Tailored endocrine therapy – ready for clinical practice

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Introduction

Over the last few decades, several medical endocrine therapies have been developed for breast cancer treatment. These provide a number of alternative approaches to hormonal therapy that may be exploited to enhance the efficacy and tolerability of the therapeutic opportunity provided by the estrogen dependence of a large proportion of breast carcinomas. As well as choice of individual agent, consideration must be given to the possible value of combination therapy and the optimal use of the agents in sequence.

More recently, advances in the molecular understanding of estrogen signalling and interactive pathways in breast cancer cells, together with translational studies of the importance of these pathways to clinical response and resistance have begun to identify rational concepts for the utilisation of these treatment options in individual patients. Such tailored therapy is in its infancy. This article seeks to identify some of the most relevant data that underpin the developing concepts and to assess the extent to which they are ready for routine application in the clinic.

Options for endocrine therapy

While some of the available agents are effective in both pre- and post-menopausal women, others are effective only in one of these groups. They are therefore discussed below according to these circumstances.

Premenopausal patients

Tamoxifen

Tamoxifen and related agents such as toremifene and raloxifene bind competitively with the estrogen receptor (ER) and block the binding of estrogens. This leads to a mixed agonist/antagonist action in a manner that varies according to prevailing estrogen levels and the tissue under consideration. Overall antagonism is more apparent in circumstances of high estrogen activity [1]. Thus, in premenopausal women, antagonism of estrogen is apparent in most tissues. The pharmacology of tamoxifen in women with intact ovarian function is complicated, however, by the inhibition of estrogenic feedback on the hypothalamus that leads to enhanced gonadotrophin secretion and stimulation of ovarian activity. In most patients, this leads to continued ovarian/uterine cyclical function but with plasma estrogen levels that may be several-fold higher than normal [2]. While it is possible, and perhaps likely, that these high estrogen levels may compromise full anti-estrogenic activity, pharmacokinetic modelling indicates that despite this the ER is >95% occupied by tamoxifen or its metabolites and clinical effectiveness is apparent at a level that appears relatively similar to that seen in postmenopausal women and in premenopausal women treated with ovarian ablation [3].

Gonadotropin releasing hormone (GnRH) agonists

Over recent years, the availability of medical agents that lead to reversible ovarian ablation has led to fewer surgical or radiotherapeutic ablations. The agonists lead to down-regulation of pituitary sensitivity to endogenous GnRH stimulation and to markedly decreased gonadotrophin secretion leading to a loss of cyclical ovarian function. Plasma estrogen levels fall to values similar to those seen in postmenopausal women but mean levels may be marginally higher since there is evidence of a persistent low level of follicular activity. The application of tamoxifen alongside a GnRH agonist is more effective than either alone in advanced disease [4] and an aromatase inhibitor added to a GnRH agonist at relapse with the agonist alone provides further responses in many patients [5]. Each of these combinations is now being assessed in early disease.

Postmenopausal patients

Tamoxifen

In postmenopausal patients, tamoxifen and its metabolites have been calculated to occupy more than 99.9% of the available ERs [3]. Tamoxifen has been the

standard of care for the first-line hormonal therapy of steroid receptor-positive breast cancer for more than two decades. When given as adjuvant therapy for 5 years to such patients, recurrence rate and mortality are substantially reduced [6]. Data from the ATAC trial in which the effectiveness of tamoxifen alone was poorer than anastrozole and the combination of tamoxifen plus anastrozole was equivalent to tamoxifen alone appears to confirm the importance of the agonist activity of tamoxifen to its clinical efficacy [7].

Aromatase inhibitors

Aromatase is the enzyme that converts androgens to estrogens. Several inhibitors of it have been developed for the treatment of breast cancer and three are now in widespread use: the non-steroidal inhibitors anastrozole and letrozole and the steroidal inhibitor (or inactivator) exemestane. Each of these suppresses whole body aromatisation in postmenopausal women by over 95%, with letrozole achieving greater than 99% suppression. A series of adjuvant trials have now demonstrated that the aromatase inhibitors are more effective, and overall, better tolerated than tamoxifen, although there are problems related to increased bone loss in association with the profound estrogen deprivation [8].

The optimal duration of treatment is yet to be determined, and some recent data demonstrating that aromatase inhibition after two or three years of tamoxifen is better than continued tamoxifen have led to debate as to the most appropriate starting adjuvant therapy. There are data from correlative research studies that may help address this issue. There is general acceptance that the large majority of postmenopausal patients with early breast cancer should have an aromatase inhibitor included in their adjuvant treatment at some stage [9].

Tailoring endocrine therapy

The choice of whether to administer endocrine therapy of some type is almost entirely dependent on the presence of significant amounts of ER (alpha). Interpretation of clinical data related to ER is affected by the means by which the receptor measurements were made.

Measurement of ER

The definition of the ER status of a breast carcinoma is nowadays made almost always by immunohistochemistry using one of a number of monoclonal antibodies. However, ER status of patients that entered clinical trials that have reported recently may have been measured by different methodology. Having been pioneered by clinical scientists such as the late Bill McGuire during the late 1970s, ER analysis became increasingly common through the 1980s with the ligand-binding assay or dextran-coated charcoal assay being the most frequently used methodology. This involved the homogenisation of unfixed tissue (normally >100 mg) and the derivation of a cytosol that was then incubated with saturating concentrations of radioactive estradiol. Estradiol that was not bound to ER was removed with dextran-coated charcoal to allow the concentration of the receptor to be assessed by the stoichiometric nature of the binding of the radioactive estradiol. The availability of monoclonal antibodies to ER in the late 1980s offered an alternative biochemical assay, the enzyme immunoassay. Both of these assays have the disadvantage of needing significant amounts of fresh tissue as well as being laborious and expensive to conduct.

The conduct of immunohistochemistry allows ER to be assessed inexpensively in almost all good histology departments but its interpretation and scoring remains contentious with a variety of cut-offs being used. There are compelling data to indicate that ER expression in only 1% of breast cancer cells has significant consequences for clinical outcome such that tumors of this type should be regarded as ER positive [10]. The sensitive analyses conducted nowadays have led to a circumstance with a bimodal distribution of ER values in which almost all tumors are found to ER negative or strongly positive with only a small proportion showing intermediate values.

Phenotype of ER-positive breast cancer

There are a number of key correlates with positive ER status that are generally associated with good prognosis. For example, there is significantly higher expression in low grade than high grade tumors. Proliferation as measured by S-phase in a very large study was negatively related to ER and this is also the case with other indices of proliferation [11].

However, there is a large amount of molecular, biological and clinical heterogeneity among ER+ tumors and it is this that is allowing a consideration of whether there may be differential benefit of the tumors from treatment with different endocrine agents and therefore additional tailoring of therapy once positive ER status has been established.

HER2 status

Only about 10% of ER-positive tumors are HER2 positive but this still means that about 50% of HER2-positive tumors are ER positive. A series of studies indicate that HER2-positive breast cancer gains less benefit from tamoxifen than HER2 negative disease [12]. There are two neoadjuvant studies comparing tamoxifen with either letrozole or anastrozole that suggest that this partial resistance may not occur with aromatase inhibitors.

In a study conducted by Eiermann et al. [13], 337 postmenopausal women who were ER and/or progesterone-receptor (PR) positive on pre-treatment biopsy were randomly assigned to either primary letrozole or tamoxifen. In 237 women, a biopsy was also available for central testing of HER2/EGFR [14]. In the ER-positive tamoxifen-treated patients the response rate was 21% for those who expressed EGFR and/or HER2 and 42% in those who were EGFR and HER2 negative, although this difference did not reach statistical significance ($p=0.095$). A novel finding was that in ER-positive patients who were also EGFR and/or HER2 positive, the response rate was significantly higher to letrozole than to tamoxifen (88% vs 21%, $p=0.0004$). In contrast, there was no significant difference between response rates to letrozole and tamoxifen in the ER-positive, EGFR- and HER2-negative patients (54% vs 42%, $p=0.078$).

In the IMPACT study, 330 post-menopausal women with operable breast cancers were randomised to receive three months of neoadjuvant anastozole, tamoxifen or the combination [15]. Thirty-four of 239 (14%) per protocol treated ER-positive patients were HER2 positive. In these patients the response rate to anastrozole (58%) was higher than that to tamoxifen (22%) although this did not reach statistical significance ($p=0.09$).

The suggestion from these studies is that women with HER2-positive tumors are more likely to respond to aromatase inhibitors than to tamoxifen. Many clinicians now preferentially treat HER2-positive patients with an aromatase inhibitor rather than tamoxifen despite the small numbers of patients in these studies and the neoadjuvant as opposed to adjuvant nature of the trials.

Progesterone receptor

Few ER negative tumors express PR, but those that do have a good prospect of response to endocrine therapy. In ER-positive tumors, the expression of PR has little bearing on benefit from tamoxifen as adjuvant therapy [6], but does have prognostic significance. A retrospective subgroup analysis of the ATAC trial revealed that the benefit of anastrozole over tamoxifen was substantially greater in PR negative than in PR-positive patients [16]. If confirmed by other adjuvant trials of aromatase inhibitors, this result could markedly influence the tailoring of choice of endocrine therapy for postmenopausal women. The explanation of the greater impact of anastrozole in PR negative patients is not clear but might be at least partly dependent on the inverse relationship between expression of PR and both HER2 and EGFR.

Molecular profiling

Rapid-throughput, genome-wide mRNA expression profiling has been applied in numerous studies of breast cancer prognosis over the last few years. An early study of this type created a new division of ER-positive breast carcinomas by unsupervised hierarchical clustering: luminal A and B with the former of these having a better prognosis [17]. However, the robustness of this categorization is not proven and the significance for response to endocrine therapy has not been tested. Indeed, there are few results at all from molecular profiling to date that have an impact in relation to tailoring of hormonal therapy.

Two important studies have reported 2- and 21-gene signatures respectively that identify patients that have a good or poor prognosis during tamoxifen therapy but these relate more to the value of added chemotherapy [18,19]. Each of these and any other molecular discriminator that have been constructed using a tamoxifen-treated cohort require confirmation of their value in other circumstances, e.g. in aromatase inhibitor treated patients, before they are applied in the respective circumstance. Collections of samples from some of the large adjuvant trials of aromatase inhibitors versus or in sequence with tamoxifen have been made and the application of molecular analyses to these samples may be expected to assist in deriving new approaches to tailoring endocrine therapy.

New targeted therapies

Recent data revealing the major improvement in outcome for HER2-positive early breast cancer patients treated with trastuzumab in addition to chemotherapy have highlighted the value of new agents targeted at particular molecular abnormalities and the need for accurate diagnostics to identify this population. As yet, it remains to be demonstrated that the addition of trastuzumab to endocrine therapy has similar advantages and indeed whether these advantages might differ between tamoxifen and estrogen deprivation

treatment. Nonetheless, it is near certain that there will be further developments soon in this field that provide for tailoring of endocrine therapy with these agents.

Summary

There are emerging molecular data that indicate that choice of type of endocrine therapy according to tumor phenotype may be possible. The first of these depends on commonly measured features such as PR and HER2, but in the near future, we can expect this to be extended substantially, particularly in the circumstances of combination therapy with new targeted agents.

References

1 Wakeling AE, Valcaccia B. Antioestrogenic and antitumour activities of a series of non-steroidal antioestrogens. *J Endocrinol* 1983, **99**, 455–464.
2 Ravdin PM, Fritz NF, Tormey DC, Jordan VC. Endocrine status of premenopausal node-positive breast cancer patients following adjuvant chemotherapy and long-term tamoxifen. *Cancer Res* 1988, **48**, 1026–1029.
3 Dowsett M, Haynes BP. Hormonal effects of aromatase inhibitors: focus on premenopausal effects and interaction with tamoxifen. *J Steroid Biochem Mol Biol* 2003, **86**, 255–263.
4 Klijn JG, Blamey RW, Boccardo F, *et al.* Combined Hormone Agents Trialists' Group and the European Organization for Research and Treatment of Cancer. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001, **19**, 343–353.
5 Dowsett M, Stein RC, Coombes RC. Aromatization inhibition alone or in combination with GnRH agonists for the treatment of premenopausal breast cancer patients. *J Steroid Biochem Mol Biol* 1992, **43**, 155–159.
6 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005, **365**, 1687–1717.
7 Dowsett M, Howell A. Breast cancer: aromatase inhibitors take on tamoxifen. *Nat Med* 2002, **8**, 1341–1344.
8 Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med* 2003, **348**, 2431–2442.
9 Winer, EP, Hudis C, Burstein HJ, *et al.* American Society of Clinical Oncology. Technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 2005, **23**, 619–629.
10 Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol* 1999, **17**, 1474–1481.
11 Wenger CR, Beardslee S, Owens MA, *et al.* DNA ploidy, S-phase, and steroid receptors in more than 127,000 breast cancer patients. *Breast Cancer Res Treat* 1993, **28**, 9–20.
12 Ring A, Dowsett M. Human epidermal growth factor receptor-2 and hormonal therapies: clinical implications. *Clin Breast Cancer* 2003, **4**, S34–S41.
13 Eiermann W, Paepke S, Appfelstaedt J, *et al.* Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. *Ann Oncol* 2001, **12**, 1527–1532.
14 Ellis MJ, Coop A, Singh B, *et al.* Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001, **19**, 3808–3816.
15 Smith IE, Dowsett M, Ebbs SR. et al Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen or both in combination: the IMPACT multicentre double-blind randomized trial. *J Clin Oncol* 2005, **23**, 5108–5116.
16 Dowsett M, Cuzick J, Wale C, *et al.* Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status. *J Clin Oncol* 2005, in press.
17 Sorlie T, Tibshirani R, Parker J, *et al.* Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA. 2003, **100**, 8418–8423.
18 Ma XJ, Wang Z, Ryan PD, *et al.* A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. *Cancer Cell* 2004, **5**, 607–616.
19 Paik S, Shak S, Tang G, *et al.* A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004, **351**, 2817–2826.