti-H2N therapy. This was combined with a cytotoxic chemotherapy in the form of either docetaxel or nab-paclitaxel and, if the patient was able to tolerate, carboplatin. Dose de-escalation and stopping components of the cytotoxic therapy was left up to the discretion of the treating medical oncologist. Typically, adding carboplatin, also known as TCHP protocol, was reserved for younger patients with aggressive tumors, as this therapy is often poorly tolerated. Most patients were able to tolerate dual anti-H2N therapy with a taxane alone, also known as the THP protocol. During the study period, the number of cycles of chemotherapy during neo-adjuvant treatment was determined by the treating oncologist. The most commonly recommended number of neo-adjuvant cycles used in prior studies is six although some patients received less than six cycles based on the discretion of the medical oncology team. All patients were generally recommended to have a year of adjuvant trastuzumab after surgery.

Data was analyzed for hormone receptor status, type and duration of neo-adjuvant treatment, clinical stage, surgical therapy, and pathologic outcomes. Our primary endpoint was the rate of pCR after definitive surgical therapy. pCR was defined as no residual invasive or in-situ disease in the breast or axillary nodes. The impact of molecular subtype and neo-adjuvant treatment on pCR was evaluated. We also examined the rate of axillary nodal involvement in patient with and without clinically involved axilla at presentation. Any patient with clinically positive nodes before neo-adjuvant therapy was recommended for a full ALND regardless of clinical response to therapy. Patients with clinically negative nodes before and after neo-adjuvant treatment were offered SLNB. Finally, we compared the type of surgery performed in these patients with their pathologic outcomes to determine if surgical therapy could be tailored differently in this population.

RESULTS

The first patient treated with neo-adjuvant dual anti-H2N therapy was in January 2013. Fourteen patients have been treated since that point and were included for analysis. 7 of the 14 (50%) were ER receptor negative, and 7 of 14 (50%) were ER receptor positive. 9 of 14 (64%) had six cycles of neo-adjuvant chemotherapy prior to surgery while the remaining 5 of 14 (36%) had either four or five cycles. Neo-adjuvant therapy caused side-effects including bone discomfort, fatigue, diarrhea, mild neuropathy, changes in taste, myalgias, and neuralgias. These were generally mild. The 5 patients who underwent less than six cycles prior to surgery had been recommended to stop neo-adjuvant therapy based on excellent clinical response and not intolerance to the therapy.

All of our patients had a clinical response to neo-adjuvant therapy based on clinical exam. 9 of 14 (64%) of the patients had a mastectomy and 5 of 14 (36%) had breast conserving surgery. No patient who underwent a mastectomy had greater than a 5 cm residual tumor or multifocal disease on pathology and, in retrospect, could have been considered for breast conservation. After definitive surgical treatment, final pathology showed a 50% (7 of 14) pCR. 2 of 7 (29%) patients with ER+H2N+ molecular subtypes had pCR. Conversely, 5 of 7 (71%) of ER-H2N+ patients showed pCR. Thus, the ER-HRN+ genotype were associated with improved response rate. The 7 patients without a pCR had tumor shrinkage percentages ranging from 27% to 95%. This was calculated based on imaging size versus pathologic size: [1 – (pathologic size/greatest imaging size)]. One patient with inflammatory cancer could not characterize the tumor size adequately prior to neo-adjuvant therapy, was found to have residual invasive disease at surgery, and was not used in the tumor shrinkage calculations. 4 of the 5 (80%) patients who did *not* complete all 6 cycles of neo-adjuvant therapy did not have a pCR. Thus, completing six cycles of neo-adjuvant therapy was associated with an improved chance of pCR.

All but one of the patients had axillary nodal evaluation at surgery. This single patient had metastatic bone-only disease and the primary tumor was removed without axillary evaluation. 7 of 14 (50%) patients had SLNB done during definitive surgery. No SLNB specimens contained tumor. 6 of 14 (43%) patients had full ALND due to clinically positive nodes at the time of diagnosis. Of the ALND specimens, only 2 of the 6 (33%) contained residual tumor; one specimen had 1 positive node, and the other specimen had 2 positive nodes. Overall, only 2 of 14 (14%) of the specimens contained nodal disease after neo-adjuvant therapy.

DISCUSSION

We observed a pCR rate of 50% of our patients treated with neo-adjuvant dual anti-H2N chemotherapy. This is similar to rates seen in previous trials [4,5,8]. In addition, our cohort had an excellent clinical response to neo-adjuvant therapy with a tumor shrinkage rate of 27% to 95% in patients who did not enjoy a pCR. No patient had residual disease over 5 cm in size. This observation suggests that breast conserving therapy may be an option for women even if they were not candidates before neo-adjuvant treatment. As 64% of women treated thus far in our institution underwent mastectomy, stronger consideration for breast conservation will be given here forward for our patients.

In our population, 80% of patients who received less than 6 cycles of neo-adjuvant treatment had residual tumor at the time of surgery. Dual anti-H2N therapy does not currently have an approved indication in the postoperative adjuvant setting. Thus, without the full six cycles prior to surgery, patients are not currently receiving two full treatments of dual blockade which may impact long term outcomes. The hormone receptor status also greatly influences the pCR rate. Similar to previous studies, we showed that the pCR rate was only 29% in ER+H2N+ molecular subtypes whereas ER-H2N+ tumors enjoyed a 71% pCR rate [7].

It appears that axillary lymph nodes respond to neo-adjuvant chemotherapy in a fashion similar to the primary tumor in the breast. Considering the vigorous responses of primary tumors, the outcomes and management of the axillary lymph nodes in this patient population should be re-examined. The discrepancy in surgical management of axillary lymph nodes after neo-adjuvant therapy has been previously documented [8]. However, to our knowledge there are no specific data published focusing on the histological status of the axillary nodes in patients with H2N over-expressed tumors treated with dual targeted therapy. In our data, the six patients who underwent ALND all had clinically positive nodal disease prior to neo-adjuvant therapy yet only two had residual low-volume disease on pathology. No patient with a sentinel lymph node biopsy during the definitive surgery was found to have axillary metastasis. Given the overall positive sentinel lymph node rate of nearly 40% in our institution, this implies a positive response of the axillary nodes to neo-adjuvant therapy as well. The ACOSOG Z1071 (Alliance) trial looked at rates of false negative SNLB in patients with clinically positive axillary nodes who received neo-adjuvant chemotherapy. Their analysis suggests that 10% of patients would have had a false negative SLNB had they not had complete ALND [9]. Although our cohort is small, our results suggest the possibility that dual anti-H2N therapy is efficacious enough to be considered separately from other forms of neo-adjuvant therapy in assessing the possibility of using SLNB in patients with clinically positive nodes who have a good clinical response to treatment.

The main weakness of this study is the small sample size. Similar results have been shown with much larger data sets as referenced. As such, this study was intended as an audit of our own patient's outcomes with similar treatment with the hopes of directing our future care. In our institution, there are three main considerations we intend to pursue when treating H2N over-expressed disease. First, breast conserving therapy for patients with tumors over 5cm prior to neo-adjuvant therapy may be an option. Second, all patients should receive 6 cycles of neo-adjuvant therapy when possible. And last, sentinel lymph node biopsy with selective ALND may be appropriate in more patients than our current practice standards permit.

Based on the amount of H2N over-expression and patients presenting with Stage II or III disease, however, nearly 200 women with breast cancer were evaluated to produce the fourteen patients evaluated in our study. We plan to continue to collect data to increase our sample size over time, however it is noteworthy that our patients attained a similar rate of pCR while presenting with more advanced disease.

An additional weakness in this study was the occasional minor discrepancies in pre-treatment tumor size when multiple imaging modalities were employed. A more standardized imaging protocol would be beneficial to determine a more precise expected tumor regression measurement.

CONCLUSION

Treatment with neo-adjuvant dual anti-H2N therapy afforded a clinical response of 50% in our institution. The pCR rate was even higher in patients with ER-H2N+ tumors. In our population, the rate of residual disease in the axillary nodes after neo-adjuvant therapy was only 14%; residual axillary disease was only seen in the nodes that were clinically positive prior to treatment. Patients with clinically positive axillary nodes at presentation, who enjoy a good clinical response to neo-adjuvant chemotherapy, may be good candidates for SLNB as opposed to full ALND.

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Cite this article

Losh J, Waxman K, Slater E, Ouwendijk R, Kim D, et al. (2017) Outcomes with Combination Neo-adjuvant Chemotherapy for HER2Neu Over-Expressed Breast Cancer. J Surg Transplant Sci 5(2): 1050.