Review

De-escalating Treatment Strategies for Patients with Human Epidermal Growth Factor Receptor-2 (HER2)-Positive Early-Stage Breast Cancer

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Simple Summary: Almost one in five patients with breast cancer have an aggressive subtype that expresses Human Epidermal Growth Factor-2 (HER2) receptor. The introduction of anti-HER2 therapy, like trastuzumab and pertuzumab, had dramatically improved its treatment outcomes. However, such therapy is lengthy, costly, and can result in substantial cardiac toxicities. In this review, we discuss ways to de-escalate anti-HER2 therapy by shortening treatment course, to less than the 12-month standard, or minimize companion chemotherapy. New molecular tools are emerging that should help physicians select which patients with HER2-positive breast cancer benefit most from aggressive and lengthy treatment regimens utilizing single or dual anti-HER2 therapy alone or in combination with chemotherapy.

Abstract: Almost one fifth of breast cancer cases express Human Epidermal Growth Factor-2 (HER2), and such expression is associated with highly proliferative tumor and poor prognosis. The introduction of anti-HER2 therapies has dramatically changed the natural course of this aggressive subtype of breast cancer. However, anti-HER2 therapy can be associated with substantial toxicities, mostly cardiac, and high cost. Over the past few years, there has been growing interest in de-escalation of anti-HER2 therapies to minimize adverse events and healthcare costs, while maintaining the efficacy of treatment. Data from clinical observations and single-arm studies have eluted to the minimal impact of anti-HER2 therapy in low-risk patients, like those with node-negative and small tumors. Though single-arm, the APT trial, in which patients with node-negative, small tumors received single-agent paclitaxel for 12 cycles plus trastuzumab for 1 year, was a practice-changing study. Several other recently published studies, like the PERSEPHONE trial, have shown more convincing data that 6 months of trastuzumab is not inferior to 12 months, in terms of disease-free survival (DFS), suggesting that de-escalating strategies with shorter treatment may be appropriate for some low-risk patients. Other de-escalating strategies involved adaptive, response-directed approach, and personalized therapy that depends on tumor genomic profiling.

Keywords: breast cancer; HER2; trastuzumab; pertuzumab; de-escalation; personalized medicine; targeted therapies; adjuvant therapies; neoadjuvant therapies

1. Introduction

Breast cancer continues to be the most diagnosed cancer among women worldwide [1,2]. Almost one in five women with breast cancer has human epidermal growth factor receptor-2 (HER2)-positive disease, which means over 450,000 cases are diagnosed every year worldwide [3–5]. HER2-positive breast cancer is known for its aggressive clinicopathological features and poor prognosis [6,7]. However, this aggressive behavior can be offset by the utilization of anti-HER2 targeted therapy. In one of the earliest clinical trials examined the clinical impact of anti-HER2 therapy, Slamon et al. had shown that the prognosis of patients with HER2-positive metastatic breast cancer, when treated with

trastuzumab, become similar to those with HER2-negative disease [8]. In early-stage breast cancer (EBC), several major clinical trials and meta-analyses had established the great benefit of trastuzumab and pertuzumab when combined with chemotherapy; both in the adjuvant and neoadjuvant settings [9–13]. However, there is a disagreement on aggressiveness of therapy in a subgroup of HER2-positive patients with low-risk features. This group includes those with node negative disease and small tumors, more so with tumors size at 10 mm or smaller (T1a-T1b). The management of such patients is highly variable across physicians and institutions [14–16]. In a recent study that investigated the variations in clinical management of patients with node-negative small tumors, investigators utilized an online questionnaire conducted across 70 breast medical oncologists in Spain. The questionnaire included 37 questions regarding management decisions of HER2-positive early breast cancer. Oncologists' responses were very heterogenous; 53% would recommend upfront surgery, thus avoiding neoadjuvant therapy for node negative tumors measuring 1.0 cm or less. When asked about de-escalating the duration of anti-HER2 therapy for small tumors, 56% and 69% of responders were open to de-escalate the duration of adjuvant trastuzumab in pT1bN0 and pT1aN0 tumors, respectively [17]. Clinicopathological features, like young age, negative estrogen receptors (ER), high grade and high Ki-67 may influence the aggressiveness of suggested treatment for patients with node-negative small tumors [17]. In this review, we will discuss the rationale for de-escalation first, then address de-escalation strategies.

2. Rationale for De-Escalation

De-escalation refers to strategies that intend to reduce the duration, intensity, or complexity of the anti-HER2 treatment or the companion chemotherapy without compromising treatment outcomes [18]. Emerging data suggest that for certain low-risk patients, less intensive regimens, including both the anti-HER2 agents and the chemotherapy, may achieve comparable outcomes to standard aggressive protocols. Identifying these subsets through biomarkers and clinical characteristics is crucial for effective de-escalation.

2.1. Toxicity Reduction

Anti-HER2 therapies, particularly when combined with chemotherapy, can cause significant adverse effects, most importantly cardiotoxicity, but also include gastrointestinal and hematologic toxicities. De-escalation may thus improve the quality of life of such patients.

2.1.1. Cardiac Toxicity

Patients with breast cancer are at higher risk for cardiac adverse events secondary to chemotherapy; mostly anthracyclines and anti-HER2 therapy [19,20]. Radiation therapy, especially when it involves left-sided tumors, may add to this risk. In a recently published study, 829 patients with breast cancer (median age at diagnosis 54.2 years) who completed chemotherapy, including cardiotoxic agents, underwent echocardiographic screening every 2 years. Cardiac dysfunction was defined as left ventricular ejection fraction (LVEF) <50% after therapy initiation and included early- and late-onset cardiac dysfunction. Both anthracyclines and anti-HER2 (trastuzumab/pertuzumab) were given to 6.2% of the patients, while 16% received trastuzumab/pertuzumab alone, 39.7% received anthracyclines alone, and 38.1% received radiation alone. At a median follow-up of 8.6 (range, 1.8-39.8) years, and a total of 2,808 echocardiograms performed, the cumulative incidence of cardiac dysfunction increased from 1.8% at 2 years to 15.3% at 15 years from therapy initiation. In multivariable analysis, anthracyclines and trastuzumab/pertuzumab [hazard ratio (HR), 3.92, 95% CI, 1.74-8.85], anthracyclines: HR, 2.35 (95% CI, 1.25-4.4) and non-Hispanic Black race; HR, 2.15 (95% CI, 1.37-3.38) were important determinant of cardiac toxicity. Early-onset cardiac dysfunction was most prevalent among patients exposed to the combination of anthracyclines and trastuzumab/pertuzumab, while late-onset cardiac dysfunction was most prevalent among anthracycline and radiation exposed patients [21]. Such findings provide evidence to support the need for echocardiographic surveillance for several years after treatment with cardiotoxic agents and

suggest a need to optimize cardiovascular risk factors to mitigate this potentially serious adverse event. Additionally, potential cardiac dysfunction can be a rationale to de-escalate anti-cancer therapy, when possible.

2.2. Cost-Effectiveness

Anti-HER2 therapy is lengthy and expensive, and the financial burden on patients themselves and healthcare systems can be substantial [22–24]. Obviously, de-escalation can lead to significant cost savings. In a systematic review aimed to systematically review economic evaluation (EE) of adjuvant trastuzumab compared with chemotherapy alone for HER2-positive EBC, authors included 22 eligible studies from high-income (HICs) and upper-middle income countries (UMICs). Incremental cost-effectiveness ratios (ICERs) were within the cost-effectiveness thresholds of HIC, but not UMIC [25]. Several other studies, from low-income countries (LIC) reached a conclusion that one-year of adjuvant trastuzumab therapy for HER2-positive EBC, when compared to chemotherapy alone, may not represent value for money in such countries [26–29]. Obviously, things can be even worse when dual anti-HER2 therapy, both trastuzumab and pertuzumab, is used in the adjuvant or neoadjuvant therapy [30,31]. The introduction of generic drugs and biosimilars, if priced at a significant discounted rate, especially for resource-restricted countries, should improve patients' access to such drugs [32,33].

3. Approaches to De-Escalation

Several strategies have been explored to de-escalate the therapy for patients with HER2-positive disease, including the anti-HER2 therapy itself, the companion chemotherapy, or both. This de-escalation can range from reducing the duration of therapy to minimizing the use of concurrent chemotherapy.

3.1. Shortening the Duration of Trastuzumab

Since its introduction, and based on many clinical trials, the standard duration of trastuzumab therapy has been 12 months [9]. However, several trials have attempted to shorten this duration to 6 months or shorter (Table 1).

Table 1. Duration of anti-HER2 therapy, short versus long.

Variables	Study [References]	Publication Dates	Key Findings
One Year versus 2 Years	HERA trial [34]	2005 & 2013	2 years is not better than one year (HR 0.99; 95% CI, 0.85-1.14, P=0.86) 2 years was associated with more grade 3-4 adverse events and decrease in LVEF
9 Weeks versus 12 Months	FINHER [35]	2008	9-weeks of trastuzumab tended to have better dDFS than chemotherapy only (HR 0.65; 95% CI, 0.38 -1.12; P= 0.12) LVEF remained unaltered
	SOLD trial [36,37]	2018, 2024	9 weeks is not non-inferior to 12 months for DFS No substantial difference in dDFS and OS between the short and long group
	Short HER [38]	2023	9 weeks is not non-inferior to 12 months (in higher risk patients with N4+)
6 Months versus 12 Months	PHARE Trial [39,40]	2013 & 2019	6 months is not non-inferior to 12 months Cardiac events: 5.7% (12-Month), 1.9% (6-Month), P<0.0001

	PERSPHONE Trial [41]	2019	6-month is not inferior to 12 months; 4-year DFS 89.4% (6-month), 89.8% (12-month), HR 1.07, 90% CI 0.93-1.24, non-inferiority P=0·011 6-month treatment was associated with fewer severe adverse events
Meta-analysis (Short versus Long Duration)	6 studies (Patients treated between 1999-2015) [42]	2019	DFS and OS were significantly improved with the 12-month trastuzumab regimen compared to shorter ones

HER2: Human epidermal growth factor-2; HR: Hazard ratio: LVEF: Left ventricular ejection fraction; dDFS: Distant disease-free survival; DFS: Disease-free survival; OS: Overall survival; N4+: Four or more axillary lymph nodes involved.

3.1.1. Longer Is Not Necessarily Better

The landmark study, the HERA (HERceptin Adjuvant) trial had a third arm compared 2 years versus 1 year of trastuzumab therapy after standard adjuvant chemotherapy, neoadjuvant chemotherapy, or both in 5102 patients with HER2-positive EBC [9]. After a median follow-up of 8 years, 2 years of adjuvant trastuzumab was not more effective than one year of treatment (HR 0·99; 95% CI, 0.85-1.14, P=0.86). However, grade 3-4 adverse events and decrease in LVEF during treatment were reported more frequently in the 2-year treatment group (20.4% and 7.2%) than in the 1-year group (16.3% and 4.1%), respectively [34].

3.1.2. Ultrashort Trastuzumab, the 9-Week Attempt

The FINHER Study

The FINHER was among the very first studies that attempted to shorten the duration of anti-HER2 therapy. However, the chemotherapy regimen used is not among the known standard ones now or back then. In this study, 1010 patients with node-positive or high-risk node-negative breast cancer were randomly assigned to receive three cycles of docetaxel or vinorelbine, followed in both groups by three cycles of FEC (fluorouracil, epirubicin, and cyclophosphamide). Women with HER2-positive disease (n=232) were assigned to receive or not receive trastuzumab for 9 weeks, along with docetaxel or vinorelbine. After a median follow-up of 62 months, patients treated with trastuzumab tended to have better distant disease-free survival (dDFS) than those treated with chemotherapy only (HR 0.65; 95% CI, 0.38 -1.12; P= 0.12). The median LVEF of trastuzumab-treated patients remained unaltered during the 5-year follow-up, however, only one woman treated with trastuzumab was diagnosed with heart failure [35]. Though this trial did not compare long versus shortened trastuzumab therapy, it did pave the way for more studies to address this question. Additionally, patients included were high-risk (by inclusion criteria); the de-escalation strategies might not be their best option, if they can tolerate such therapy.

The SOLD Trial

The SOLD, an open label randomized clinical trial, was closer to the standard of care in its choice of chemotherapy. A total of 2176 patients with HER2-positive EBC, were randomized into two groups and chemotherapy regimen was identical in the two groups; 3 cycles of 3-weekly docetaxel plus trastuzumab for 9 weeks, followed by 3 cycles of FEC. The first group (short trastuzumab) received no further trastuzumab, while the other group continued the drug for one full year from the start date. The study was updated recently, at a median follow-up of 8.1 years, noninferiority of the 9-week trastuzumab treatment could not be demonstrated for disease-free survival (DFS). However, the 5-year and 10-year OS rates were comparable between the 9-week (95.0% and 89.1%) and 1-year

groups (95.9% and 88.2%); HR for all time points, 1.20; 90% CI, 0.94-1.54). Four patients (0.2%) died of a cardiac cause, 3 (75.0%) of these patients received trastuzumab for 9 weeks [36,37].

The ShortHER Trial

This is the third study attempting the shorter 9-week trastuzumab therapy, was updated and published recently. The ShortHER2 was a phase-3 noninferiority, randomized trial comparing 9 weeks versus 12 months of adjuvant trastuzumab with chemotherapy in patients with HER2-positive EBC. Patients were randomized to anthracycline-taxane combination chemotherapy plus 12-month or 9-week of trastuzumab. At a median follow-up of 9 years, the 10-year DFS for the whole group was similar; 77% versus 78% in the long versus short trastuzumab arm, respectively. Ten-year OS was also similar; 89% versus 88% in the long versus short arm, respectively. However, findings were not the same when higher risk patients with ≥ 4 involved axillary lymph nodes (N4+) were considered. In this high-risk subgroup, the 10-year DFS rates in the long versus short arm were 63% versus 53%, and the 10-year OS rates in long versus short arm was 84% versus 64%. The updated analysis of the ShortHER trial showed that 12-month trastuzumab continues to be the standard treatment for patients with high-risk (N4+) disease. However, numerically, the differences for the patients at low- (N0) or intermediate-risk (N1-3) are negligible [38].

3.1.3. Six Months versus 12 Months Trastuzumab

The PHARE Trial

Given the failure of the 9-week regimen, it was natural to try a longer course of trastuzumab. The PHARE trial was an open label, randomized, phase 3 trial in many centers in France. Patients with HER2-positive EBC who had breast-axillary surgery, was treated with at least four cycles of chemotherapy and up to 6 months of trastuzumab were randomized to continue trastuzumab for another 6 months (12 months total duration; control group) or to discontinue trastuzumab at 6 months (6 months total duration; experimental group). A total of 1691 patients were randomized to receive 12 months of trastuzumab and 1693 to receive 6 months of trastuzumab. After a median follow-up of 42.5 months, the 2-year DFS was 93.8% in the 12-month group and 91.1% in the 6-month group (HR 1.28; 95% CI, 1.05-1.56; P=0.29). Cardiac events were reported significantly more in patients treated with the 12-month trastuzumab than those in the 6-month group; 5.7% versus 1.9%, P<0.0001 [39]. The study was updated few years later; at a median follow-up of 7·5 years, authors concluded that shorter duration of anti-HER2 is not non-inferior to the standard 12-month regimen [40].

PERSEPHONE Trial

This phase III trial compared 6 months versus 12 months of adjuvant trastuzumab in HER2-positive early breast cancer. It demonstrated non-inferiority of the shorter regimen in terms of DFS, suggesting that 6 months could be a viable option for many patients. In this open-label, randomized phase 3 non-inferiority trial, patients with HER2-positive EBC were recruited from 152 centers in the UK. Patients had to have a clear indication for chemotherapy and were randomized to receive either 6-month or 12-month trastuzumab every 3 weeks, intravenously or subcutaneously, given in combination with chemotherapy. At a median follow-up of 5·4 years, DFS events occurred in 13% of 2044 patients in the 6-month group and in 12% of 2045 patients in the 12-month group. Four-year DFS was 89·4% in the 6-month group and 89·8% in the 12-month group (HR 1.07; 90% CI, 0.93-1.24), non-inferiority P=0.011. Additionally, the 6-month trastuzumab treatment was associated with fewer severe adverse events (19%) compared to 24% in the 12-month group, P=0·0002. Additionally, fewer patients in the 6-month group stopped the drug early because of cardiotoxicity; 3% compared to 8%, P<0·0001 [41].

3.1.4. The Meta-Analysis

Controversy continues regarding the optimal duration of trastuzumab, especially so after the encouraging results of PERSEPHONE trial. This meta-analysis was performed to reassess the efficacy and safety of shorter durations of trastuzumab. A total of 11,496 patients who were enrolled in 6 studies were eligible. Disease-free survival was significantly improved with the 12-month trastuzumab regimen compared to shorter ones (HR= 1.13; 95% CI 1.03-1.25; P = 0.01). Similarly, OS was significantly better (HR= 1.16; 95% CI 1.01-1.32; P= 0.03). Survival benefits were more pronounced in patients with ER-negative and node-positive disease. However, patients treated with shorter duration experienced significantly fewer cardiac events (OR 0.52; 95% CI 0.43-0.62; P < 0.00001) [42].

Given the above data, and despite the well documented increased risk of cardiotoxicity, 12 months of adjuvant trastuzumab treatment offer considerable survival advantage and should continue to be the standard and preferred treatment for HER2-positive EBC. However, shorter durations of trastuzumab therapy can be considered for patients with cardiac disease, those with small tumors and node-negative disease especially in resource-restricted countries.

3.2. De-Escalating Concurrent Chemotherapy

Concurrent chemotherapy, with anti-HER2 therapy adds to toxicity, inconvenience and cost of therapy. Several trials have evaluated reduced-intensity chemotherapy regimens with anti-HER2 in patients with low-risk HER2-positive EBC (Table 2).

Table 2. De-escalation of chemotherapy.

Strategy	Variables	Studies [References]	Publication date(s)	Key Findings
De-escalating Concurrent Chemotherapy	Single agent paclitaxel weekly for 12 weeks plus trastuzumab for 12 months	APT-trial (Single arm) [43–45]	2015, 2019, 2023	10-year iDFS: 91.3% 10-year RFI: 96.3% 10-year OS: 94.3% 10-year BCSS: 98.8%
	T-DM1 vs Paclitaxel (12 weeks) plus Trastuzumab (12 months)	ATEMPT trial (Randomized) [46,47]	2021, 2024	**Efficacy** (T-DM1 arm) 5-year iDFS: 97.0% 5-year RFI: 98.3% 5-year OS: 97.8% 5-year BCSS: 99.4% **Efficacy** (TH arm) 5-year iDFS: 91.1% **Adverse events**: No difference in CRT in both groups
Monotherapy with anti-HER2 Agents (No chemotherapy)	Elderly Patients (70-80 years) Trastuzumab alone versus Trastuzumab plus chemotherapy	RESPECT (Open-label randomized) [50]	2020	Trastuzumab monotherapy is not non inferior to trastuzumab plus chemotherapy Combination was associated with more AE and more deterioration in HRQoL

iDFS: Invasive disease-free survival; RFI: Relapse-free interval; OS: Overall survival; BCSS: Breast cancer specific survival; TH: Paclitaxel plus Trastuzumab; CRT: Clinically relevant toxicities; AE: Adverse events; HRQoL: Health related quality of life.

3.2.1. The APT Trial

The Apt (Adjuvant Paclitaxel and Trastuzumab) was designed to address de-escalating chemotherapy in patients with small, node-negative, HER2-positive EBC. In this phase 2 study, 410

patients with HER2-positive, node-negative, small breast cancer with tumors 3 cm or smaller, were treated with weekly paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab alone for 9 more months, to finish a total of 12 months of therapy. The primary analysis demonstrated a 3-year DFS of 98.7% [42]. In a follow up analysis with a median follow-up of 6.5 years, the 7-year DFS was 93% with only 4 (1.0%) distant recurrences, 7-year recurrence-free interval (RFI) was 97.5% and the 7-year OS was 95% [43]. On further follow up, the 10-year invasive disease-free survival (iDFS) was 91.3% (95% CI, 88·3-94·4), 10-year RFI was 96.3% (95% CI, 94.3-98.3) and 10-year overall survival was 94.3% (95% CI, 91.8-96.8), and 10-year breast cancer-specific survival (BCSS) was 98.8% (95% CI, 97.6-100.0), Table 3 [45].

Table 3. Survival Outcomes of patients treated on the APT trial.

Outcome	At 3-year (2015)	At 7-year (2019)	At 10-year (2023)
Invasive Disease-Free Survival (iDFS)	98.7 (95% CI, 97.6 - 99.8),	93% (95% CI, 90.4-96.2)	91.3% (95% CI, 88.3-94.4)
Recurrence-Free Interval (RFI)	99.2% (95% CI, 98.4-100.0)	97.5% (95% CI, 95.9-99.1)	96.3% (95% CI, 94.3-98.3)
Overall Survival (OS)	NR	95.0% (95% CI, 92.4-97.7)	94.3% (95% CI, 91·8-96·8)
Breast cancer-specific survival (BCSS)	NR	98.6% (95% CI, 97.0-100.0%)	98.8% (95% CI, 97.6-100.0)

iDFS: Invasive disease-free survival; RFI: Relapse-free interval; OS: Overall survival; BCSS: Breast cancer specific survival; CI: Confidence interval; NR: Not reported.

3.2.2. The ATEMPT Trial

The study was designed to compare the incidence of clinically relevant toxicities (CRTs) in patients treated with ado-trastuzumab emtansine (T-DM1) versus paclitaxel-trastuzumab (TH) and to evaluate iDFS in patients receiving T-DM1. Patients with stage-I, HER2-positive EBC (n=497) were randomly assigned 3:1 to T-DM1 (n=383) or TH (n=114). T-DM1 was given every 3 weeks for 17 cycles (total one year), while TH was given weekly for 12 weeks, followed by trastuzumab alone every 3 weeks for 39 weeks (total one year). There was no difference in CRT in both groups; 46% of patients on T-DM1 and 47% of patients on TH. At its initial publication in 2021, T-DM1 was associated with excellent results; the 3-year iDFS was 97.8% [46]. The trial was updated in June 2024; after a median follow-up of 5.8 years, the 5-year iDFS was 97.0%, the RFI was 98.3%, the OS was 97.8% and the BCSS was 99.4%. Though the study was not powered to study the difference between TH and T-DM1, the 5-year iDFS in the TH arm was 91.1% [47].

3.2.3. ADAPT Trial

Several clinical trials have tried to plan and direct a personalized therapy for HER2-postive breast cancer patients based on their initial response. The ADAPT trial is a prospective, phase 2 study investigating the potential of personalized treatment based on early response to neoadjuvant therapy. Initial results indicate that patients who achieve pCR after short-term preoperative therapy might be candidates for de-escalated post-operative treatment. Patients (n=134) were randomized to 12 weeks of trastuzumab and pertuzumab with or without weekly paclitaxel. Early response was defined as a decline in Ki-67 from baseline by 30% or more, or low cellularity (<500 invasive tumor cells) at biopsy performed 3 weeks after starting therapy. The pCR rate in the taxanes and dual blockade was unexpectedly high at 90.5%, compared to 36.3% in the non-chemotherapy arm. Among the trastuzumab/pertuzumab arm, 24/92 (26.1%) were classified as non-responders, and only 8.3% achieved pCR rate compared with 44.7% in responders (38/92). The study concluded that early non-responders treated with dual anti-HER2 therapy, without chemotherapy, strongly predict failure to achieve pCR [48]. In a follow up analysis, authors found that omission of further chemotherapy had

no negative impact on iDFS in patients with pCR and concluded that weekly paclitaxel plus dual HER2 blockade for 12 weeks can be a de-escalated neoadjuvant regimen in patients with HR-negative, HER2-positive EBC [49].

3.3. Monotherapy with Anti-HER2 Agents

For patients with small, low-risk tumors or those with contraindications to chemotherapy, anti-HER2 monotherapy might be an option. Studies have shown that trastuzumab monotherapy can be effective in specific patient populations, though it is generally less effective than combination therapy.

RESPECT Trial

In one open-label, randomized controlled study, 275 patients aged 70-80 (mean age, 73.5) years with surgically treated HER2-positive patients with EBC received trastuzumab alone or trastuzumab plus chemotherapy. The study was designed to see if trastuzumab alone is not inferior to trastuzumab plus chemotherapy. After a mean follow up of 4.1 years, the 3-year DFS was 89.5% with trastuzumab monotherapy versus 93.8% with trastuzumab plus chemotherapy (HR 1.36; 95% CI, 0.72-2.58; P= 0.51). So, the study failed to show that trastuzumab monotherapy is not inferior, however, the observed loss of survival without chemotherapy [restricted mean survival time (RMST)] differed by only -0.39 months at 3 years. Adverse events were more common with the combination arm and that translated into more deterioration in health-related quality of life (HRQoL) at 2 months (31% for trastuzumab monotherapy versus 48% for trastuzumab and chemotherapy; P=0 .016), and at 1 year (19% v 38%; P= 0.009). Though the noninferiority for trastuzumab monotherapy was not met, given the added toxicity, poor quality of life and the little observed loss of survival without the addition of chemotherapy (less than a 1 month at 3 years), trastuzumab monotherapy can be considered an alternative adjuvant therapy option for selected older patients like those enrolled in the "RESPECT" trial [50].

4. Biomarker-Guided Therapy

4.1. Image-Guided Therapy (PHERGain Trail)

As a continuation of the personalized approach, the PHERGain trail was conducted to optimize patient selection for anti-HER2 therapy utilizing positron emission tomography (PET) scan to identify patients who are likely to benefit from de-escalated neoadjuvant treatment. A total of 356 patients with HR-positive and HER2-positive breast cancer were randomized to two cycles of conventional TCHP regimen (docetaxel, carboplatin, trastuzumab and pertuzumab) versus chemotherapy-free regimen with trastuzumab and pertuzumab in combination with endocrine treatment. Early metabolic response was evaluated by FDG-PET at baseline and after two cycles. Patients in the standard arm continued to receive TCHP for four more cycles. In the experimental arm, early responders continued to receive six more cycles of chemo-free treatment, while the non-responders were switched to receive six courses of TCHP. Following the eight cycles of neoadjuvant chemotherapy-free group, a total of 38% of early responders achieved pCR and had a 3-year iDFS of 98.8%. However, when taken together, patients in the experimental arm had lower iDFS (95.4%) compared to the standard arm (98.3%). More outcome results, including OS, are still eagerly awaited [51,52].

Biomarkers that help predict response to anti-HER2 therapies can enable more personalized treatment approaches and thus de-escalation. The HER2DX risk score and tumor-infiltrating lymphocytes (TILs) are being studied to tailor therapy intensity based on individual risk profiles.

4.2. HER2DX Risk Score

Researchers from Spain and United States attempted to develop and validate a new risk scoring system (HER2DX) that can help oncologists decide on treatment aggressiveness of breast cancer

patients with HER2-positive disease. The scoring system employs both clinical and genomic data to predict treatment response (pCR) and survival in early-stage HER2-positive breast cancer based on a 27-gene expression plus clinical features, tumor size and nodal staging. The genomic data utilizes 4 gene expression signatures tracking tumor cell proliferation, immune infiltration, luminal differentiation, and the expression of the HER2 amplicon. Various data sets, mostly based on the shortHER2 database, were used to train, then verify and validate the predictive model. The HER2DX risk score was significantly associated with DFS in the ShortHER2 database (P=0.002), and in an independent combined validation database; the 5-year DFS in the low-risk group was 97.4% compared to 84.7% in the high-risk group, P=0.005. Overall survival was also better in the low-risk group (5-year OS: 95.8%) compared to 93.1% in the high-risk group, P=0.016. Additionally, continuous HER2DX pCR likelihood score was significantly associated with pCR, P< 0.0001 [53].

In another independent study designed to test the ability of the HER2DX assay to predict the likelihood of pCR in patients with early-stage HER2-positive breast cancer who are receiving a de-escalated neoadjuvant therapy, pretreatment tumor biopsy samples from 80 of 97 patients enrolled in the single-arm, multicenter, prospective phase 2 DAPHNe clinical trial were used for HER2DX assay. Patients had newly diagnosed stage II-III HER2-positive disease and were treated with neoadjuvant paclitaxel weekly for 12 weeks plus trastuzumab and pertuzumab every 3 weeks for 4 cycles. The HER2DX pCR score was significantly associated with pCR; the pCR rates was 92.6% in the HER2DX high, 63.6% in the medium, and 29.0% in the low pCR score groups (high versus low odds ratio, 30.6; P < .001). Researcher concluded that the HER2DX pCR score assay may predict pCR following treatment with de-escalated neoadjuvant paclitaxel with trastuzumab and pertuzumab in patients with early-stage HER2-positive disease, and as such, the HER2DX pCR score might guide management decisions by identifying patients who are candidates for de-escalated approaches [54]. Several other studies reached similar conclusions [55–57].

5. Future Directions and Conclusions

As our understanding of HER2-positive breast cancer biology advances, future research will hopefully refine de-escalation strategies further. Integration of tumor genomic profiling may help identify patients who might benefit from less intensive therapy. Future research should focus on exploring the molecular heterogeneity of HER2-positive breast cancer to identify new prognostic and predictive biomarkers which could pave the way toward the development of truly personalized less burdensome treatment options. Collecting and analyzing data from routine clinical practice (real-world data) to validate de-escalation approaches, away from the very stringent clinical trials setup, should help move such approaches faster. Additionally, exploring novel combinations of targeted therapies may help avoid or reduce the need for traditional toxic chemotherapy.

In conclusion, treatment de-escalation of HER2-positive breast cancer patients holds promise for reducing both toxicity and costs, while maintaining efficacy and outcomes. We believe that the current available evidence justifies some of the de-escalation strategies addressed in this review, especially in resource-restricted countries.

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