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Overview

New Developments and Future Directions in Systemic Therapy

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Abstract

Adjuvant systemic therapies for breast cancer have led to a significant reduction in the risk of relapse and improvement in overall survival. However, a substantial proportion of breast cancer patients still ultimately experience relapse with metastatic disease. Here we review recent progress in trials of systemic therapies, including endocrine therapy, chemotherapy and targeted therapies for breast cancer. A current challenge for translational research is to identify drivers of resistance that may be amenable to therapy, as well as potential compensatory mechanisms that might limit the effectiveness of novel therapies. Unfortunately, not all targeted agents entering clinical trials will show sufficient efficacy to be approved for use. We highlight key findings from trials of novel agents, and the need for further research to identify biomarkers of response to systemic therapies in breast cancer.

Key words: Angiogenesis; breast cancer; chemotherapy; endocrine therapy; targeted therapy

Statement of Search Strategies Used and Sources of Information

A Pubmed search was carried out using the following: endocrine therapy for breast cancer, targeted therapy for breast cancer, chemotherapy for breast cancer.

Introduction

Breast cancer is a heterogeneous disease with different molecular subtypes, prognoses and responses to therapy [1]. At the time of diagnosis in the clinic, breast cancers are broadly divided in hormone-positive tumours that express oestrogen receptor and/or progesterone receptor, *ERBB2* amplified (HER2-positive) tumours and triple-negative tumours characterised by the absence of expression of oestrogen receptor, progesterone receptor or HER2. For oestrogen receptor-positive tumours, endocrine therapy is pivotal to systemic therapy, and for many patients with early breast cancer this may be very successful adjuvant therapy without the requirement for chemotherapy. For HER2-positive tumours, outcomes have been transformed since the introduction of the monoclonal antibody trastuzumab, whereas for triple-negative tumours the best treatment option remains unclear.

Unfortunately, despite these successful adjuvant therapies for each subgroup, a substantial proportion of patients with breast cancer still ultimately relapse with metastatic disease. Improved understanding of the biology of breast cancer has led to the identification of a number of novel molecular targets amenable to therapeutic intervention. Challenges remain in identifying patients who would probably respond to these targeted therapies, and how best to combine treatments to overcome compensatory loops that drive the emergence of drug resistance. Results from key recent studies of systemic therapy in advanced breast cancer are outlined below, together with considerations for trial design and further research that is required to transform these therapies into life-saving treatments in the early breast cancer setting.

Oestrogen Receptor-positive Breast Cancer — Advances in Adjuvant Endocrine Therapy

Until recently, tamoxifen had been the gold standard of adjuvant endocrine therapy for oestrogen receptor-positive

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breast cancer. The results of the most recent Early Breast Cancer Trialists Collaborative Group overview involving over 21 000 women have shown that tamoxifen for about 5 years reduces the risk of death by around one-third in the first 15 years (relative risk 0.71). The proportional risk reduction was not significantly affected by age, the use of chemotherapy, nodal status or expression of progesterone receptor status; with an absolute benefit relating to an absolute risk of recurrence. Highly oestrogen receptor-positive disease (≥200 fmol/mg) was associated with an even greater benefit, with a hazard rate ratio for breast cancer mortality with tamoxifen of 0.53 compared with 0.67 in marginally oestrogen receptor-positive disease [2]. However, patients still relapse despite tamoxifen, and more effective therapies are required.

In the last decade, the aromatase inhibitors have shown superior risk reduction over tamoxifen in postmenopausal early breast cancer [3,4]. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, anastrozole was compared with tamoxifen and with the combination of the two drugs and was shown to be superior to both in terms of disease-free survival (DFS) (hazard ratio 0.86, 95% confidence interval 0.78–0.95; $P = 0.003$) in hormone receptor-positive patients at a median follow-up of 120 months [3]. Similarly, the BIG-198 trial compared letrozole with tamoxifen in a four-arm study design as follows: letrozole monotherapy; tamoxifen monotherapy; sequential tamoxifen then letrozole; sequential letrozole then tamoxifen; all for a total of 5 years. At a median follow-up of 8.7 years, letrozole was significantly better than tamoxifen in terms of both DFS (hazard ratio 0.82, 95% confidence interval 0.74–0.92) and overall survival (hazard ratio 0.79, 95% confidence interval 0.69–0.90) [4]. There have also been several trials that have reported a benefit in risk reduction with the use of adjuvant aromatase inhibitors given after an initial 2–3 years of tamoxifen versus tamoxifen for 5 years [5–9]. However, the BIG-198 study found no advantage to the switch compared with letrozole upfront (8 year DFS 85.9% versus 87.5%) [4]. Similarly, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial reported no significant difference in DFS at a median follow-up of 5.1 years [9]. Therefore, current evidence does not support the use of a switching strategy over an aromatase inhibitor upfront, although patient age, cost and relative toxicities with each of the therapies may also influence the choice of therapy and some oncologists will opt for a switching strategy or even tamoxifen alone in very low-risk groups.

Issues in Premenopausal Oestrogen Receptor-positive Breast Cancer

An important question in oestrogen receptor-positive premenopausal early breast cancer is whether the addition of ovarian suppression/ablation to adjuvant tamoxifen (and chemotherapy where appropriate) is superior to tamoxifen alone.

A landmark analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-30 trial reported that premenopausal women with oestrogen receptor-positive breast cancer who were treated with anthracycline and taxane chemotherapy and subsequently developed amenorrhea for 6 months in the 24 months from randomisation had an improved overall survival outcome (hazard ratio for death 0.52; $P = 0.002$). The differences were not apparent in oestrogen receptor-negative patients and could not be explained by differences in the dose of drug received between those patients with amenorrhea and those without [10,11]. These observations suggest that the addition of ovarian suppression to premenopausal oestrogen receptor-positive patients receiving endocrine therapy (without chemotherapy-induced amenorrhea) may potentially be beneficial. The recent Stockholm substudy of the Zoladex in Premenopausal Patients (ZIPP) trial reported that the addition of zoladex to tamoxifen was not found to be superior to either modality alone, although this study did contain a relatively high proportion of patients with lower risk disease (T1, N0 tumours) [12].

Other studies have investigated whether an aromatase inhibitor with concomitant ovarian ablation/suppression may prove superior to tamoxifen in premenopausal women with no overall survival benefit reported so far [13]. Both these issues are being addressed prospectively in the Suppression of Ovarian Function Trial (SOFT), where 3000 premenopausal women with hormone receptor-positive disease have been randomised to tamoxifen alone, tamoxifen with ovarian ablation/suppression or exemestane with ovarian suppression for 5 years. The results from this study will hopefully finally determine the role for ovarian suppression in premenopausal breast cancer.

Strategies to Overcome Endocrine Resistance by Maximal Oestrogen Receptor Blockade

Despite the use of adjuvant endocrine therapy, long-term efficacy can be limited by disease relapse and the development of resistance after adjuvant endocrine therapy. Evidence of the retention of a functional oestrogen receptor pathway after acquired resistance to tamoxifen/oestrogen deprivation therapy has led to the development of novel endocrine therapies designed to deliver maximal oestrogen receptor signalling blockade. Fulvestrant was developed as an oestrogen receptor antagonist that binds to the receptor and prevents oestrogen receptor dimerisation, leading to rapid degradation and loss of cellular oestrogen receptor. Preclinical evidence showed efficacy *in vitro* and *in vivo*, particularly when combined with oestrogen deprivation [14,15]. However, in phase III studies, fulvestrant has not proven more effective than treatment with the steroidal aromatase inhibitor exemestane in patients with prior exposure to a non-steroidal aromatase inhibitor [16,17]. This may in part be explained by an inadequate 250 mg dose of fulvestrant used in these studies, given results from the CONFIRM trial, which reported superiority in terms of progression-free survival (PFS) with the 500 mg versus the 250 mg dosing schedule [18]. Furthermore, the recent phase II Fulvestrant-First Line Study Comparing Endocrine