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E12. Predictors of resistance to hormonal therapy in breast cancer

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Endocrine therapy with selective oestrogen receptor modulators (SERMs), such as tamoxifen, or agents leading to oestrogen deprivation, gonadotrophin-releasing hormone (GnRH) agonists in premenopausal and aromatase inhibitors in postmenopausal women, are widely used in the treatment of all stages of breast cancer. Resistance to such treatments can be intrinsic and occur at first exposure or acquired after initial response. The identification of predictors of resistance to these agents is important for the appropriate selection of patients for treatment. Additionally, where these predictors are mechanistically involved in the resistance, their identification is important for the development and application of new agents targeted at the pathways involved.

It has become increasingly clear that only those patients that present as positive for oestrogen receptor (ER)-α and/or progesterone receptor (PgR) benefit from hormonal therapy of any sort. The small fraction of patients that are ER-PgR+ (<5% of total in almost all reports) is important to define as they do show benefit, despite having no measurable ER. Some data indicate that ER-β expression may be associated with a poorer likelihood of response to endocrine therapy, but the data are not sufficiently compelling to assess this marker routinely [1]. Most patients continue to show ER+ disease at relapse during endocrine therapy, but approximately 15% of patients treated with tamoxifen show no ER in relapsed lesions [2].

The growth factor receptors, HER2 and epidermal growth factor receptor (EGFR), are less frequently positive in ER+ breast cancers, but there is increasingly strong evidence that tumours in which one or both are co-expressed with ER show a reduced likelihood of benefit from tamoxifen. This evidence comes from a series of adjuvant studies of tamoxifen (none of which is individually persuasive in this regard) and 2 neoadjuvant studies of tamoxifen versus an aromatase inhibitor [3,4]. Of particular interest, ER+-HER2/EGFR+ tumours showed a better response to the aromatase inhibitors in these latter studies. This may be due to cross-talk between the growth factor receptor and ER signalling pathways that in model systems leads to sensitisation of the ER to oestrogen stimulation and to the agonist effects of tamoxifen [5].

PgR expression is thought to be highly dependent on the classical mechanism of ER-oestrogen response element signalling. There is recent evidence that there may be differential benefit from aromatase inhibitors and tamoxifen according to the PgR status of ER tumours. A retrospective subgroup analysis in the arimidex, tamoxifen, alone or in combination (ATAC) adjuvant trial of anastrozole versus tamoxifen versus the combination of anastrozole and tamoxifen found that patients that were ER+PgR+ or ER+PgR- had a similar recurrence-free survival (RFS) on anastrozole, but that patients that were ER+PgR- faired much worse on tamoxifen than the ER+PgR+ patients. This resulted in a substantially greater benefit for anastrozole over tamoxifen in the ER+PgR- than in the ER+PgR+ patients, although greater benefit over tamoxifen remained in the latter group. There is significant co-segregation of growth factor receptor-positivity with PgR-negativity. Therefore, it may be growth factor receptor-positivity that is responsible for this differential benefit and PgR expression may be a marker of this mechanism. This possibility will be examined by growth factor receptor measurements in a retrospective collection of excised tumours from the ATAC trial in study TA/01 (also known as TransATAC).

Almost all studies of response and resistance in breast cancer depend on clinical measurement of tumour growth or regression and the linkage of this to putative biochemical or molecular markers of response/resistance. By such clinical measures, approximately 50% of

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ER+ patients may be deemed responsive or have long-term stable disease with first-line therapies. If, instead, one examines the effects on tumour cell proliferation (the major determinant of tumour growth changes due to hormonal therapy), it is clear that reduced proliferation, as measured by the nuclear marker Ki67, occurs in approximately 90% of ER+ patients treated with aromatase inhibitors and 80% with tamoxifen. Thus, measurements with molecular markers indicate that the great majority of ER+ breast cancers have some dependence on oestrogen, but that this may be insufficient to lead to regression for many.

In summary, oestrogen antagonism and oestrogen deprivation are major therapeutic strategies of known benefit in breast cancer. However, not all patients benefit from therapy and almost all that present with advanced disease relapse during therapy. The major determinant of *de novo* resistance is ER-negativity. While relapse is sometimes associated with the development of ER-negative disease, in most patients ER persists. Instead, growth factor receptors and their associated downstream pathways appear to be intimately involved in the mechanisms of acquired resistance. There is increasing evidence that the mechanisms of resistance differ, at least partially, between tamoxifen and aromatase inhibitors.

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