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Management of HER-2/neu-positive metastatic breast cancer

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ABSTRACT

We reviewed therapies for the management of HER2-overexpressing metastatic breast cancer. HER2-overexpressing breast cancers have a distinctive molecular signal and distinctive clinical characteristics. They are associated with an adverse prognosis, relative resistance to certain types of therapies (i.e. tamoxifen), and responsiveness to anthracyclines and taxanes. Anti-HER2 therapies such as trastuzumab and lapatinib have revolutionised the treatment of breast cancer and can dramatically improve outcomes in women with HER2-overexpressing metastatic breast cancer. Response to these targeted agents is improved when used in combination with cytotoxic agents such as anthracyclines and taxanes. However, there is an approximate 13% (taxanes) to 27% (conventional anthracyclines) risk of cardiotoxicity with these combinations. The novel anthracycline, pegylated liposomal doxorubicin, shows efficacy similar to that of conventional doxorubicin and may offer significantly less cardiotoxicity; this should be confirmed in phase III clinical trials. Lapatinib is an oral small molecule targeting HER2 with promising antitumour activity in the metastatic setting and a potential for reduced cardiotoxicity as compared with trastuzumab. Neoadjuvant as well adjuvant trials involving lapatinib, trastuzumab or their combination have started recrutiment worldwide.

1. Introduction

Breast cancer is a markedly heterogenous disease. There is increasing evidence that molecular profiling will allow for selection of the best treatment or combination of treatments based on the genetic composition of the primary tumour. Gene expression analysis reveals at least four breast cancer subtypes, including basal-like, HER2-positive, luminal subtype A and luminal subtype B.[1] Each subtype has unique characteristics, including different prognoses.[2] These characteristics are demonstrated in the primary tumour and remain unchanged in metastatic lesions.[2–4]

HER2 is overexpressed in about 20% of breast cancers[5] and is associated with a worse prognosis compared with breast cancer in women who do not overexpress HER2.[6] HER-2 overexpression predicts for relative resistance to tamoxifen,[7,8] for response to chemotherapy with anthracyclines[9,10] and paclitaxel[11,12] and for response to targeted therapy with the anti HER2 monoclonal antibody trastuzumab.[13–15] In a pooled analysis of seven trials in which trastuzumab was administered for metastatic breast cancer (MBC), a relationship was found between a decrease from baseline in HER2 levels and response rate, duration of response, time to progression (TTP) and overall survival. A statistically significant improvement in each of these parameters was observed in patients with more than a 20% decrease in HER2 versus patients with less than a 20% decrease in HER2 following treatment with trastuzumab. The mechanism behind this observation is not known but presumably the consequence of an effective blockade of the HER2 receptor by the monoclonal antibody or an efficient internalization of the HER2 receptor following trastuzumab binding to its receptor.[16]

Trastuzumab is now commonly administered to all women with HER2-overexpressing breast cancer. While trast-

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uzumab monotherapy leads to response rates raging from 12% to 26%,[13,15,17] the combination of trastuzumab with taxane-containing chemotherapy regimens yields response rates as high as 73% and represents our current most powerful strategy in HER2-overexpressing MBC.

2. Trastuzumab

2.1. *Trastuzumab–anthracycline regimens*

The introduction of regimens combining trastuzumab with anthracycline represented a major advance in the treatment of HER2-overexpressing MBC. With the addition of trastuzumab to an anthracycline–cyclophosphamide regimen, median time-to-tumour progression increased by 48% (from 6.1 months to 7.8 months, $p < .001$), median time-to-treatment failure increased by 43% (5.6 versus 7.2 months, $p < .001$) and median survival increased by18% (21.4 months versus 26.8 months, $p = .16$) compared with the same chemotherapy alone. The improvement in median survival reached statistical significance when trastuzumab plus chemotherapy (either anthracycline–cyclophosphamide or paclitaxel) was compared with either type of chemotherapy alone (25.1 months versus 20.3 months, $p = .046$).[14]

Cardiotoxicity became evident during the course of trastuzumab clinical trials. Cardiac dysfunction was reported in 27% of women with metastatic disease treated with trastuzumab in combination with an anthracycline and 13% when trastuzumab was combined with paclitaxel. In most cases, the dysfunction improved with standard medical management.[18]

In an attempt to reduce the risk of cardiotoxicity, regimens were modified and trastuzumab was administered after completion of anthracycline-containing chemotherapy. While it may be effective in the adjuvant setting, the impact of this strategy in the metastatic setting appears limited. In an analysis of cardiac tolerability in patients with MBC treated with trastuzumab, the incidence of cardiac events (defined as an asymptomatic decline in left ventricular ejection fraction [LVEF] below 50%; LVEF decrease of 20 percentage points compared with baseline; or signs or symptoms of congestive heart failure [CHF]) was 28% at a median follow-up of 34 months, similar to the incidence observed with concurrent administration in the seminal trastuzumab trial. Most patients received prior anthracyclines (85%) but only 6% received anthracyclines concomitant with trastuzumab.[19]

The continued high incidence of cardiotoxicity despite the switch to sequential administration of trastuzumab and an anthracycline may be due in part to pre-existing cardiac deficits resulting from prior anthracyclines, unrelated comorbidities placing patients at increased risk for cardiotoxicity or to the growing use of trastuzumab in the adjuvant setting.

These data suggest the need for alternative strategies to deliver chemotherapy-trastuzumab regimens in the metastatic setting. Combination regimens with pegylated liposomal doxorubicin, taxanes (paclitaxel with or without carboplatin or docetaxel), vinorelbine and capecitabine have been evaluated with success. Other potentially less cardiotoxic anti-HER2 therapies, such as lapatinib, may be a good alternative to trastuzumab in the future.

2.2. *Trastuzumab–pegylated liposomal doxorubicin (PLD) regimens*

The conventional wisdom that concomitant anthracyclines and trastuzumab be reserved for use in clinical trials because of the high incidence of cardiotoxicity is being challenged by clinical data demonstrating the safety and efficacy of a pegylated liposomal doxorubicin (PLD)–trastuzumab regimen in HER2-overexpressing MBC. Compared with conventional doxorubicin, PLD is associated with a longer circulation half life (73.9 h versus <10 min), lower circulating concentrations of free doxorubicin in the blood and higher doxorubicin concentrations in the tumour.[20] In a phase III monotherapy study conducted in women with MBC, PLD provided similar clinical efficacy and significantly reduced cardiotoxicity compared with conventional doxorubicin (Fig. 1). The incidence of alopecia, vomiting, and myelosuppression was also significantly reduced in patients treated with PLD, but hand–foot syndrome (HFS), stomatitis and mucositis were more common.[20]

In a phase II study, trastuzumab plus PLD was administered to 30 women with HER2-overexpressing breast cancer. Prior chemotherapy or trastuzumab for MBC was not permitted, however 13 women had received prior adjuvant anthracyclines at a cumulative mean dose of 251 mg/m^2 for doxorubicin and 530 mg/m^2 for epirubicin.[21]

The objective response rate with PLD plus trastuzumab was 52% and 38% had stable disease (Table 1). Progression-free survival was 12.0 months. Median overall survival (OS) had not been reached, but 1-year estimated OS was 76.9% (95% CI, 62.1%, 95.1%). Mean baseline LVEF was greater than 50% at baseline and after 4 and 6 cycles of treatment (Fig. 2). Three patients developed asymptomatic LVEF declines; there were no cases of symptomatic CHF. Most HFS was grade 1 or 2 and there was no grade 4 HFS.[21] The risk of HFS can be further reduced by using a maximum PLD dose intensity of 10 mg/m^2 per week or 40 mg/m^2 every 4 weeks without a significant difference in response or survival rates compared

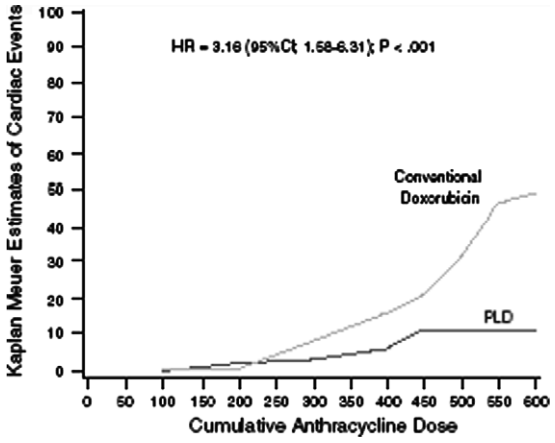

Fig. 1 – Cumulative percentage of cardiac events (⩾20% LVEF decrease from baseline but still normal; ⩾10% LVEF decrease from baseline to below institutional lower limit of normal; signs and symptoms of CHF versus cumulative anthracycline dose for PLD or conventional doxorubicin[20] (reprinted from O'Brien et al. with permission).

Table 1 – Phase II study of pegylated liposomal doxorubicin 50 mg/m^2 IV every 4 weeks for 6 cycles plus trastuzumab 2 mg/kg IV weekly for 24 weeks in HER2-overexpressing metastatic breast cancer (MBC)

Patients evaluable for response, *n*	29
Patients evaluable for safety, *n*	30
Mean cycles of PLD administered, *n*	5.4
Mean PLD dose per cycle, mg/m^2	48.1
Prior adjuvant anthracyclines, *n* (%)	13 (43)[b]
Objective response, % (95% CI)	52% (32.5–70.6%)
Anthracycline exposed, % (95% CI)	50% (21.2–77%)
Anthracycline naïve, % (95% CI)	53% (24.8–77%)
Stable disease, % (median duration)	37.9% (weeks)
Cardiac toxicity,[c] *n* (%)	3 (10%)

a 4 mg/kg loading dose week 1.
b Mean cumulative anthracycline dose in the adjuvant setting. Doxorubicin = 251 mg/m^2, epirubicin = 530 mg/m^2.
c Defined as clinical signs and symptoms of CHF in association with at least a 10% decline in LVEF from baseline to a value below the lower limit of normal; a 15% or greater decline from baseline in LVEF in an asymptomatic patient; <10% decline in LVEF from baseline in an asymptomatic patient and an absolute value <45% on MUGA scan.

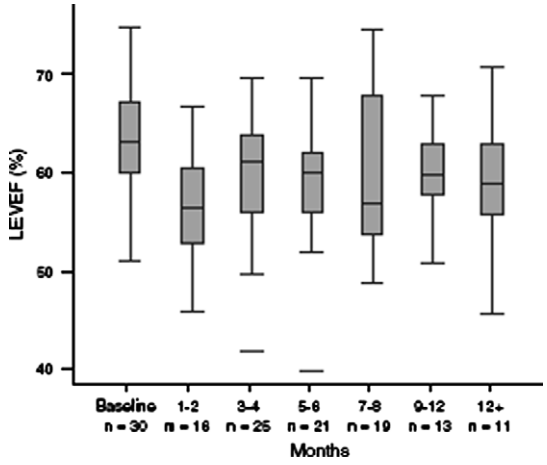

Fig. 2 – LVEF over time in patients treated with PLD plus trastuzumab. The standard span (whiskers) is 1.5 times the interquartile range outside the first and second quartiles. Outliers beyond the standard span are shown with a single horizontal line.[21] (reprinted from Chia et al. with permission.)

with a dosing schedule of 50 mg/m^2 every 4 weeks.[22] These encouraging data need to be confirmed in a larger phase II or III setting.

The cardiac safety of the trastuzumab–PLD combination in 15 patients with MBC was evaluated in a multicenter phase II study. PLD 40 mg/m^2 was given on day 1 and repeated every 28 days, trastuzumab 4 mg/kg loading dose was given on day 2 followed by 2 mg/kg given every 28 days with PLD. Overall, 3 patients experienced echocardiogram changes. The authors concluded that this combination therapy should be evaluated in larger studies.[23]

2.3. *Trastuzumab–taxane regimens*

Trastuzumab–taxane combinations have been evaluated in phase II and III studies (Table 2). Both docetaxel and paclitaxel have been used, with or without carboplatin. Docetaxel has become the more commonly used taxane in Europe. A randomised phase III study comparing monotherapy with docetaxel or paclitaxel in MBC, reported that docetaxel was superior in terms of OS and TTP, but was associated with more haematologic toxicity.[29]

Taxane–trastuzumab regimens demonstrate objective response rates raging from 38% to 73%. One large phase III study reported a significantly greater response rate with the addition of carboplatin to paclitaxel plus trastuzumab,[27], whilst a second large phase III study reported no benefit with the addition of carboplatin to docetaxel and trastuzumab.[28] Median time-to-progression is approximately 10 months and median overall survival ranges from 22 to 42 months when trastuzumab is combined with a taxane with or without carboplatin.

Cardiac dysfunction (all grades) is reported in 3% to >50% of patients receiving the trastuzumab–taxane combination; available data suggests that most events are grade 1 or 2. Aside from cardiac dysfunction, neuropathy, alopecia and nausea are the most troubling complications of these regimens.

2.4. *Other trastuzumab-chemotherapy combinations*

Phase II studies have also reported on combinations of trastuzumab with capecitabine and vinorelbine. Trastuzumab plus capecitabine yielded a response rate of 45% and median time-to-progression of 6.7 months in 27 women who had been pretreated with anthracyclines and/or taxanes in the neoadjuvant, adjuvant, or palliative settings. Side effects included HFS (84%, no grade 4) and significant haematologic toxicity (grade 3 or 4, 11%). There was one case (4%) of heart failure.[30]

Trastuzumab plus vinorelbine yielded a response rate of 75% when used in 40 patients with HER2-overexpressing MBC. Prior chemotherapy was administered in the adjuvant (30%) or metastatic (25%) setting or in both (28%) and included anthracyclines and taxanes. Median time-to-progression ranged from 34 weeks in patients receiving first-line therapy to 16 weeks when administered as second- or third-line therapy. Significant haematologic toxicity was observed, with 43% of patients experiencing grade 3 or 4 events.[31]

2.5. *Outstanding clinical issues*

2.5.1. *Administration schedule*

Trastuzumab has been administered on a weekly or every 3 week schedule. Initial clinical trials used a loading dose of 4 mg/kg followed by a weekly dose of 2 mg/kg; however, retrospective pharmacokinetic analysis reporting a trastuzumab half-life of 28.5 days supports less frequent dosing.[32] Phase II studies demonstrate the efficacy and safety of the more convenient every 3 week trastuzumab regimen (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks) either alone[33] or in combination with chemotherapy[34] in women with MBC. However, some clinicians still prefer weekly dosing in

Table 2 – Trastuzumab–taxane combinations in HER2-overexpressing metastatic breast cancer (MBC)

Study	Phase/prior chemotherapy regimens for MBC	Regimen (number of patients)	Objective response rate (%)	Median time-to-progression (months)	Median overall survival (months)	Cardiac events
Slamon et al.[14]	Phase III/None	H 2 m/kg[a] weekly P 175 mg/m^2 every 3 weeks (n = 92)	38%	6.9	22.1	13%[b]
		P 175 mg/m^2 every 3 weeks (n = 96)	16% (P < 0.001)	3.0 (P < 0.001)	18.4 (P = 0.17)	1%[b]
Seidman et al.[24]	Phase II/Up to 3, including anthracyclines and taxanes	H 2 mg/kg[a] P 90 mg/m^2 Administered weekly (n = 95)	61% (ITT) 67–81% (HER2+)	NR	NR	3.2% – severe cardiac complications (less serve cases not reported)
Esteva et al.[25]	Phase II/Up to 2	H 2 mg/kg D 35 mg/m^2 Administered weekly for 3 weeks, then rest 1 week (n = 30)	63% (ITT) 67–76% (HER2+)	9	NR	27% – asymptomatic decreases in LVEF; 3% – CHF (grade 3)
Marty et al.[26]	Phase II/None	H 2 mg/kg[a] weekly D 100 mg/m^2 every 3 weeks (n = 92)	61%	11.7	31.2	48% – LVEF decrease <15% 11% – LVEF decrease ⩾ 15% 1% – absolute LVEF <40%
		D 100 mg/m^2 every 3 weeks (n = 94)	34% (P = 0.0002)	6.1 (P = 0.0001)	22.7 (P = 0.0325)	54% – LVEF decrease <15% 6% – LVEF decrease ⩾15%
Robert et al.[27]	Phase III/none	H 2 mg/kg[a] weekly P 175 mg/m^2 every 3 weeks Administered for 6 cycles, then H alone until disease progression (n = 98)	36%	NR	32.2	2% grade 3 or 4 (grades 1–2 not reported)
		H 2 mg/kg[a] weekly P 175 mg/m^2 every 3 weeks C AUC 6 every 3 weeks Administered for 6 cycles, then H alone until disease progression (n = 98)	52% (P = 0.04)	NR	35.7 (P = 0.76)	0 – grades 3 or 4 (grades 1–2 not reported)
Forbes et al.[28]	Phase III/none	H 2 mg/kg[a] weekly D 100 mg/m^2 every 3 weeks Administered for 8 cycles, then H 6 mg/kg alone every 3 weeks until progression (n = 131)	73%	11.1	Not reached	8.4% – LVEF event (grades 1–3)
		H 2 mg/kg[a] weekly D 75 mg/m^2 every 3 weeks C AUC 6 ever 3 weeks Administered for 8 cycles, then H 6 mg/kg alone every 3 weeks until progression (n = 132)	73%	10.4 (P = 0.57)	41.7 (P = 0.2, log rank)	9.1% – LVEF event (grades 1–2)

C, carboplatin; D, docetaxel; H, trastuzumab; ITT, intent-to-treat population; NR, not reported; P, palitaxel.

a 4 mg/kg loading dose week 1.

b Defined as clinical signs and symptoms of CHF in association with at least a 10% decline in LVEF from baseline to a value below the lower limit of normal; a 15% or greater decline from baseline in LVEF in an asymptomatic patient; <10% decline in LVEF from baseline in an asymptomatic patient and an absolute value <45% on MUGA scan.

patients with symptomatic disease in view of more rapid achievement of steady state blood concentrations.

Whilst the trend in the adjuvant setting is to assess shorter durations of trastuzumab administration, the ideal duration of trastuzumab administration in the metastatic setting is an open question and the benefit of continuing trastuzumab after disease progression is unknown. There are ongoing randomised trials addressing this important economic issue.

2.5.2. *Cardiac monitoring*

Because of the risk of cardiotoxicity with trastuzumab when used alone or in combination with chemotherapy, cardiac function must be monitored on a routine basis. Risk factors for cardiotoxicity include anthracycline exposure and advanced age. Patients should be monitored for signs and symptoms of cardiotoxicity and LVEF evaluated at baseline and every 3 months during treatment. Patients with a baseline LVEF below the institution's lower limit of normal should not receive trastuzumab. Trastuzumab should be discontinued in patients whose LVEF falls below the institutions' lower limit of normal during the course of treatment, but may be reinstituted if the LVEF returns to or exceeds the institution's lower limit of normal in an asymptomatic patient.

2.5.3. *Brain metastases*

Women with HER2-overexpressing tumours are at increased risk for brain metastases,[35] even when they respond to treatment outside the central nervous system (CNS). There is evidence from adjuvant trials that the brain is often the first site of relapse in women treated with trastuzumab.[36] Thus, whilst our best current therapy for HER2-overexpressing breast cancer demonstrates impressive efficacy in controlling non-CNS disease, it appears to be less effective in controlling CNS metastases.

Ongoing randomised trials comparing trastuzumab and lapatinib in combination with taxanes will show whether the small molecule is able to reduce the incidence of brain metastases whilst maintaining a similar level of antitumour activity outside the CNS.

2.6. *Other anti-HER2 therapies*

Other anti-HER2 therapies are emerging and show considerable promise as alternatives to trastuzumab or in patients with HER2-overexpressing breast cancers that progress despite trastuzumab. Lapatinib is the most advanced at a clinical level; this orally active small molecule is a tyrosine kinase inhibitor of HER2 and HER1. This dual blockade of signalling may be more effective than the single-target inhibition of trastuzumab because there is considerable cross-talk between HER2 and other HER-family receptors.

An international phase III study demonstrated that lapatinib plus capecitabine is more effective than capecitabine alone in women with HER2-overexpressing MBC that progressed despite prior treatment with anthracyclines, a taxane and trastuzumab. Objective response was achieved in 22% of women in the lapatinib–capecitabine group versus 14% of women receiving capecitabine alone ($p = .09$); median TTP was 8.4 months versus 4.4 months, respectively (<.001). The incidence of cardiotoxicity was low, with four cases of asymptomatic cardiac events in the combination therapy group (2.4%). Other notable adverse events included diarrhoea (60%) and HFS (49%), both primarily grade 1 or 2. Of particular interest was a reduction in the incidence of progressive CNS metastases in women receiving lapatinib (4 cases versus 11 cases; $p = .10$),[37] suggesting that unlike trastuzumab, lapatinib may achieve therapeutic concentrations in the CNS. These data must be confirmed.

Based on available data and a relatively short follow-up, lapatinib-induced cardiotoxicity seems much less frequent

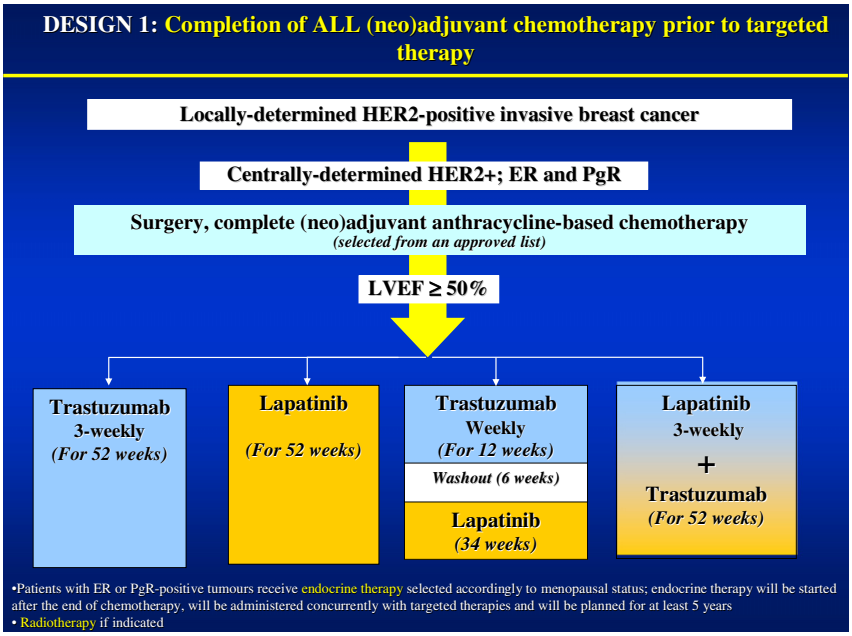

Fig. 3 – Design of ALTTO trial. Completion of ALL (neo)adjuvant chemotherapy prior to targeted therapy.

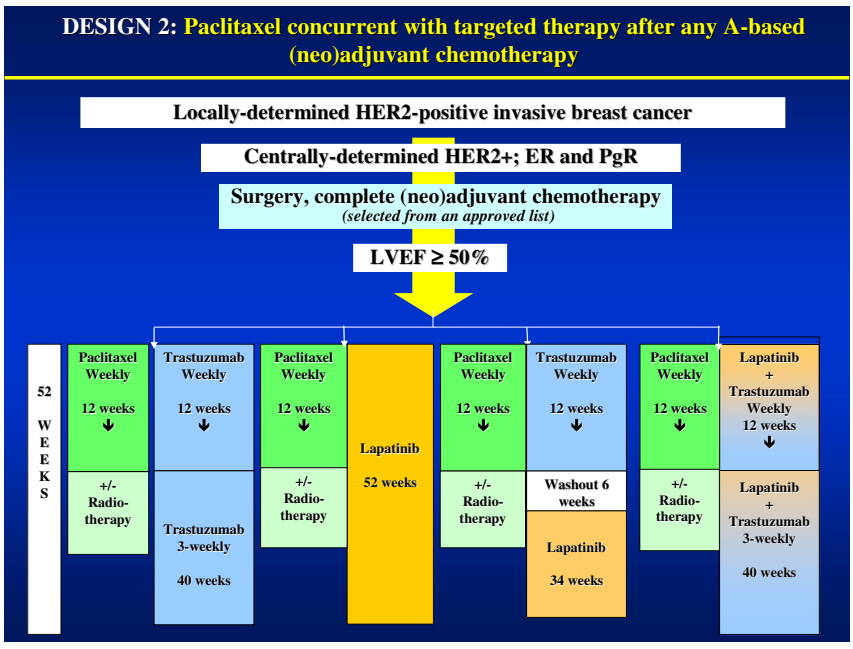

Fig. 4 – Design of ALTTO trial. Paclitaxel concurrent with targeted chemotherapy after any (A) based (neo)adjuvant chemotherapy. A, antracycline.

than that reported with trastuzumab (Perez et al. presented at ASCO 2007). A definite statement relative to this reduced cardiotoxic potential should wait mature results from the ongoing trastuzumab/lapatinib adjuvant trial ALTTO (Figs. 3 and 4).

Preliminary data for 5 patients enrolled on a phase I trial of lapatanib given in combination with PLD were recently presented.[38] Patients with metastatic or recurrent breast cancer receive lapatanib 1500 mg daily until disease progression and PLD was given every 29 days up to a maximum of 8 cycles. Preliminary efficacy data after at least 2 cycles of therapy included 1 partial response, 2 patients with stable disease, and 2 patients with progressive disease. Reported grade 3 or 4 toxicities included fatigue, septic arthritis and headache. Of note, 1 patient experienced an LVEF decrease to less than 50%. The investigators concluded that this was a disease related effect and not a result of the treatment. The trial is ongoing and continues to accrue patients.

Other targeted therapies undergoing evaluation in HER2-overexpressing breast cancer include KOS-953 (17-AAG or geldanamycin), a heat shock protein 90 inhibitor and HKI-272, an irreversible pan erbB receptor tyrosine kinase inhibitor.

3. Conclusions

In patients with breast cancer, HER2-overexpression defines a new disease entity. Ideally, gene-expression profiling of breast cancer tumours will enable clinicians to tailor treatments to the underlying biological characteristics of the individual tumour. The overwhelming data demonstrating preferential benefit from anti-HER-2 directed therapy (i.e. trastuzumab and lapatinib), anthracyclines and paclitaxel in HER2-overexpressing breast cancer support routine HER2 testing in patients with invasive breast cancer.

Our recognition of the biological diversity of breast cancer has led to a better understanding of the disease. Just as breast cancer is a heterogeneous disease, HER2-overexpressing breast cancer is a heterogeneous disease. As our understanding unfolds, it becomes obvious that there are numerous layers to the underlying biological features of HER2-overexpressing breast cancer. The co-expression of other molecular markers, such as p-53 or topoisomerase II alpha, along with HER2, may further define disease subgroups that will affect how patients respond to therapy.

The main objectives in metastatic disease are disease control, relief of symptoms, improved quality of life and prolonged survival. Thus, close scrutiny of adverse events is an important component of disease management. Previously, cardiotoxic potential was not considered a major concern in women with MBC. However, the risk of cardiotoxicity is gaining importance as the disease is better controlled and patients with MBC are able to live longer, more productive lives. Trastuzumab plus PLD in combination appears to be associated with the lowest risk of cardiotoxicity amongst trastuzumab–anthracycline based regimens. Phase III clinical trials are needed to confirm this observation. Lapatinib offers another potential option and we await clinical trials evaluating a PLD–lapatinib combination in MBC.

Conflict of interest statement

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