Addressing the future: combination with targeted therapies, adjuvant setting and beyond

Paul E. Goss

The potential mechanisms of *de novo* and acquired resistance to endocrine therapy are increasingly being understood and potential treatment options that offer a therapeutic alternative in patients exhibiting resistance are being explored. Any efforts directed towards improving patient outcomes beyond aromatase inhibitors (AIs) in the adjuvant setting are likely to be focused on blocking endocrine and other pathways simultaneously, either upfront or in sequence. In particular, targeted therapies either alone or in combination with AIs may improve clinical outcomes – the results of ongoing clinical trials will shape the future treatment of breast cancer. *Anti-Cancer Drugs* 19 (suppl 2):S3–S5 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2008, **19 (suppl 2)**:S3–S5

Keywords: adjuvant therapy, endocrine, targeted therapies, aromastase inhibitors, endocrine resistance

Massachusetts General Hospital Cancer Center

Patients with breast cancer are undoubtedly better off today than in the past. Two-thirds of all breast cancer patients are amenable to adjuvant aromatase inhibitor (AI) therapy: either as 5 years of initial treatment or following an early or late switch from initial tamoxifen therapy. An AI should now be a part of adjuvant endocrine therapy for all but a few patients.

The challenge for clinical researchers is to advance the field further – achievements have been made in terms of elevating the traditional disease-free survival (DFS) curves but how can clinicians do better? A number of clinically relevant key questions exist that need to be answered. The optimal duration of treatment remains to be determined and ongoing trials are looking at longer treatment periods to clarify whether 10 or 5 years of adjuvant therapy would provide better outcomes. The optimal agent and how to best sequence current treatment options also requires further research.

Clinical research of AI therapies in premenopausal women currently lags about 10 years behind that for postmenopausal women. It remains to be determined whether ovarian function suppression (OFS) adds to tamoxifen's benefits, and additionally whether OFS with an AI is better than tamoxifen [1]. Additionally, it has yet to be established whether OFS with tamoxifen is the same as, or better or worse than with an AI, and whether there are differences among the AIs.

Preclinical data in ovariectomized rats indicate that the steroidal AI exemestane enhances bone strength [2], prevents bone loss [3] and exerts protective effects on end-organ functions that were not observed with the nonsteroidal AI letrozole [2].

There will be a wealth of efficacy and toxicity data in the adjuvant treatment setting and on contralateral breast cancer risk (prevention rates) from trials currently in progress:

- the MA.27 head-to-head trial comparing anastrozole and exemestane in almost 7000 women with early stage, hormone receptor-positive breast cancer;
- the Femara versus Anastrozole Clinical Evaluation (FACE) trial comparing letrozole with anastrozole in ~4000 women with hormone receptor-positive breast cancer; and
- two placebo-controlled prevention trials comparing anastrozole and exemestane with placebo – a trial of exemestane versus placebo (ExCel) and the International Breast Cancer Intervention Study 2 (IBIS-2) comparing anastrazole and placebo.

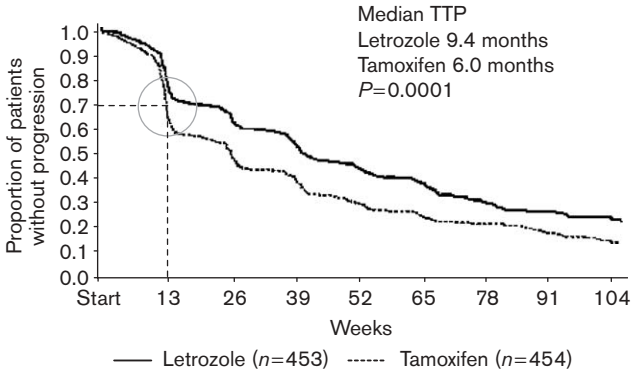
These trials will add crucial knowledge regarding the efficacy of the AIs in the adjuvant setting as well as in the prevention of breast cancer. Furthermore, the MA.27 trial will provide evidence of whether the steroidal AI exemestane is superior to the nonsteroidal anastrozole in terms of either toxicity or efficacy.

Approximately 30% of patients with oestrogen-receptor-positive (ER+) metastatic breast cancer fail to show any response to the best endocrine therapy available (Fig. 1). Thus, there appears to be a *de novo* inherent resistance to AIs in approximately one-third of hormone-sensitive breast cancer patients [4].

Three potential mechanisms of ER+ resistance to AIs may be hypothesized. The first is oestrogen hypersensitivity. The pressure exerted by long-term oestradiol deprivation causes the cancerous cells to adapt and the ER levels to increase. The membrane ER pathway is

0959-4973

Fig. 1



Proportion of patients responsive to endocrine therapy [4]. (adapted with permission from Ref. [4]).

upregulated and mitogen-activated protein kinase levels increase and in turn are responsible for phosphorylating the ER. Essentially, hypersensitivity to oestradiol reflects cross-talk between ER-mediated and growth factor-mediated pathways [5].

Two trials exist in the metastatic setting investigating 'complete oestrogen blockade'; one completed and one still ongoing. The completed study in ER + postmenopausal women has demonstrated the equivalence of letrozole versus atamestane plus toremifene in terms of time to progression (11.2 months for both arms) [6]. The results of a second trial comparing anastrozole versus anastrozole plus fulvestrant are awaited with interest.

The second potential mechanism involves oestrogen sensitivity and alternative pathway signalling. For example, the insulin-like growth factor-1 (IGF) receptor ligands promote cell growth and survival *in vitro* and mediate treatment resistance *in vivo* [7,8]. Oestradiol (E2) stimulates IGF-1R phosphorylation, and E2 and IGF-1R act synergistically to promote cell proliferation and anti-apoptosis. A treatment approach aimed at circumventing this potential method of resistance and improving outcomes relative to monotherapy involves the combination of antioestrogen therapy plus novel targeted therapy. Preclinical data demonstrate a synergy between the IGF-1R antibody CP-751,871 and tamoxifen; this combination reduced tumour size to a greater extent than either agent administered alone [9]. An ongoing international, multicentre, randomized phase II clinical trial in ER +postmenopausal women with metastatic breast cancer ($n = 150$) is investigating exemestane alone or in combination with CP-751,871.

Ongoing trials are also investigating the combination of E2 deprivation plus anti-HER2 (Human epithelial growth factor receptor 2) therapy in postmenopausal patients who have HER + or HER – ER + metastatic breast cancer. In another trial, TAnDEM, in HER2 + ER – postmenopausal patients the combination of anastrozole plus trastuzumab improved median progression-free survival (4.8 vs. 2.4 months; $P = 0.0016$) and overall survival (28.5 vs. 23.9 months) relative to anastrozole monotherapy [10].

Preliminary evidence indicates that in metastatic disease, upon progression, there is a 25% conversion into seropositive HER2 levels [11]. An ongoing trial in HER2 + /– women ($n = 1200$) aims to prove this hypothesis. This trial compares letrozole alone or in combination with lapatinib with the aim of determining whether anti-HER2 therapy can obviate a possible escape mechanism of HER2 – breast cancer involving upregulation of the HER2 pathway.

The multicentre Tykerb (lapatinib) Evaluation After Chemotherapy (TEACH) trial has just been initiated; patients who have prevalent HER2 + breast cancer will be randomized to lapatinib versus placebo for 1 year. Approximately half of these patients are ER + and some are currently taking endocrine therapy that will allow investigators to evaluate the interaction between endocrine therapy and anti-HER2 therapy in the adjuvant setting.

The PI3-kinase/AKT pathway also appears to be particularly important in breast cancer. AKT upregulation may contribute to a more aggressive phenotype. AKT activation predicts a worse outcome for breast cancer patients treated with endocrine therapy [12]. Molecules such as HER2, which potently couple to the PI3-kinase/AKT pathway, may confer resistance to tamoxifen. AKT signalling mediates resistance to antioestrogen therapy related to HER2 overexpression [13,14]. Mammalian target of rapamycin (mTOR) inhibition restores responses to tamoxifen in breast cancer cells with high levels of AKT expression [15]. Synergistic *in vitro* and *in vivo* effects have been observed with combined antioestrogen therapy and mTOR inhibition [16].

An important neoadjuvant randomized phase II trial, is currently investigating the combination of RAD001, an mTOR inhibitor, plus letrozole compared with RAD001 monotherapy in 250 patients; a number of target tumour biomarkers are being investigated as proof of principle as to whether this agent shows promise in combination with letrozole.

The third potential mechanism of endocrine resistance may involve oestrogen-independent/unrelated alternate pathway signalling. Both ER and vascular endothelial growth factor are associated with tumour growth in breast cancer. Vascular endothelial growth factor inhibition prevents the 'angiogenic switch' which in turn prevents

tumour development. Antiangiogenesis agents have established efficacy in breast cancer, and antioestrogen therapy is also antiangiogenic – providing a rationale for combining AIs and antiangiogenesis treatment. At present, a phase I/II trial is investigating the combination of endocrine therapy and angiogenesis inhibition with exemestane and sunitinib in postmenopausal women with HER2– metastatic breast cancer who have had no prior chemotherapy in the advanced setting. The results of this trial may lead to the routine combination of these types of agents.

In summary, mechanisms of *de novo* and acquired resistance to endocrine therapy are increasingly being understood. Blocking endocrine and other pathways simultaneously, either upfront or in sequence, is likely to be a necessary step to improve the outcomes of patients beyond AIs in adjuvant therapy. Understanding the hierarchy of targets will be an important challenge for scientists to make the therapeutic task simpler.

Conflicts of interest: Paul Goss is a consultant to Pfizer, AstraZeneca and Novartis. He has received honoraria from Pfizer, Novartis and AstraZeneca.

References

1 Francis P, Fleming G, Nasi ML, Pagani O, Perez E, Walley B. Tailored treatment investigations for premenopausal women with endocrine responsive (ER+ and/or PGR+) breast cancer : The SOFT, TEXT and PERCHE trials. *Breast* 2003; **12 (Suppl 1)**:S44 Abstract P104.

2 Goss PE, Qi S, Cheung AM, Hu H, Mendes M, Pritzker KP, *et al*. Effects of the steroidal aromatase inhibitor exemestane and the non-steroidal aromatase inhibitor letrozole on bone and lipid metabolism in ovariectomized rats. *Clin Cancer Res* 2004; **10**:5717–5723.

3 Goss PE, Qi S, Josse RG, Pritzker KP, Mendes M, Hu H, *et al*. The steroidal aromatase inhibitor exemestane prevents bone loss in ovariectomized rats. *Bone* 2004; **34**:384–392.

4 Mouridsen H, Gershanovich M, Sun Y, Perez-Carnon R, Boni C, Monnier A, *et al*. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001; **19**:2596–2606.

5 Johnston SR, Martin LA, Head J, Smith I, Dowsett M. Aromatase inhibitors: combinations with fulvestrant or signal transduction inhibitors as a strategy to overcome endocrine resistance. *J Steroid Biochem Mol Biol* 2005; **95**:173–181.

6 Goss P, Bondarenko IN, Manikhas GN, Pendergrass KB, Miller WH Jr, Langecker P, Blanchett D. Phase III, double-blind, controlled trial of atamestane plus toremifene compared with letrozole in postmenopausal women with advanced receptor-positive breast cancer. *J of Clinical Oncology* 2007; **25**:4961–4966.

7 Song RX, Barnes CJ, Zhang Z, Bao Y, Kumar R, Santen RJ. The role of Shc and insulin-like growth factor 1 receptor in mediating the translocation of estrogen receptor alpha to the plasma membrane. *Proc Natl Acad Sci U S A* 2004; **101**:2076–2081.

8 Pollack MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer* 2004; **4**:505–518.

9 Cohen BD, Baker DA, Soderstrom C, Tkalcevic G, Rossi AM, Miller PE, *et al*. Combination therapy enhances the inhibition of tumor growth with the fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody CP-751, 871. *Clin Cancer Res* 2005; **11**:2063–2073.

10 Mackey JR, Kaufman B, Clemens M, Bapsy PP, Vaid A, Wardley A, *et al*. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2006; **100 (Suppl 1)**:5–6.

11 Carney WP, Neumann R, Lipton A, Leitzel K, Ali S, Price CP. Monitoring the circulating levels of the HER2/neu oncoprotein in breast cancer. *Clin Breast Cancer* 2004; **5**:105–116.

12 Perez-Tenorio G, Stahl O, Southeast Sweden Breast Cancer Group. Activation of AKT/PKB in breast cancer predicts a worse outcome among endocrine treated patients. *Br J Can* 2002; **86**:540–545.

13 Kurokawa H, Lenferink AE, Simpson JF, Pisacane PI, Sliwkowski MX, Forbes JT, *et al*. Inhibition of HER2/neu (erbB-2) and mitogen-activated protein kinases enhances tamoxifen action against HER2-overexpressing, tamoxifen-resistant breast cancer cells. *Cancer Res* 2000; **60**:5887–5894.

14 Kurokawa H, Arteaga CL. ErbB (HER) receptors can abrogate antiestrogen action in human breast cancer by multiple signaling mechanisms. *Clin Can Res* 2003; **9**:511S–515S.

15 deGraffenried L, Friedrichs W, Fulcher L, Gavriil M, Frost P, Greenberger LM. The mTOR inhibitor, CCI-779, restores tamoxifen response in breast cancer cells with high Akt activity [abstract]. *Eur J Cancer* 2002; **38 (Suppl 7)**: 158.

16 Zhang Y, Sadler T, Annable T. Combination therapy for treating breast cancer using the antiestrogen, ERA-923 and the mTOR inhibitor, CCI-779 [abstract]. *94th Annual Meeting of the American Association for Cancer Research* 2003; 739.