Introduction

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Treating breast cancer has always been a challenge for physicians. During the past several decades, proper treatment has required an interdisciplinary approach for maximizing benefit from treatments yet reducing unnecessary damage or costs. These terms of tailoring therapies have been applied for all fields of treatment, including surgery, radiation therapy, and medical systemic therapies. Current developments attempt to spare normal tissue and normal organ function (introducing e.g., sentinel node biopsy), boosting radiation to the tumour bed (positive results observed especially for younger women) and partial breast irradiation, and **targeted systemic treatments** tailored according to markers of responsiveness to therapies.

Breast cancer was the first malignancy for which targeted therapies were developed. The therapeutic effects of endocrine manipulations have been known for many decades. Ovarian function suppression, selective oestrogen receptor modulators (SERMs, e.g., tamoxifen), high-dose progestins, aromatase inhibitors, and selective oestrogen receptor deregulators (SERDs, e.g., fulvestrant) are all currently used in the treatment of women with breast cancer, provided their tumour is endocrine responsive.

The demonstrated efficacy of chemotherapy, resulting from a non-targeted cytotoxicity, led to the development of a large spectrum of treatments for various breast cancer settings (overt metastases, large primary breast cancer, and micrometastases presumed to be responsible for relapse after primary surgery). The strategy of tailoring treatments according to the individual need, using information on disease and patient' s characteristics, has been neglected in favour of a more *simplified* approach of "one size fits all". Similar to other modern operations management of health care, this approach is problematic because it depersonalises care and decreases attention on the uniqueness of individuals. Obviously we should consider evidence of treatment efficacy obtained from prospective clinical trials using well-defined populations. Care must be taken, however, to understand whether interactions between characteristics of disease and patient influence the magnitude of treatment effect in a way which might change the cost–benefit balance used in the therapeutic decision making process. It is therefore inappropriate to base individual treatment decisions exclusively on data derived from studies that show a benefit "on average" for an entire population which is heterogeneous in terms of endocrine responsiveness and menopausal status. These two, disease and patient characteristics, are important examples to understand the inherent problem of relying on data from trials in which treatments were tested *across the board* of responsiveness features. An average benefit might be obtained by using one therapy for all patients with a broad spectrum of characteristics defined for inclusion in some trials, but might not be confirmed in another trial conducted prospectively in a more selected population. There are, therefore, several issues that one should consider when selecting systemic treatment for patients with breast cancer:

1. Aim of treatment: The primary treatment objective heavily depends upon the clinical context: it is to prevent disease recurrence following surgery and the adjuvant treatment program, and it is to maintain control of disease progression in the advanced disease setting. These are two distinct goals of therapy for which the suggested treatment would obviously differ, and for which there are different efficacy evaluations. The efficacy of postoperative adjuvant therapies can only be determined with respect to relatively long-term outcomes within a randomised trial population. By contrast, the efficacy of systemic treatments for assessable cancer, given either before surgery (i.e., primary treatments for operable or locally advanced breast cancer) or for metastases, can be determined after short-term therapeutic exposure. *Quality of life considerations* are frequently incorporated in the evaluation of therapy for advanced disease, while acceptance of toxicity is higher in the adjuvant setting due to the curative intent of this treatment program.

2. Breast cancer-related features: The demonstration of oestrogen receptor (ER) or progesterone receptor (PgR) in tumour cells using immunohistochemical staining is a powerful predictive marker of endocrine responsiveness. The absence of staining

for ER and PgR is associated with absence of response to endocrine therapies and a higher degree of responsiveness to chemotherapy. Similarly, the demonstrated efficacy of trastuzumab in reducing early relapses in patients who had a HER2 over-expressed or amplified (HER2-POS) breast cancer, allowed the inclusion of this marker into the list of essential features to indicate for best treatment choice.

3. Choice of adjuvant systemic therapies: The selection of adjuvant treatments is based on recognizing the separate nature of endocrine unresponsive, endocrine responsive and HER2-POS breast cancer.

4. Patient-related features: Menopausal age is a major determinant in treatment choice. Use of tamoxifen, ovarian function suppression and aromatase inhibitors are dependent upon ovarian endocrine activity.

5. Preoperative systemic treatment: Some types of disease presentation might require this type of approach: large primary breast cancer, locally advanced disease and inflammatory breast cancer. Either chemotherapy or, occasionally, endocrine therapies are used when the reduction in tumour size would allow breast conservation.

6. New drugs for targeting malignant breast cancer cells, stroma and vessels: These areas of research require that targets for therapeutics become better known and understood. «Over-the-board» trials with a treatment applied indiscriminately to patients with no accounting for endocrine responsiveness are probably not feasible any more in terms of ethics, yield, and costs.

Treatment of patients with breast cancer, and to some extent also strategies to prevent the disease, have undergone rapid progress in recent years. Understanding more about the features that predict response to available therapies is one of the most important contributors to such progress. It is essential that therapeutic trials in this disease be planned, analysed and reported separately for patient cohorts defined according to the endocrine responsiveness of the tumour. Tailoring treatments according to the best chance of response for individuals rather than applying all available therapies *across the board* to all patients must become the standard approach to achieve a wiser use of both therapeutic and diagnostic resources.