Chairman's introduction

Breast cancer is the most common malignant disease in women and the second leading cause of cancer death in women in the western world. Although the prognosis of primary breast cancer has improved significantly over the past 20 years, a significant proportion of patients will still experience recurrence, and, eventually, the vast majority of these patients will die from the disease.

Recurrent breast cancer represents a clinically very wide and heterogeneous scenario, ranging from isolated local recurrence to rapidly progressive multiorgan metastatic disease, and requires a multidisciplinary approach involving disciplines of local therapy (surgery, radiotherapy), oncology, radiology, pathology and basic research). In addition, a large proportion of patients have, as a result of the disease and its treatment, physical, physiological and socio-economic complaints requiring another broad spectrum of expertise.

The objectives of treatment of locally recurrent and metastatic breast cancer differ. Locally recurrent breast cancer is potentially curable provided a progressive local approach with surgery and/or radiotherapy is used, as emphasised by Drs. Overgaard and Christiansen. Their review gives detailed recommendations about the evidence-based optimal approach in isolated local and loco-regional recurrences with and without distant metastases, but also regrets that a series of questions remain unanswered due to the lack of clinical trials.

Drs. Overgaard and Christiansen have also prepared recommendations for local therapy of metastatic disease such as bone metastases, medullary compression, central nervous system (CNS) metastases, visceral metastases and malignant effusions. Clearly, clinical trials are lacking in this area, including trials attempting to analyse the value of aggressive local approaches along with systemic therapy in metastatic breast cancer.

In metastatic breast cancer, the major aim of oncological therapy is to achieve palliation and prolongation of life; cure is observed only occasionally. Another aim is to use this setting as a model to develop regimens to be applied later in the adjuvant situation. Thus, in general, systemic approaches demonstrated to prolong time to progression have been proven to reduce mortality when used as adjuvant therapy.

The systemic anti-neoplastic modalities include endocrine therapy and chemotherapy. As a result of recent developments in molecular biology, a new group of drugs is now being introduced, of which the antibody trastuzumab, inhibiting the erbB-2-dependent signal transduction, has now become standard in clinical practice.

Recent years have seen the introduction of two new groups of drugs in the endocrine therapy of advanced breast cancer, which I shall discuss in my review in this section. These include anti-oestrogens with less agonist–antagonist action compared to tamoxifen, which has been standard first-line therapy for approximately 20 years, and the third-generation aromatase inhibitors. Unfortunately, none of the new anti-oestrogens have demonstrated superiority over tamoxifen. Third-generation aromatase inhibitors, however, have demonstrated an improved therapeutic index compared to the past second-line standards aminoglutethimide and progestins, and recently, third-generation aromatase inhibitors have demonstrated at least equivalence or superiority over tamoxifen in the first-line treatment in post-menopausal women. The oestrogen and/or progestin receptor remains the test to predict sensitivity to endocrine therapy and, taking advantage of recent developments in molecular biology, translational research is now underway to develop additional predictive tests of sensitivity to the individual endocrine therapies.

Chemotherapy has remained the treatment of choice for patients with receptor-negative and/or rapidly progressive disease with major visceral involvement, and for patients no longer responsive to endocrine therapy. However, for this group trastuzumab now represents an additional option, provided the tumour expresses HER-2, defined as an overexpression of 3+ score by immunohistochemistry or gene amplification by fluorescent *in situ* hybridisation (FISH).

Piccart et al. have reviewed the role of the three major generations of cytotoxic drugs or combinations: CMF (cyclophosphamide, methotrexate, 5-fluorouracil), the anthracyclines and the taxanes as well as other drugs active in breast cancer such as vinorelbine, gemcitabine and capecitabine.

Key areas of continued research include the optimal duration of chemotherapy according to the response to the therapy, and whether to use the more

active drugs sequentially or in combinations. In general, the combinations produce higher response rates, but only a few trials have demonstrated improved time to progression or survival, and that at the expense of increased toxicity. Another area is related to the optimal scheduling of the taxanes, and high priority should be given to translational research studies designed to identify potential new markers to predict sensitivity to the individual cytotoxic agents. Trastuzumab is active both as a single agent and in combination with chemotherapy, as reviewed by Dr. Piccart and colleagues, who also emphasise critical issues related to the determination of the HER-2 status.

Several questions remain unanswered regarding the optimal use of trastuzumab, including schedule (weekly or 3-weekly), its use in combination with chemotherapy (concomitantly or sequentially), and the optimal chemotherapy to use in combination.

Based on the available evidence, Dr. Piccart and colleagues suggest a treatment algorithm for patients with metastatic breast cancer according to prior exposure to the cytotoxic agents in the adjuvant setting and according to the HER-2 status.

During the course of the disease, the majority of patients will develop bone metastases. As a result of increased bone resorption, this condition is associated with significant morbidity in terms of pain, hypercalcaemia, fractures and medullary compression. Over the past 10 years, the bisphosphonates have been demonstrated to be a valuable additional approach for the treatment of metastatic disease, as reviewed by Dr. Coleman. Orally- (clodronate, pamidronate) and intravenously- (pamidronate, ibandronate, zoledronic acid) administered drugs have all been shown to reduce morbidity related to bone metastases and, when added to endocrine therapy or chemotherapy, pamidronate prolonged the time to progression in bone. Zoledronic acid is the most potent bisphosphonate in clinical development, and has demonstrated clinical superiority over pamidronate in terms of treatment of hypercalcaemia and in reducing the frequency of other bone-related events.

Ongoing and future studies should answer the questions of the optimal route of administration of the bisphosphonates (orally, intravenously) and the proper time of administration during the course of the disease. Studies should further evaluate the potential apoptotic effect on tumour cells.

It is hoped that the four reviews in this section will provide useful information to help guide the oncologist and other involved specialists in the multidisciplinary management of locally recurrent and metastatic breast cancer.

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