Poor-prognosis estrogen receptor-positive disease: present and future clinical solutions

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Abstract: Use of chemotherapy for patients with estrogen receptor (ER)-positive breast cancer has been a conflicting issue. Recent studies have identified predictive markers allowing identification of poor-prognosis ER-positive breast cancers in need of more aggressive therapy. In general, tumours belonging to the so-called luminal B class, tumours expressing a high Ki67, human epidermal growth factor receptor 2 (HER-2) overexpression or a high score on the Oncotype DX gene expression profile reveal a poor prognosis compared with ER-rich tumours of the luminal A class. In contrast, recent studies have shown these tumours, contrasting tumours of the luminal A class, to benefit from more aggressive anthracycline-containing chemotherapy including a taxane. In the case of metastatic disease, patients with HER-2-positive, ER-positive tumours may benefit from having endocrine therapy and an anti-HER-2 agent administered in combination.

Keywords: breast cancer, chemotherapy, endocrine therapy, estrogen receptor, human epidermal growth factor receptor 2, prognosis

Introduction

The term ‘poor-prognosis estrogen receptor (ER)-positive disease’ may cover different breast cancer categories. Importantly, traditional prognostic factors such as lymph node positivity indicate an inferior prognosis among all breast cancers independent of ER status. From a therapeutic perspective, however, multiple lymph node metastases inflict little controversy, in as much as lymph node status is not predictive to sensitivity for either endocrine treatment or chemotherapy.

In contrast, optimal treatment of ER-positive tumours harbouring a poor prognosis based on biological characteristics presents a different scenario. Among such parameters, many prognostic parameters are predictive of therapy efficacy [Lønning *et al.* 2007]. It is conventional wisdom that the response to endocrine therapy, in the metastatic and adjuvant situation, depends on ER expression levels. Thus, Harvey and colleagues found a benefit for tamoxifen *versus* no endocrine treatment in the adjuvant setting for tumours expressing an Allred ER score as low as 3 [Harvey

et al. 1999]. However, they found a linear correlation between levels of ER scores and the risk of having a relapse; the highest score was associated with the best prognosis. Consistent with that, studies conducted three decades ago revealed a higher response rate for endocrine therapy among patients with metastatic breast cancer with tumours expressing high ER levels *versus* those expressing moderate and low ER levels as measured by ligand binding assay [McGuire, 1978]. Similarly, human epidermal growth factor receptor 2 (HER-2) overexpression has been shown to be associated with a higher relapse rate among ER-positive tumours whether treated with tamoxifen or an aromatase inhibitor compared with HER-2 negative tumours [Dowsett *et al.* 2008; Rasmussen *et al.* 2008]. In addition, while merging evidence indicates lack of benefit from adding a taxane to anthracycline-containing chemotherapy or even use of anthracycline-containing chemotherapy among ER-rich luminal A class tumours [Albain *et al.* 2010; Hugh *et al.* 2009; Penault-Llorca *et al.* 2009], the benefit of having ‘more aggressive’ chemotherapy in

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ER-positive tumours belonging to the luminal B class, ER-positive tumours overexpressing the HER-2 or ER-positive tumours with a high proliferation rate (in general belonging to either the luminal B or the HER-2 class) is a more complex issue to address.

This review discusses contemporary evidence evaluating response to chemotherapy and endocrine treatment in patients with ER-positive tumours revealing a poor prognosis phenotype based on biological characteristics. In addition, the benefit of using anti-HER-2 treatment with endocrine therapy in ER-positive tumours revealing HER-2 overexpression is considered.

Use of chemotherapy

The long-term benefits of adjuvant chemotherapy preventing breast cancer relapse and improving overall survival is well documented through the Oxford meta-analysis [Abe *et al.* 2005]. While adjuvant chemotherapy on average may improve long-term survival by about 30%, conflicting evidence indicates the hazard ratio (HR) may be different among patient groups. While the 2005 overview analysis indicated a higher benefit from chemotherapy among patients harbouring ER-negative tumours than those with ER-positive tumours and a higher benefit among patients less than 50 years old than those aged 50–69 years, the recent 2011 overview found the benefits from chemotherapy independent of patient age as well as ER receptor status [Early Breast Cancer Trialist Collaborative Group, 2011]. Data indicating that chemotherapy in combination with endocrine therapy has a similar benefit among patients with ER-positive tumours and those with ER-negative tumours are surprising, in particular as these data contrast with data from several large controlled studies (see below). A full explanation of this discrepancy is not currently available. However, the meta-analysis included different multicenter studies, many of which did not include a central assessment of ER status. This review summarizes and discusses data obtained in individual studies showing the potential predictive role of ER status and other biochemical parameters in measuring therapy response. However, recent overview results should be taken into account when summarizing the evidence.

The potential impact of patient age on benefit from chemotherapy is of interest to our

understanding of the effects of endocrine therapy. Thus, a possible explanation as to why chemotherapy could be of particular benefit in young women is chemotherapy-induced loss of ovarian function in premenopausal women. Most patients participating in older studies received treatment with conventional cyclophosphamide, methotrexate and 5-fluorouracil (5-FU) (CMF) chemotherapy with a higher propensity for causing permanent loss of ovarian function compared with contemporary anthracycline-containing regimens [Petrek *et al.* 2006]. Yet there are several conflicting observations of the potential benefits from amenorrhea for different patient groups and with respect to therapy outcome. Thus, Swain and colleagues recently reported amenorrhea lasting for over 6 months to be associated with improved outcome among patients with ER-positive as well as ER-negative breast cancers treated with different doxorubicin plus docetaxel-containing regimens [Swain *et al.* 2010]. Considering ovarian suppression among patients subsequently treated with tamoxifen, conventional wisdom held the effect of tamoxifen to be independent of circulating estrogen levels. However, this hypothesis has not been properly evaluated in randomized phase III studies. While the Austrian ABCSG-12 protocol randomized premenopausal women to goserelin in combination with either anastrozole or tamoxifen, there was no control arm with patients receiving tamoxifen monotherapy [Gnant *et al.* 2009]. Evidence from some small studies of metastatic breast cancer have indicated a benefit of ovarian ablation combined with tamoxifen compared with tamoxifen monotherapy [Klijn *et al.* 2000, 2001], but so far this combined approach has not gained general acceptance.

Analysing the results from three large Cancer and Leukemia Group B (CALGB) studies – evaluating the importance of anthracycline dose intensity, the addition of paclitaxel or dose-dense (2-weekly) *versus* regular 3-weekly dose density [Berry *et al.* 2006] – for each strategy the benefit was higher among patients with ER-negative tumours compared with patients with ER-positive tumours who were also receiving tamoxifen (Table 1). The extent to which this interaction may be due to concomitant administration of tamoxifen or the intrinsic biology of the ER-positive tumours is difficult to measure as current guidelines recommend endocrine therapy for all patients with ER-positive tumours who are considered eligible for chemotherapy.

Table 1. Key studies reporting different parameters predicting benefits of adding chemotherapy, drug dose/density or adding taxanes to anthracycline-containing chemotherapy in estrogen receptor (ER)-positive breast cancers treated with endocrine therapy.

Regimen tested	Tumour type	Predictive factor	Result	Reference
Tam+/- anthra-cont chemo	ER+	21 gene (Oncotype DX)	High score predicts efficacy of chemo	[Albain <i>et al.</i> 2010]
Anthra dose	ER+/-	ER+ versus ER-	Benefit for ER-, not ER+ tum	[Berry <i>et al.</i> 2006]
Add pacl to anthra	ER+/-	ER+ versus ER-	Benefit for ER-, not ER+ tum	[Berry <i>et al.</i> 2006]
DD anthra/tax chemo	ER+/-	ER+ versus ER-	Benefit for ER-, not ER+ tum	[Berry <i>et al.</i> 2006]
Add pacl to anthra	ER+	HER-2 overexpression	Benefit with pacl in HER2+ tum	[Hayes <i>et al.</i> 2007]
TAC versus FAC regimen	ER+	HER-2 overexpression	Benefit with TAC in HER2+ tum	[Hugh <i>et al.</i> 2009]
TAC versus FAC regimen	ER+	Tumour 'class'	Some benefit with TAC in Lum B tum	[Hugh <i>et al.</i> 2009]
Add doce to FEC 100	ER+	<i>Ki67</i>	Benefit adding doce with high <i>Ki67</i>	[Penault-Llorca <i>et al.</i> 2009]*
Add doce to FEC 100	ER+	HER-2 overexpression	No benefit of adding doce HER-2+	[Penault-Llorca <i>et al.</i> 2009]*

*In this study, the number of FEC 100 cycles was reduced from six in the control arm to three in the arm adding sequential doce to FEC 100. Thus, patients having doce probably got a sub-optimal accumulated dose of anthracyclines. Anthra, anthracycline; cont, containing; DD, dose dense; doce, docetaxel; ER-, estrogen receptor negative; ER+, estrogen receptor positive; FAC, fluorouracil (5-FU), doxorubicin and cyclophosphamide regimen; FEC, 5-FU, epirubicin and cyclophosphamide regimen; HER-2, human epidermal growth factor receptor 2; Lum B, Luminal B; pacl, paclitaxel; TAC, docetaxel, doxorubicin and cyclophosphamide regimen; tam, tamoxifen; tum, tumour.

Several trials in the neoadjuvant and the adjuvant settings have reported a benefit of anthracycline dose escalation but up to a certain 'threshold' level in HER-2-positive tumours [Henderson *et al.* 2003; Muss *et al.* 1994; Paik *et al.* 1998; Petit *et al.* 2001; Pritchard *et al.* 2006]. More recently, this has been linked to coamplification of topoisomerase II [Knoop *et al.* 2005; Press *et al.* 2011; Tanner *et al.* 2006], an anthracycline target whose gene is located close to the HER-2 gene on chromosome 17.

The work by Perou, Sørli and colleagues [Sørli *et al.* 2001], revealing breast cancer may be separated into distinct classes based on gene expression profiling (Figure 1), has strongly influenced our thinking about the impact of breast cancer biology on treatment. Analysing patient outcome for FAC (fluorouracil 500 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m²) versus TAC (docetaxel 75 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m²) given every 3 weeks for six cycles in the Breast Cancer International Research Group (BCIRG) 001

trial, Hugh and colleagues [Hugh *et al.* 2009] evaluated the potential predictive role of gene expression profiles [Sørli *et al.* 2001] defined by immunohistochemistry, and the impact of HER-2 overexpression and tamoxifen treatment in the subgroup of patients harbouring ER-positive tumours (Table 1). Notably, while most ER-positive tumours do not overexpress HER-2 – 50% of all HER-2-positive tumours are actually ER-positive but, on average, at low levels (see references in Kaufman *et al.* [2009]).

The findings from the BCIRG trial [Hugh *et al.* 2009] provide interesting information about the complex interactions among the effects of chemotherapy, antihormonal treatment and intrinsic tumour biology. As mentioned above, it is not possible to give a full biological explanation because nearly all patients with ER-positive tumours will not receive adjuvant chemotherapy without also receiving endocrine treatment. Looking at disease-free or overall survival in the total study population, patients classified as having luminal A tumours had the best prognosis.

Figure 1. Gene expression patterns of 85 experimental samples from 78 breast cancers, three benign tumours and four benign tissues. Figure to the left, full cluster diagram. The letters C–G refer to the human epidermal growth factor receptor 2 (HER-2) amplicon cluster (C), cluster of unknown significance (D), basal epithelial cell-enriched cluster (E), normal breast-like cluster (F), and luminal epithelial gene cluster containing estrogen receptors (G). Adapted from [Sørli *et al.* 2001] with permission. Lum, luminal.

Patients with tumours classified as luminal B had an ‘in-between’ outcome, while patients with triple-negative and HER-2 overexpressing tumours had poor relapse-free and overall survival rates. Thus, the study by Hugh and colleagues reproduced the original observations by Sørli and colleagues [Sørli *et al.* 2001, 2003] revealing a prognostic impact from this classification independent of whether adjuvant therapy was administered or not (Figure 2). Comparing the two treatment arms, a clear benefit can be seen from adding docetaxel in patients with HER-2 overexpressing or triple-negative tumours, with a limited benefit for luminal B tumours and no advantage for luminal A tumours (Table 1). For the subgroup of ER-positive tumours, a benefit from docetaxel was observed in tumours overexpressing HER-2. Interestingly, inclusion of tamoxifen strongly improved outcome among patients with ER-positive, HER-2-negative tumours treated with TAC or FAC. In contrast, no benefit from TAC compared with FAC was observed among ER-positive, HER-2-negative tumours. For patients overexpressing HER-2, a

Figure 2. Prognostic impact of the different tumour classes among patients not receiving any systemic adjuvant treatment (A) and patients with stage III breast cancers treated in our clinic with neoadjuvant chemotherapy (weekly doxorubicin or 3-weekly 5-fluorouracil with mitomycin) with tamoxifen for estrogen receptor (ER)-positive tumours (B). Figure (A) depicts relapse-free survival while (B) depicts overall survival. Reproduced with permission from [Sørli *et al.* 2003]. Adj endo, adjuvant endocrine therapy; Adj tam, adjuvant tamoxifen.

moderate benefit from tamoxifen was observed among patients receiving FAC chemotherapy. In contrast, no benefit from tamoxifen was observed among patients with HER-2 overexpressing tumours treated with TAC. Notably, these subgroup analyses need to be interpreted carefully due to the limited number of patients with ER-positive tumours overexpressing HER-2 and because the number of patients with ER-positive tumours not receiving endocrine therapy was small. A benefit of adding a taxane to anthracycline-containing chemotherapy in ER-positive tumours overexpressing HER-2 (but not HER-2-negative, ER-positive tumours) was also found in the CALGB 9344/INT0148 study [Hayes *et al.* 2007].

Evaluating predictive factors in patients with ER-positive tumours randomized to treatment with either FEC (5-FU, epirubicin and cyclophosphamide) 100 for six cycles or FEC100 for three cycles followed by docetaxel (100 mg/m² for three cycles), Penault-Llorca and colleagues found elevated Ki67 expression (defined as >20%

of the tumour cells revealing positive staining) to predict a benefit from adding docetaxel to the regimen (Table 1) [Penault-Llorca *et al.* 2009]. In contrast to the data from Hugh and colleagues [Hugh *et al.* 2009] this study revealed a nonsignificant detrimental effect of adding docetaxel to treatment for patients with HER-2 overexpressing tumours. There may be several explanations for this finding. Here, like in the study by Hugh and colleagues, the number of ER-positive, HER-2 overexpressing tumours was low, and the discrepancy could be because of chance only. However, in the study by Penault-Llorca and colleagues, contrasting the study of Hugh and colleagues, the number of anthracycline-containing cycles was reduced from six to three in the docetaxel arm. Taking into consideration the benefit of anthracycline dose escalation in HER-2-positive tumours (see above), the study design may well have contributed to this result. It should be noted that these trials were both conducted prior to implementation of trastuzumab in the adjuvant setting. Taking into account the benefit of concomitant chemotherapy and trastuzumab, the results of these studies may have been different if trastuzumab had been administered in combination [Gianni *et al.* 2011; Perez *et al.* 2011].

Finally, analyzing tumour samples from the South West Oncology Group (SWOG)-8814 study evaluating the addition of CAF (cyclophosphamide, doxorubicin and 5-FU) to adjuvant tamoxifen for ER-positive breast cancers, Albain and colleagues evaluated the predictive role of the 21-gene or Oncotype DX signature (Table 1) [Albain *et al.* 2010]. This signature was first developed as a prognostic parameter in patients with ER-positive tumours treated with tamoxifen [Paik *et al.* 2004]; here, a low score was associated with a good prognosis. Subsequently, it was also shown to predict benefit from CMF chemotherapy in the same population of patients with ER-positive tumours having tamoxifen treatment [Paik *et al.* 2006]. Adding chemotherapy to tamoxifen, the benefit was confined to patients with a high score on the 21-gene signature, indicating a benefit of chemotherapy among patients with a poor prognosis on tamoxifen monotherapy. In their analysis of the SWOG-8814 study, Albain and colleagues confirmed a benefit from adding anthracycline-containing chemotherapy to treatment of patients with a high score on the 21-gene signature. In contrast, no improvement was recorded among patients with a low score on the 21-gene signature.

Taken together, these study data reveal an improved benefit for chemotherapy among patients with ER-negative tumours compared with those with ER-positive tumours. Clearly, there is a differential effect among ER-positive tumours as revealed by markers like HER-2 overexpression, Ki67 expression, classification by hierarchical clustering and the 21-gene signature. Apart from HER-2 overexpression, which together with topoisomerase II expression should be considered a predictive marker for identifying a drug target, classification of ER-positive tumours into luminal A *versus* B class, tumours revealing low *versus* high Ki67 expression or tumours revealing a low *versus* high score on the 21-gene signature to a large extent provide overlapping information. The 21-gene signature measures tumour proliferation, and luminal B tumours on average reveal a higher Ki67 compared with luminal A tumours [Cheang *et al.* 2009]. Therefore, any of these methods can characterize ER-positive tumours with a good prognosis probably with no need for chemotherapy *versus* those that are at higher risk of relapse and may benefit from having chemotherapy in combination with endocrine treatment.

Use of endocrine therapy

While endocrine therapy has been reported to be of benefit in tumours expressing ER immunostaining in only a few percent of their cells [Hammond *et al.* 2010], endocrine therapy in the adjuvant (Table 2) and in the advanced setting is of greater benefit for tumours expressing high receptor levels compared with those expressing low levels [Harvey *et al.* 1999; McGuire, 1978]. Among ER-positive tumours, low ER expression levels and high Ki67 in general characterize tumours belonging to the luminal B not the luminal A class (see the discussion in Lønning *et al.* [2005]). While about 10% of ER-positive tumours reveal HER-2 overexpression [Penault-Llorca *et al.* 2009], among the subgroup (15–20% of all breast cancers) revealing HER-2 amplifications or overexpression, about half are ER positive [Perez *et al.* 2011; Untch *et al.* 2008]. Therefore, endocrine therapy remains a potential treatment option for about half the HER-2 amplified tumours. Similar to tumours belonging to the luminal B class [Sørli *et al.* 2001, 2003], ER-positive tumours overexpressing HER-2 in general express ER at a lower level compared with ER-positive tumours of the luminal A class [Konecny *et al.* 2003]. Thus, the potential impact of Ki67 status and HER-2 amplification or

Table 2. Key studies reporting different parameters predicting benefits of endocrine adjuvant/neoadjuvant therapy in estrogen-receptor-positive (ER+) breast cancers.

Regimen	Setting	Predictive factor	Result	Reference
Tamoxifen	adjuvant	ER level by IHC	Correlation between ER+ level and effect of therapy	[Harvey <i>et al.</i> 1999]
Tamoxifen	adjuvant	ER level by IHC	Correlation between ER+ level and effect of therapy	[Dowsett <i>et al.</i> 2008]
Anastrozole	adjuvant	ER level by IHC	Correlation between ER+ level and effect of therapy	[Dowsett <i>et al.</i> 2008]
Tamoxifen	adjuvant	HER-2+/- by IHC	HER-2 overexpression reduced benefit of therapy	[Dowsett <i>et al.</i> 2008]
Anastrozole	adjuvant	HER-2+/- by IHC	HER-2 overexpression reduced benefit of therapy	[Dowsett <i>et al.</i> 2008]
Tamoxifen	adjuvant	HER-2+/- by IHC	HER-2 overexpression reduced benefit of therapy	[Rasmussen <i>et al.</i> 2008]
Letrozole	adjuvant	HER-2+/- by IHC	HER-2 overexpression reduced benefit of therapy	[Rasmussen <i>et al.</i> 2008]
Tamoxifen	neoadjuvant	Ki67 drop at 2 weeks	Ki67 reduction predicted outcome	[Dowsett <i>et al.</i> 2007]
Letrozole	neoadjuvant	Ki67 drop at 2 weeks	Ki67 reduction predicted outcome	[Dowsett <i>et al.</i> 2007]

HER-2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

overexpression on sensitivity to endocrine therapy should be carefully examined.

Neoadjuvant studies by Dowsett and colleagues have indicated a low Ki67, in particular when determined after 2 weeks on endocrine therapy, to predict a good long-term outcome for patients having neoadjuvant treatment with either tamoxifen or an aromatase inhibitor (Table 2) [Dowsett *et al.* 2007]. In their original report on the 21-gene Oncotype DX gene expression profile, Paik and colleagues reported a low score to predict a good prognosis among patients having tamoxifen adjuvant treatment [Paik *et al.* 2004]. Thus, a low proliferation score, whether assessed by Ki67 expression or the Oncotype DX score, seems to predict benefit from endocrine treatment but a smaller benefit from more 'aggressive' chemotherapy compared with a high proliferation score.

Studies conducted more than a decade ago revealed HER-2 overexpression to reduce the response to endocrine therapy with tamoxifen [Berns *et al.*

1995; Houston *et al.* 1999] but also to other endocrine treatment options like droloxifen, megestrol acetate and the second-generation aromatase inhibitor, fadrozole [Leitzel *et al.* 1995; Yamauchi *et al.* 1997] in metastatic disease. Interestingly, data from two neoadjuvant studies indicated the benefit of letrozole [Ellis *et al.* 2001] and anastrozole [Smith *et al.* 2005] over tamoxifen to be particularly high in HER-2 overexpressing tumours. However, more recent data from the TransAtac study [Dowsett *et al.* 2008] and the BIG 1-98 study [Rasmussen *et al.* 2008] indicate that aromatase inhibitors may reduce the HR for a relapse compared to tamoxifen in the adjuvant setting to about the same extent in patients with HER-2-positive and HER-2-negative tumours (Table 2).

Recent studies have shown that neoadjuvant treatment of HER-2-positive tumours with various anthracycline- and taxane-containing chemotherapy regimens including trastuzumab produce pathological complete response rates (pCR) in the range of 30–40% [Gianni *et al.*

2010; Untch *et al.* 2010, 2011], which is about twice the response rate generally reported among patients with tumours of normal HER-2 status. So far, data are inconclusive as to whether the pCR in HER-positive, ER-positive tumours may differ from the response in HER-2-positive, ER-negative tumours [Untch *et al.* 2010, 2011]. However, the fact that clinical and pathological complete responses exceed what may be observed for patients with ER-positive tumours having neoadjuvant endocrine therapy provides little opportunity for studies randomising ER-positive HER-positive patients between neoadjuvant endocrine therapy and chemotherapy. However, because the majority of these patients do not achieve an optimal response to chemotherapy with trastuzumab, alternative second-line solutions are required. Some patients having a sub-optimal response to chemotherapy may benefit from having endocrine therapy in combination with anti-HER-2 treatment. To proceed in this area, markers predictive for a pCR on chemotherapy with trastuzumab should be identified. Such markers may allow for selection of patients with tumours not sensitive to chemotherapy for whom primary endocrine therapy with trastuzumab should be evaluated.

The general opinion is that HER-2 overexpressing or amplified tumours have an inferior response to endocrine therapy compared with HER-2-positive tumours. However, the extent to which this relates to HER-2 overexpression *per se*, a higher level of KI67 compared with HER-2-negative tumours or the fact that these tumours, on average, express ER at a lower concentration compared with HER-2-negative tumours is not fully understood.

Combining anti-HER-2 and endocrine therapy

Two randomized studies addressed the impact of adding trastuzumab to anastrozole [Kaufman *et al.* 2009] or lapatinib to letrozole [Johnston *et al.* 2009] in patients with ER-positive, HER-2-positive metastatic breast cancer. Both studies revealed a significant benefit from combining an anti-HER-2 agent with an aromatase inhibitor. Interestingly, in the study by Johnston and colleagues, they also enrolled patients with ER-positive but HER-2-negative tumours [Johnston *et al.* 2009]. While no benefit from lapatinib was reported for the whole patient group with HER-2-negative tumours, a predefined subanalysis revealed a nonsignificant benefit from having

lapatinib in the group of patients who had a relapse less than 6 months after terminating adjuvant tamoxifen. The hypothesis behind this study is that HER-2 upregulation may also confer resistance to endocrine therapy in a subgroup of ER-positive tumours not overexpressing HER-2, and this has gained support from experimental and translational studies. Thus, trastuzumab has been shown to counteract letrozole resistance in cells and xenografts not overexpressing HER-2 [Sabnis *et al.* 2009]. Further, in a recent study, neoadjuvant treatment with aromatase inhibitors was found to upregulate HER-2 mRNA expression levels in tumours not amplified for HER-2 [Flageng *et al.* 2009]. It is of substantial interest to confirm the results obtained by Johnston and colleagues in independent studies.

More recently, the results from two smaller studies evaluating combined endocrine and anti-HER-2 treatment for ER-positive, HER-2-positive metastatic breast cancers have been reported. The Study of the Efficacy and Safety of Letrozole Combined with Trastuzumab in Patients with Metastatic Breast Cancer (eLETRA study) [Huober *et al.* 2009] was prematurely closed due to poor accrual. Considering the 92 patients randomized to letrozole *versus* letrozole with trastuzumab, median time to progression was extended from 3.3 to 14.1 months but did not reach statistical significance due to the small number of patients. Finally, by showing 8 out of 11 patients revealing previous resistance to anastrozole and trastuzumab monotherapy to benefit (show response or stable disease beyond 6 months) from the two compounds administered in combination, the study by Koeberle and colleagues supports the hypothesis that there may be a positive synergism between these compounds [Koeberle *et al.* 2011].

Summary

Considering adjuvant treatment, we now have the possibility of identifying patients with ER-positive tumours likely to benefit from anthracycline-based chemotherapy and from having a taxane added in sequence. HER-2 overexpressing or amplified tumours seem to show improved benefit from having a taxane added to the treatment regimen. The fact that ER-positive, HER-2 overexpressing tumours seem to gain less benefit from endocrine therapy compared with ER-positive, HER-2-negative tumours further underlines that these patients need chemotherapy and should not

be deprived of such treatment in the adjuvant setting. The only exception may be patients whose medical condition excludes use of chemotherapy.

The second group of patients with ER-positive tumours likely to benefit from chemotherapy are those revealing a 'high' Ki67 score, expressing moderate to low ER levels, revealing a luminal B gene expression signature or having a high recurrence score according to the Oncotype DX assay [Paik *et al.* 2004]. To a large extent, these groups overlap. However, some patients may qualify for chemotherapy based on the value of one or perhaps two of these parameters.

Neoadjuvant (primary medical) treatment is an area for further research. The first goal should be to identify predictive markers for a pCR to chemotherapy (in general) and to chemotherapy combined with trastuzumab in HER-2-positive tumours. Thereafter, patients with ER-positive tumours not likely to achieve a pCR to chemotherapy may be subject to further trials exploring optimal antihormonal treatment in the primary setting.

As for metastatic disease, we face a different scenario. Metastatic breast cancer remains a noncurable disease and any treatment option is palliative. Considering quality of life, endocrine therapy compares favourably with cytotoxic compounds, and anti-HER-2 treatment is generally well tolerated. While HER-2-positive tumours usually have a lower response rate to endocrine therapy compared with HER-2-negative tumours, the findings from recent studies revealing a benefit from adding trastuzumab or lapatinib to treatment with an aromatase inhibitor provides options for endocrine therapy including anti-HER-2 treatment for these patients. Patients with endocrine-sensitive tumours may respond to multiple agents administered in sequence [Lønning, 2004, 2009]. Similarly, there seems to be a lack of cross resistance between anti-HER-2 agents like trastuzumab and lapatinib or pertuzumab. In addition, patients progressing on treatment with trastuzumab and chemotherapy seem to benefit from extending trastuzumab treatment into their next chemotherapy regimen [Baselga *et al.* 2010; Blackwell *et al.* 2009; von Minckwitz *et al.* 2009]. Interestingly, patients previously progressing on trastuzumab treated with lapatinib had improved time to progression if trastuzumab was added in combination [Blackwell *et al.* 2010]. Because there is a lack of complete cross resistance among

different anti-HER-2 therapies, optimal sequential or combined use of antiendocrine and anti-HER-2 agents may significantly improve therapy for patients with metastatic ER-positive, HER-2-positive breast cancer.

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