Journal of Steroid Biochemistry & Molecular Biology 131 (2012) 93–100

Contents lists available at SciVerse ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Presurgical (neoadjuvant) endocrine therapy is a useful model to predict response and outcome to endocrine treatment in breast cancer patients

Jürgen Geisler[a,*], Ian Smith[b], William Miller[c]

[a] Institute of Clinical Medicine, Division of Medicine and Laboratory Sciences, University of Oslo, Norway and Akershus University Hospital, Department of Oncology, N-1478 Lørenskog, Norway
[b] Royal Marsden Hospital, Department of Medicine, Breast Unit, Fulham Road, London SW3 6JJ, UK
[c] University of Edinburgh, Crewe Road South, Edinburgh EH4 2XU, Scotland, UK

ARTICLE INFO

Article history:
Received 23 October 2011
Received in revised form 9 December 2011
Accepted 11 December 2011

Keywords:
Breast cancer
Presurgical treatment
Tamoxifen
Aromatase inhibitor
Anastrozole
Letrozole
Exemestane
Translational research

ABSTRACT

Endocrine therapy of breast cancer has been improved continuously during the last decades. Currently, aromatase inhibitors are dominating treatment algorithms for postmenopausal women with hormone-receptor positive breast cancer while tamoxifen still is the most widely used drug for premenopausal women. Several research tools and study designs have been used to challenge established drugs and develop the field of antihormonal therapy. One pivotal study option has been the observation of clinical responses during presurgical/neoadjuvant endocrine therapy (PSET/NET). This strategy has several major advantages. First, the breast tumor, still present in the patient's breast during therapy, can be followed by clinical observations and radiological measurements and any treatment effect will be immediately registered. Second, tumor biopsies may be obtained before initiation and following therapy allowing intra-patient comparisons. These tumor-biopsies may be used for the evaluation of intra-tumor changes associated with drug treatment. As examples, presurgical breast cancer trials have been used to evaluate intra-tumor estrogen levels during therapy with aromatase inhibitors and also to study mechanisms involved in the adaptation processes to estrogen suppression. Biomarker studies have provided information that may be used for patient selection in the future. Finally, recently published results from presurgical trials testing combinations of classical endocrine drugs and novel targeted therapies have produced promising results.

Contents

* Corresponding author at: Institute of Clinical Medicine, Division of Medicine and Laboratory Sciences, University of Oslo & Dept. of Oncology, Akershus University Hospital, Sykehusveien 25, N-1478 Lørenskog, Norway. Tel.: +47 02900; fax: +47 67 96 3820.
E-mail address: juergen.geisler@medisin.uio.no (J. Geisler).

0960-0760/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2011.12.006

1. Introduction

Presurgical and neoadjuvent systemic therapy of breast cancer patients has been established for several decades preferably as a tool to down-stage large or locally advanced, inoperable breast cancer with the final goal of enabling mastectomy and lumpectomy after systemic therapy. While presurgical chemotherapy is the treatment of choice for younger patients, evidence from clinical trials shows postmenopausal women with estrogen receptor (ER) positive tumors may benefit from systemic antihormonal therapies. A major advantages of PSET is the opportunity to evaluate clinical responses directly in an individual patient by monitoring the behavior of the primary tumor. Recommendations on the use of presurgical systemic therapy of operable breast cancer patients have been published by international expert panels [1]. In addition, to reviewing the challenges of PSET seen from a translational-research perspective in the present review, the authors will especially address the question whether PSET/NST are useful models by which to predict response and outcome to endocrine treatment (both in terms of identifying predictive and prognostic markers and directly predicting tumor behavior in other clinical settings). Taking into consideration the strong trend towards personalized medicine in medical oncology, large biopsies from a primary tumor allow extended laboratory investigations on the same material and a comprehensive understanding of drivers and potential predictive markers in an individual tumor. Additionally consideration will be given to whether presurgical endocrine therapies have contributed to our understanding of the breast cancer disease in general and whether this knowledge may be transferred into other situations like treatment in the adjuvant setting.

2. Major clinical challenges related to PSET/NET

One of the major clinical challenges associated with presurgical systemic therapy of breast cancer is to find suitable and reliable techniques to measure antitumor effects. Traditionally, physicians measured tumor size by caliper measurements every 3–4 weeks. While this technique is easy and cheap, several pitfalls have to be kept in mind. First, these measurements may show large inter-personal variations. In the worst case, clinical disease response/progression may only reflect different techniques of physicians. Second, tumors located in deeper parts of the breast, especially tumors in large breasts may be difficult to assess. In addition, variable inflammation and intercurrent bleeding due to necrosis may effect the tumor size independent of the tumor response. Finally, mucinous breast tumors may be difficult to assess for response because changes may be due to mucin content rather than real tumor burden [2]. As a consequence of these problems, more objective techniques need to be implemented to evaluate the clinical responses during ongoing presurgical therapy.

In the past, antitumor-effects during presurgical therapy have been monitored (in addition to frequent clinical caliper measurements) by either mammography and/or ultrasound measurements [3]. Due to the fact that especially ultrasound measurements are difficult to compare and to monitor, other methods like magnetic resonance imaging (MRI), contrast-induced computed tomography (CT) and positron emission tomography (PET) are more frequently used nowadays [4–6]. However, it is important to state that the imprecision that accompanies all these methods still causes significant fractions of false-positive and false-negative results [7–9]. Thus, the responsible oncologist often has to use several methods in parallel to evaluate the actual tumor response and to determine the right time window for definite surgery in an individual patient.

Pathological assessment of responses during systemic therapy of locally advanced breast cancer (LABC) is an established standard procedure and of pivotal importance [10]. While a complete pathological response (pCR) is the goal of presurgical chemotherapy, other pathological grading systems are necessary to adapt the pathological evaluation to the comparable mild effects of systemic antihormonal therapy with only a few patients experiencing a complete pathological response. Recently, statistically significant different relapse-free survival data have been shown for patients experiencing pathological responses during systemic presurgical antihormonal therapy compared to non-responders [11], suggesting pathological responses (pCR and pPR) to be associated with a favorable prognosis.

3. Identification of predictive and prognostic biomarker

The estrogen receptor (ER) status in breast cancer tissue is one of the strongest predictive markers for neoadjuvant antihormonal therapy [12–15]. Moreover, the degree of ER-expression (in % of cancer cells) is a well established clinical tool to define distinct subgroups of patients with highly endocrine-responsive tumors (ER positive in 50–100% of cells), incomplete endocrine responsive tumors (1–50% of cells ER positive) and non-responsive tumors (ER-expression in < 1% of cells). Recently, the ER-expression itself as well as ER-regulated genes have become essential part of novel test systems used for the identification of tumor signatures like the 21-gene-recurrence score® or the MammaPrint® [16].

The oncogenic plasma membrane tyrosine kinases HER1 (epidermal growth factor receptor) and HER2 (human epidermal growth factor receptor type 2; ErbB2) have been shown to impact on breast cancer prognosis in general and on the efficacy of several treatment options for breast cancer including endocrine therapy. HER2 is overexpressed in about 15–20% of all breast cancer cases. Several investigators have reported on the HER1/HER2 status from crucial preoperative trials involving endocrine treatments [17–20]. Thus, results from the pivotal P024-study comparing tamoxifen with letrozole in the neoadjuvant setting, indicated significantly higher overall response rates with letrozole than with tamoxifen in the HER1/HER2-positive subgroup of patients ($P < 0.0004$) [17,21]. While this is true for HER2-negative tumors as well, it was important to show that the superiority of AIs compared to tamoxifen was not lost in HER2-positive patients. In addition, markers of tumor proliferation like Ki67 are better suppressed by letrozole compared to tamoxifen in the subgroup of patients suffering from ER-positive breast cancer overexpressing HER1/HER2 at the same time [21]. These findings have caused several new trials looking at the effects of classical endocrine therapies (SERMs, SERDs and AIs) in combination with HER1/2 targeting drugs in the neoadjuvant setting. Recent updates from the large phase III trials comparing AIs with tamoxifen in early breast cancer have confirmed the major impact of the HER-2 status on prognosis and superior efficacy of AIs like letrozole compared to tamoxifen in the ER/HER2 co-expressing patients [22]. There is growing evidence that endocrine therapy should be combined with HER2-targeting agents in ER/HER2-positive breast cancer in probably all settings of breast cancer [23].

Tumor proliferation markers have been investigated as potential indicators of clinical responses to neoadjuvant endocrine therapy. One of the most widely used markers is the Ki-67 antigen that is expressed in all phases of the cell cycle except G0. A major challenge is still linked to the interpretation of Ki67 data. While it is considered as a standard procedure to count several hundreds of cells up to 1000 cells in every situation, there are several ways to analyze the data, including the absolute post-treatment value, the absolute change from baseline or the post-treatment value as cut-off. Recently, the term “complete cell cycle response”, meaning a Ki67 level below the detection limit of 1%, has been introduced and discussed in the literature as well [24].