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E21. What is the best therapy for ER-positive breast cancer?

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Endocrine therapy for breast cancer consists of a variety of both medical and surgical ablative treatment modalities, but ablative therapy has been almost completely replaced by medical treatments. Most endocrine therapies have more than one endocrine effect, frequently together with direct growth-inhibitory actions. In the past two decades, the number of endocrine agents available has drastically increased. Some novel approaches to endocrine therapies for breast cancer are the less toxic and more potent aromatase inhibitors, oestradiol receptor modulators (SERMS) and downregulators (''pure anti-oestrogens''), luteinising hormone-releasing hormone (LHRH) analogues, growth factor receptor antibodies and inhibitors of growth factor signal transduction. The role of progesterone receptor (PgR) modulators is, as yet, unclear. In postmenopausal metastatic breast cancer, aromatase inhibitors have replaced tamoxifen as first-line endocrine treatment, but the optimal sequence of (potential) endocrine therapies is still debated. In premenopausal metastatic breast cancer, combination treatment with a LHRH agonist and tamoxifen is most effective, but tamoxifen might also be replaced in this subgroup by an aromatase inhibitor in the near future. A number of cell biological factors predict resistance to tamoxifen treatment, and these factors will probably differ with respect to other endocrine therapies. Tumour resistance to endocrine therapy can be modified by anti-growth factor therapy. Therefore, many trials with the aim of improving the results of endocrine therapy have still to be performed.

1. Introduction

In 1896, endocrine therapy of breast cancer was first applied by means of surgical oophorectomy. Since then, a lot of surgical, radiotherapeutical and, especially, medical systemic therapies have been developed, such as adrenalectomy, hypophysectomy, ovarian or pituitary irradiation, androgens, synthetic oestrogens, high-dose progestins, aromatase inhibitors, LHRH-agonists, anti-progestins, pure anti-oestrogens, new specific oestrogen receptor modulators (SERMs) and anti-growth factor therapies. Previously, endocrine treatment was given to all patients, but during the last 15 years this treatment is being increasingly restricted to patients with hormone receptor (oestrogen receptor (ER), PgR-positive tumours) or with unknown receptor status but with a long-term disease-free interval. Until recently, tamoxifen was the standard first-line endocrine therapy for breast cancer, but now a number of other treatment options are available.

2. Predictive factors

Overall, an objective response or long-term stable disease (> 6 months) occur in approximately 50–70% of patients with ER-positive tumours. However, a significant number of patients have tumours that are resistant to endocrine therapy. Ultimately, all patients with metastatic disease will develop resistance to hormonal therapy. ER, PgR, pS2 and tissue plasminogen activator (tPA) predict a favourable response to tamoxifen treatment. By contrast, increased expression of urokinase-plasminogen activator (uPA), plasminogen activator inhibitor-1 (PAI-1), urokinase plasminogen activator receptor (uPAR), p53, epidermal growth factor receptor (EGFR), HER2/neu, vascular endothelial growth factor (VEGF) and mutations in *TP53* are associated with a worse response to endocrine treatment [1]. Recently, it has been shown that gene expression profiles and gene methylation status measured using micro-array analyses can also predict the response to endocrine therapy.

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3. Premenopausal metastatic breast cancer

Options for endocrine therapy are surgical oophorectomy, medical castration by LHRH analogues, or tamoxifen. Combined endocrine treatment with a LHRH-agonist plus tamoxifen is currently the first choice of treatment because this combination appears to be significantly superior to single endocrine therapy with respect to response rate, progression-free survival and overall survival [2,3]. Replacing tamoxifen by anastrozole in combination with goserelin caused a stronger suppression (98%) of plasma oestrogen concentrations *i.e.* from 224 to 5 pmol/l in contrast to 24 pmol/l (89% reduction) during treatment with goserelin plus tamoxifen [4]. A randomised phase II study by Milla-Santos *et al*. [5], comparing the efficacy of goserelin plus anastrozole with that of goserelin plus tamoxifen showed superior results for the combination of goserelin plus anastrozole with respect to the response rate (80% *versus* 53%), median duration of response (12.1 *versus* 8.3 months) and median survival (18.9 *versus* 14.3 months). However, confirmative studies are needed.

4. Postmenopausal metastatic breast cancer

New potent and selective aromatase inhibitors and inactivators have now replaced tamoxifen as first-line therapy for metastatic breast cancer [6–9]. They appear to be more effective than tamoxifen in patients with low ER tumour levels, ER^+ PgR^- tumours and ER^+ $HER2/neu^+$ tumours [10]. The third generation drugs, anastrozole, letrozole and exemestane, are used in many trials and in daily clinical practice.

Another new interesting compound is the 'pure anti-oestrogen', fulvestrant (Faslodex) [11–13]. Fulvestrant appears to be at least as effective as anastrozole in patients with progressive disease after first-line treatment with tamoxifen. In the first-line setting, treatment with fulvestrant showed equal anti-tumour efficacy when compared with tamoxifen. In the adjuvant setting Arimidex, tamoxifen, alone or in combination (ATAC)-trial, the combination treatment of tamoxifen and anastrozole appeared to be less effective than single treatment with anastrozole alone due to the oestrogen agonistic actions of tamoxifen in the presence of low plasma oestrogen levels. In view of the fact that fulvestrant lacks oestrogenic activities, but downregulates ER and PgR, the combination of fulvestrant with an aromatase inhibitor might improve the results of endocrine treatments for breast cancer.

Finally, treatment with high-dose progestins, androgens and high-dose oestrogens are still valuable as 3rd–5th-line treatment modalities in patients with hormone-sensitive disease after treatment with anti-oestrogens and aromatase inhibitors. The role of PgR modulators (anti-progestins) is unclear, but this category of drugs remains interesting [14].

5. Biologicals

Overexpression of HER2/neu, EGFR and VEGF are frequently associated with hormone-resistant tumours. Antibodies against (receptors of) these growth factors or signal transduction inhibitors of their pathways can reduce tumour growth in preclinical experimental tumour models and in patients with metastatic disease. Single first-line treatment with Herceptin (anti-HER2/neu) can induce tumour remission in up to 40% of patients with HER2/neu-positive tumours, but other anti-growth factor therapies, such as gefitinib (Iressa; ZD1839) appeared to be less effective when used as single treatments. However, targeting both growth factor and ER pathways may achieve greater tumour inhibition than targeting either pathway alone, as has been shown in *in-vitro* studies.

6. Conclusions

The most important treatment modality in patients with ER^+ tumours is endocrine therapy. Chemotherapy is most important in patients with ER^- $HER2^-$ tumours and in patients with ER^- $HER2^+$ tumours Herceptin is the treatment of choice. Combination therapies of biologicals with conventional standard endocrine and chemotherapies [15] and the combination of different biological therapies are most promising strategies.

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