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Targeted Agents for HER2-Positive Breast Cancer: Optimal Use in Older Patients

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Abstract

Her-2 gene is over expressed in 15-20 percent of all breast cancers. With the advent of Her-2 directed therapies, Her-2 overexpression is no longer considered an adverse prognostic factor. Despite significant improvements in clinical outcomes with use of trastuzumab, women over the age of 65 remain underrepresented in most clinical trials. Cardiac safety in the elderly women is a major concern because of preexisting comorbidities. However, many studies suggest that the elderly patients with Her-2 positive disease derive the same benefit from trastuzumab as do their younger counterparts in both adjuvant and metastatic setting. There is limited data guiding safety and efficacy of other Her-2 inhibitors such as pertuzumab and TDM-1 in elderly patients, however, in general, these drugs have a favorable toxicity profile.

1. INTRODUCTION

Her-2 protein is over expressed in 15-20 percent of all breast cancers.[1-5] However, there are some studies, which report the incidence to be slightly lower in the elderly population.[6] Her-2 positivity is defined at immunohistochemical (IHC) score of 3+ or fluorescent in-situ hybridization (FISH) positivity (ratio of Her-2:CEP17 2). Her-2 overexpression was historically considered a predictor of poor clinical outcome.[7, 8] However, with the advent of specific Her-2 directed therapies, there have been significant improvements in outcomes of Her-2 positive breast cancer. Her-2 directed therapy in combination with chemotherapy has become the standard of care for Her-2 overexpressing breast cancer. However, in elderly populations, there is a concern for increasing toxicity, especially cardiotoxicity, when these patients also receive anthracycline-based chemotherapy regimens.

In this article, we will discuss the benefits of addition of Her-2 directed therapy in elderly patients in neoadjuvant, adjuvant and metastatic setting. We will also discuss toxicity of Her-2 directed therapy, particularly cardiac toxicity in this age group.

2. TRASTUZUMAB

There are eight big clinical trials, which demonstrate improvement of both progression free survival (PFS) and overall survival (OS) when trastuzumab is added to chemotherapy in the

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8. COMPLIANCE WITH ETHICAL STANDARDS

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adjuvant setting.[9-15] Patients over the age of 60 were underrepresented in these trials. In two of these trials, National Surgical Adjuvant Breast and Bowel Project-31 (NSABP-31) and N9831 (Figures 1 and 2), approximately 16% of the patients were 60 years of age. NSABP-31 compared four cycles of adjuvant doxorubicin (A) and cyclophosphamide (C) followed by four cycles of 3-weekly paclitaxel (T) with AC followed by concomitant paclitaxel and trastuzumab. Trastuzumab was continued for a total of 52 weeks. N9831 was a three arm study: AC followed by 12 cycles of weekly T (arm A); AC→ T followed by 52 weeks of trastuzumab (arm B); AC→T with concomitant trastuzumab which was continued for 52 weeks (arm C). Arm B was subsequently excluded from final analysis. In the joint analysis of these two trials, there was a statistically significant improvement in the disease free survival (DFS) (3 years DFS 87% vs. 75%, HR 0.48) and OS (3 year OS 94.3% vs. 91.7%, HR 0.67) for all age groups with the addition of trastuzumab. After a median follow-up of 3.9 years, this improvement in DFS and OS was also observed in the over 60 subgroup and was highly statistically significant (DFS HR 0.52: 95% CI, 0.45-0.60 and OS HR 0.61: 95% CI, 0.50-0.75).[16]

In a recently published trial, patients with stage I Her-2 positive breast cancer with the primary tumor measuring up to 3 cm in the greatest dimension (patients with micrometastases in a single axillary lymph node were eligible if an axillary dissection was completed without further evidence of lymph node involvement), were treated with paclitaxel for 12 weeks combined with trastuzumab, which was then continued for a total of 52 weeks. The DFS after 3 years of follow up was 98.7%. 33.7% of patients in this trial were over the age of 60. Although follow-up was short, this trial demonstrates high efficacy of paclitaxel-trastuzumab combination in stage I patients in whom anthracycline-based therapies may be safely avoided. [17]

In the trastuzumab pivotal phase III trial, 469 women with HER2+ metastatic breast cancer were randomized to standard chemotherapy alone (doxorubicin or epirubicin in combination with cyclophosphamide) versus chemotherapy plus trastuzumab. The addition of trastuzumab to chemotherapy was associated with longer TTP (7.4 months vs. 4.6 months, $p<0.001$), a higher ORR (50% vs. 32%, $p<0.001$), a longer duration of response (9.1 months vs. 6.1 months, $p<0.001$), a lower rate of death at one year (22% vs. 33%, $p=0.008$), a longer OS (25.1 months vs. 20.3 months, $p=0.01$) and a 20% reduction in the risk of mortality.[18] Based on this trial, trastuzumab was approved in combination with paclitaxel for first-line treatment of HER2+ MBC in 1998. Other combinations shown to be effective in this setting include docetaxel plus trastuzumab [19, 20] and vinorelbine plus trastuzumab [21]. Although efficacious, anthracycline/trastuzumab combinations are not indicated outside clinical trials in MBC due to increased risk of cardiac toxicity [22].

2.1 CARDIAC SAFETY OF TRASTUZUMAB

Her-2 signaling is involved in myocardial hemostasis and therefore Her-2 blockade is associated with myocardial injury.[23] Cardiac dysfunction from trastuzumab is often considered reversible and not associated with higher cumulative dose of trastuzumab. In contrast, anthracyclines cause oxidative damage leading to myocyte cell death and often lead to irreversible cardiac injury. Myocardial injury from anthracyclines is dose-dependent and

cumulative in nature.[24-27] Recent studies have suggested that ERB-2 (Her-2) expression up-regulates anti-oxidant enzymes, reduces basal levels of anti-oxidant species in the myocardium and prevents free-radical injury induced by doxorubicin.[28-30] Therefore, Her-2 blockade predisposes the heart to anthracycline-induced damage.[31]

No standard guidelines exist on management of trastuzumab cardiotoxicity since it is not systematically treated in all circumstances. However, beta-blockers (BB) and ACE inhibitors have some role in management. In the setting of BB and ACEI, patients can usually be re-challenged with trastuzumab without worsening heart failure.[29] In recent years, the reversibility of trastuzumab cardiotoxicity has been debated especially when used with anthracyclines. In a study performed by cardiac review and evaluation committee, 82 out of 83 patients treated with trastuzumab-based therapies and developed cardiac dysfunction were treated with heart failure therapies such as ACEI and BB. Treatment outcomes differed in the group treated with trastuzumab and AC versus that treated with trastuzumab and paclitaxel. Eight out of 39 patients in the H+AC group continued to display significant cardiac functional impairment (NYHA class III) following medical therapy while all 12 patients treated with trastuzumab + paclitaxel recovered. Moreover, in heavily pretreated patients receiving single agent trastuzumab, less impressive recovery in cardiac function is observed. [23]

In the cardiac safety analysis of HERceptin Adjuvant (HERA) trial, which compared one or two years of trastuzumab with observation alone, the incidence of significant cardiac events leading to discontinuation of trastuzumab was 5.2% in the group treated with trastuzumab for one year and 9.4% in the group treated with trastuzumab for two years. The incidence of severe congestive heart failure (CHF) was 0.8% in the trastuzumab group versus 0% in observation group. Incidence of significant decline in left ventricular ejection fraction (LVEF) was 4.1% versus 0.9%. Only 15% of the patients enrolled in this trial were older than 60 years.[32]

In a retrospective review analysis of seven phase 2 and 3 trials with trastuzumab, the incidence of cardiotoxicity was found to be 2% with trastuzumab alone, 2-13% when trastuzumab was combined with paclitaxel and 27% when combined with anthracyclines. Trastuzumab related toxicity usually improved with standard heart failure management in most cases.[28, 33-35, 18, 36, 23] The rate of symptomatic CHF ranges from 1.5 to 5.1% while the rates of asymptomatic declines in LVEF ranges from 3.5-19% in most studies.[11, 37-39, 15, 40] However, in the Surveillance, Epidemiology and End results (SEER) and Texas cancer registry medicare database analysis of 2203 elderly patients (greater than 66 years old) treated with trastuzumab, CHF rates were found to be 29.4% in trastuzumab users compared to 18.9% in non-trastuzumab users, a number which is much higher in the above mentioned studies which mostly excluded elderly patients. Older age (>80 years), hypertension, coronary artery disease and weekly administration of trastuzumab were the risk factors associated with CHF in this study.[41] In another larger series of 2046 trastuzumab users, the incidence of cardiotoxicity was 0.2% in women <50 years of age, while it was 10% in women >70 years of age irrespective of cardiovascular status. (HR for cardiac toxicity was 11.3 for women >70 years (95% CI 3.5-36.6)).[42]

In a small trial of 59 Her-2 positive elderly patients (greater than 70 years, median age 76), there were 10 cases of cardiotoxicity. Seven out of 10 patients had received concomitant chemotherapy with trastuzumab. There was only one case of symptomatic CHF. Hypertension and obesity were risk factors for cardiotoxicity in this trial.[43]

However, in the paclitaxel-trastuzumab study, only 2 patients (0.5%; 95% CI, 0.1-1.8) had grade 3 systolic dysfunction during active therapy which resolved after discontinuation of trastuzumab. Clinically significant asymptomatic decline in function was seen in 13 patients (3.2%; 95% CI, 1.7-5.4).[17] This implies that, higher cardiac toxicity observed in the trastuzumab subgroup in the HERA, NSABP-31 and N9831 trials is likely secondary to the concomitant administration of anthracyclines.

Guarneri et al. looked at 218 patients who were treated with trastuzumab for metastatic breast cancer at MD Anderson Cancer Center for one year or longer. Twenty percent of these patients were older than 60 years of age. Older age group did not have proportionally greater cardiac toxicity in this study. Out of all patients who suffered from a cardiac event, only 16.3% were older than 60 years.[44]

There is increasing evidence that trastuzumab based chemotherapy, when chosen appropriately, is safe and efficacious even in elderly populations. Cardiotoxicity is the most common reason why life saving anti-Her-2 therapy is withheld from patients. In a retrospective review of 573 patients, 92 (16%) of whom developed treatment induced cardiotoxicity (74 patients were asymptomatic), treatment was continued in 31 patients (all asymptomatic with EF > 50%). None of these patients subsequently developed heart failure. [45]

3. PERTUZUMAB

Pertuzumab is a humanized monoclonal antibody that targets the extracellular dimerization domain of Her-2 receptor. It disrupts formation of Her-2 homodimers as well as Her-1/Her-2 and Her-2/ Her-3 heterodimers , thus blocking intracellular signaling through mitogen activated protein kinase pathway (MAP kinase) and phosphatidylinositol-3 kinase (PI3 kinase) pathway, ultimately causing cell cycle arrest and apoptosis.[46]

It was first studied in metastatic Her-2 positive breast cancer which had progressed on trastuzumab only and was found to be well tolerated with LVEF remaining close to baseline when combined with trastuzumab. Objective responses were seen in 24.2% patients while stable disease was achieved in 25.8%.[47]

It is FDA approved for use in combination with trastuzumab and taxane as a first line therapy in the metastatic setting as well as in the neoadjuvant setting.

In the phase 3 CLEOPATRA trial, the combination of pertuzumab, trastuzumab and docetaxel was compared to placebo, trastuzumab and docetaxel in metastatic Her-2 positive breast cancer.[48] Out of 808 patients enrolled, 129 patients were 65 years of age or older. Results of subgroup analysis of CLEOPATRA reveal that these elderly patients have progression free survival benefit when pertuzumab is added (PFS 21.5 months versus 10.4

months HR 0.52, 95% CI 0.31-0.86). However, the incidence of diarrhea, fatigue, dysgeusia, decreased appetite, asthenia and vomiting is more frequent in the older subgroup. Age had no statistically significant association with left ventricular systolic dysfunction in this trial. Given the excellent efficacy and favorable toxicity profile of pertuzumab and trastuzumab in combination with taxanes, it should be considered first line of treatment for metastatic disease in the elderly population.[49]

Cardiac safety profile of pertuzumab has been found to be favorable in clinical trials.[50] Cardiac safety of neoadjuvant trastuzumab plus pertuzumab in combination with both anthracycline and non-anthracycline chemotherapy was tested in the phase 2 TRYPHAENA study. This was a three arm study randomizing patients to the following three arms: ARM A: 5-fluorouracil epirubicin cytoxan+ herceptin + pertuzumab (FEC+H+P)X 3→ docetaxel (T) +H+PX3; ARM B: FEC→ T+H+PX 3; and ARM C: T+carboplatin+ H+P. The incidence of significant LVEF decline to >10% below baseline or <50% was low in all three arms (5.6%, 5.3% and 3.9% in arms A, B and C respectively).[51] The currently enrolling BERENICE trial (NCRN 3113) is a multicenter phase 2 trial evaluating cardiac safety of AC followed by THP in the neoadjuvant setting in the locally advanced, inflammatory or early stage Her-2 positive breast cancer.

4. TRASTUZUMAB EMTANSINE

Trastuzumab emtansine (Kadcyla) is an antibody drug conjugate which is directed at the domain IV of extracellular domain of Her-2. It consists of a microtubule inhibitor maytansine, conjugated to trastuzumab via a thioether linker. Kadcyla is approved for use in Her-2 positive metastatic breast cancer both in second line and third line setting as per the EMILIA and TH3RESA trials respectively.[52, 53] Median age of patients enrolled in both these trials were much younger and definite studies have not been done in older patients. However, in both these phase 3 trials, the drop of LVEF <50% or greater than 15% of baseline value occurred in 1.7% and 1% of patients respectively.

In a recently published feasibility study, trastuzumab emtansine was administered for a period of 1 year after adjuvant or neoadjuvant chemotherapy with anthracycline based regimen in Her-2 positive early breast cancer. Out of 153 patients, only 11.8% were older than 65 years. Only 2.7% of the patients experienced asymptomatic decline in LVEF by >10 percentage points of <50%.[17] This is a favorable cardiac safety profile compared to the published trastuzumab trials.[14, 40]

Based on encouraging clinical data on efficacy and favorable toxicity profile of Kadcyla in adjuvant setting, the ongoing phase 2 ATEMPT trial (NCT01853748) compares paclitaxel and herceptin regimen to Kadcyla in early stage, node negative, Her-2 positive breast cancer.

The favorable toxicity profile of Kadcyla makes it an attractive option for use in elderly patients.

5. LAPATINIB

Lapatinib is a dual Her-1/Her-2 blocking agent which is approved for use in combination with capecitabine in patients with Her-2 positive metastatic breast cancer who have already received anthracycline, taxane and trastuzumab.[54] The efficacy and safety of this combination was evaluated in elderly population in a small retrospective multicenter study of 26 patients. Median age was 69 years (range : 65-82 years). Median follow up was 10 months. Overall Response Rate (ORR) was 33.4% with 1 complete response. Median PFS was 7 months (95% CI 5-8) and OS was 15 months (95% CI 11-19). Grade 3 and 4 toxicities included diarrhea (7.6%), hand-foot syndrome (3.8%) and fatigue (11.5%). No cardiac toxicities were reported.[55]

The recently reported NEOALTTO trial, adding lapatinib to trastuzumab and paclitaxel improved pCR rates in the neoadjuvant setting compared to paclitaxel/trastuzumab, paclitaxel/lapatinib. However, there was no difference on event free or overall survival.[56]

Based on the encouraging results of the NEOALTTO trial, the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial was a phase 3 trial of 8381 patients designed to compare three regimens of oral lapatinib (T+L, L alone or T→ L) to T alone. L +T arm was tested against T for superiority and the T→ L arm was tested for non-inferiority. The DFS improvement was non-statistically significant in both arms. HR for DFS was 0.84 (97.5% CI, 0.70-1.02; P=0.048; 4-yr DFS%=88% vs. 86%) for L+T vs. T and 0.93 (97.5% CI, 0.76-1.13; non-inferiority P=0.044; 4-yr DFS%=87% vs. 86%) for T→L vs. T. This was a disappointing observation, considering near doubling of pCR rates was observed in with dual T+L blockade in the neoadjuvant setting.[57]

Lapatinib was initially reported to have no cardiotoxicity[58] but subsequent reports revealed low incidence of cardiac toxicity, which is reversible in nature.[33] One of the suggested mechanism of heart toxicity of lapatinib is lack of specificity to kinase inhibition which could result in on-target and off-target collateral effects leading to myocyte damage. [59] In a comprehensive analysis, 3689 lapatinib treated patients enrolled in 49 trials; asymptomatic cardiac events were reported in 53 patients (1.4%) and symptomatic grade III and IV systolic dysfunction was observed only in 7 patients (0.2%) treated with lapatinib. [60]

6. PHOSPHATIDYL INOSITOL 3 KINASE (PI3 kinase) INHIBITORS

Although trastuzumab is highly efficacious in the metastatic Her-2 positive breast cancer, eventually most patients progress due to development of secondary resistance. Activation of PI3/AKT/mTOR pathway is thought to be one of the resistance mechanisms to trastuzumab. Everolimus is an mTOR inhibitor which has shown to potentiate the activity of trastuzumab in phase 1 and 2 studies.[61-63] In the Breast Cancer trials of Oral Everolimus-3 (BOLERO) 3 trial, 569 patients with metastatic Her-2 positive breast cancer were treated with vinorelbine and trastuzumab plus placebo versus everolimus. Everolimus group significantly prolonged PFS (7 months versus 5.78 months, HR 95% CI 0.78, 0.65-0.95, p=0.0067). However, there were significantly higher grade 3/4 toxicities in the everolimus

group.[64] Although 19% of the patients receiving everolimus were more than 65 years of age, the toxicities were not stratified according to age yet. However, in the BOLERO 2 study which compared everolimus + exemestane to exemestane alone for metastatic hormone positive breast cancer, elderly age group had the same incidence of frequency of dose modifications due to adverse events regardless of age. There was a lower incidence of headache, stomatitis, rash, nail changes, hypercholesterolemia and elevated hepatic enzymes in the elderly age group.[65] However, there is a concern for increasing toxicity when everolimus is used in the elderly patients due to its metabolism via cytochrome P450 pathway and presence of poly-pharmacy in this population.

7. CONCLUSION

With the increasing life expectancy, the number of patients with breast cancer who belong to older age group will rise. Since addition of Her-2 directed therapy has shown improvement in survival when used in elderly in both adjuvant and metastatic setting, chronological age should not be a determinant of who gets Her-2 directed therapy. Instead, functional parameters such as performance status and geriatric assessment tools should be used to determine who should be offered Her-2 directed therapy. Every effort should be exercised to reduce cardiac toxicity by exclusion of patients with significant cardiac risk factors and optimizing cardiac parameters.

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Figure 1. NSABP B-31

<http://www.nsabp.pitt.edu/B-31.asp>

AC-Adriamycin (doxorubicin) /Cyclophosphamide

Figure 2. N9831

<https://www.allianceforclinicaltrialsnoncology.org/main/cmsfile?cmsPath=/Public/Results/files/N9831-results-03142013.pdf>