E12. Progress in systemic therapy for breast cancer

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If we want to summarise 10 years of clinical research in systemic therapy for advanced breast cancer (BC) and predict the future, we may argue that:

(1) substantial progress leading to new standards of care has occurred in the field of endocrine therapy (ET);
(2) for chemotherapy (CT), progress has been mainly confined to anthracycline-resistant disease; and
(3) most of the future progress is likely to come from biological agents and their integration with the two other treatment modalities (Fig. 1)

This educational session will start with advanced BC, reviewing the 2002 standards of care and the progress that is anticipated in the next decade. A similar approach will be taken for early disease.

Endocrine therapy has been the first and is still the number one targeted systemic therapy available to treat BC. For all women with *advanced disease*, who have a reasonable disease-free interval and who do not present with life-threatening metastases, it remains our preferred upfront therapy.

In the last 5 to 10 years, it has become clear that we have not yet extracted the maximal therapeutic benefit from the oestrogen receptor (ER) molecular pathway: the 3rd generation aromatase inhibitors (AI) and, more recently, the ER downregulator Faslodex™ have successfully challenged our older hormonal agents (aminoglutethimide, megestrol acetate and even tamoxifen in advanced breast cancer), leading to new standards of care which are level-1 or level-2 evidence-based and which will be briefly summarised (Fig. 2).

As we progressively refine and optimise ET, the role of CT and especially the role of combined CT and ET, needs to be carefully re-examined. The introduction of the taxanes in the treatment of advanced BC has led to modest, but significant, improvements in the outcome of anthracycline-pretreated patients, leading to new patterns

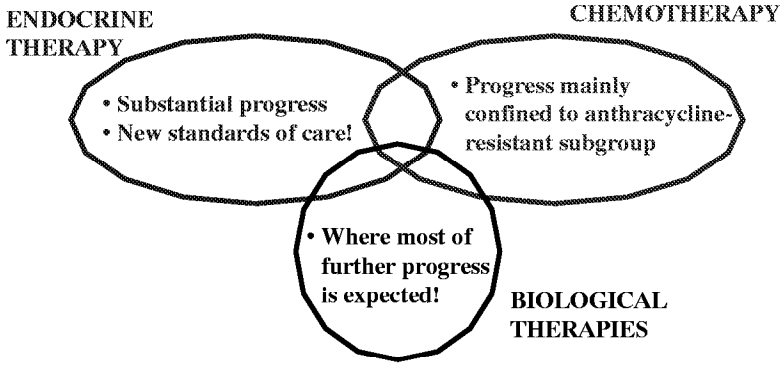

Fig. 1. Systemic treatment of breast cancer in 2001: I. Advanced breast cancer.

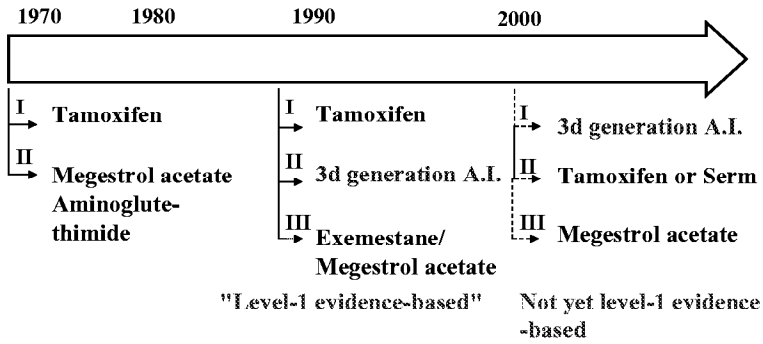

Fig. 2. Metastatic breast cancer: Optimal endocrine therapy in postmenopausal women.

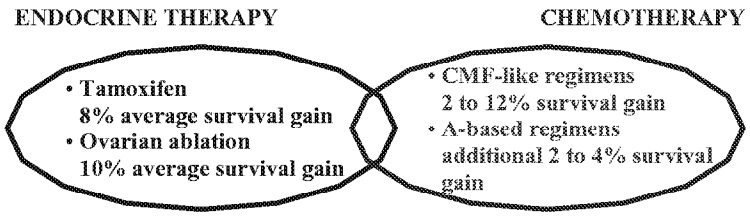

Fig. 3. Systemic treatment of breast cancer in 2001: II. Early disease.

of care for this particular subgroup. In contrast, there is as yet no consensus on a "gold-standard" first-line chemotherapy for an endocrine-resistant population taken as a whole, since trials of anthracycline-taxane combinations have failed to show consistent results in terms of response rate, time to progression and, most importantly, survival. Combined ET and CT is not recommended in advanced BC based on the lack of a demonstrable survival improvement associated with this strategy in trials conducted between 1977 and 1996. Of note, all these trials were small and underpowered, and none included a third generation AI or Faslodex™. It would be interesting to re-explore this concept, using more active hormonal agents and improved trial designs.

The time has also come to translate our growing understanding of BC biology into innovative treatment strategies: one such strategy could be to delay the onset of hormone-resistance through the use of new agents targeting specific signalling pathways important for the survival of the endocrine-resistant breast cancer cell. Ongoing or soon-to-start clinical trials based on this interesting concept and using Herceptin? (the anti-HER2 monoclonal antibody) or Iressa (the Epidermal Growth Factor receptor tyrosine kinase inhibitor) will be presented.

The outstanding clinical activity of Herceptin? in metastatic BC prompted the registration of the drug for use as monotherapy in patients with HER2-overexpressing BC who have failed anthracyclines and taxanes, as well as for use upfront in combination with paclitaxel. Possibilities for further progress with the use of Herceptin in the management of advanced B.C. will be discussed, including the combination of Herceptin with other agents targeting important signalling pathways, such as the mitogen activated kinase (MAP) kinase pathway or the phosphatidylinitosol (PI_3) kinase cell survival pathway.

In early disease (Fig. 3), the important contribution of ET to improved long-term survival has been increasingly recognised, both in young and older women whose tumours contain ERs and/or progesterone receptors.

Profound mutations are also expected soon in optimal ET for early disease, especially following the early positive results of the large Arimidex (anastrozole) vs Tamoxifen as adjuvant therapy in post menopausal women with early breast cancer (ATAC) trial showing superior efficacy and tolerability of anastrozole over tamoxifen in more than 6000 women.

Anthracyclines remain both widely used and unsurpassed by any other cytotoxic agent in the adjuvant setting. Nevertheless, it took almost 20 years to confirm the small, but real, advantage of anthracycline-based adjuvant CT over cyclophosphamide, methotrexate, 5-fluorouracil (CMF). This was mainly due to the fact that this issue was investigated in many relatively small clinical trials, instead of in a few, but sufficiently large, studies powered to detect a small difference. The lesson learned is now successfully applied to the evaluation of the taxanes' and Herceptin?'s roles in the adjuvant treatment of BC, since we observe huge international effort and collaboration in making these large clinical trials possible.

We are at a turning point in the history of how anticancer agents, including anthracyclines, are used in BC therapy: from non-selective use based on an assessment of the risk of relapse, we are moving towards treatment "tailored" to the individual patient through the use of predictive molecular markers and/or predictive gene expression profiles. This is an exciting era of progress that has the potential to maximise the clinical benefits of these important cytotoxic agents.