Editorial

Introducing a new section to *Breast Cancer Research*: Endocrinology and hormone therapy

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Published: 26 August 2003

Breast Cancer Res 2003, **5**:281-283 (DOI 10.1186/bcr646)

Abstract

Endocrine therapy is increasingly understood as the conceptual basis for the future treatment and prevention of breast cancer. Endocrine agents have considerably changed the approach to targeted treatment during the past two decades, and select endocrine agents have advanced the goal of preventing breast cancer. Progress has occurred because of a vigorous interaction between laboratory scientists and the clinical trials community. *Breast Cancer Research* is launching a new section on endocrinology and hormone therapy in order to invigorate this exchange and challenge our readers with novel concepts that might result in enhanced survival in breast cancer.

Keywords: antihormone, oestrogen receptor, selective oestrogen receptor modulation, tamoxifen

Introduction

Endocrine therapy is increasingly understood as the conceptual basis for the future treatment and prevention of breast cancer. Endocrine agents have considerably changed the approach to targeted treatment during the past two decades, and select endocrine agents have advanced the goal of preventing breast cancer. Progress has been made because of a vigorous interaction between laboratory scientists and the clinical trials community. The result is that hundreds of thousands of women who would have died now live longer, healthier lives. *Breast Cancer Research* is therefore launching a new section on endocrinology and hormone therapy to invigorate this exchange and challenge our readers with novel concepts that might result in enhanced survival in breast cancer.

As we have done previously in areas of special interest to the breast cancer community, we will mark the new section with a series of thematic reviews on the evolution of progress in endocrine therapy. One of these reviews will focus on antioestrogens and aromatase inhibitors. The ubiquitous application of the antioestrogen tamoxifen since the 1970s has radically improved the prospects for breast cancer patients and, as a result, it has generated enormous interest in new approaches to targeted therapy. All earlier antioestrogens or aromatase inhibitors failed to become accepted into general use because of excessive toxicity that prevented long-term administration. The evolving clinical trials ultimately demonstrated that, to save lives, long-term administration over 5 years is required [1]. However, key to the remarkable advances in endocrine therapy was the identification of the oestrogen receptor (ER) as the mechanism and catalyst for universal oestrogen action. Fortunately, the ER represents a critical growth and survival pathway in breast tumours, and so blocking the ER with an antioestrogen is selectively toxic to the tumour. The ER thus became an early model for molecular medicine [2]. Today, endocrine agents that exploit the ER target in one way or another are ubiquitous in medicine, with clinical studies of the use of aromatase inhibitors at all stages of ER-positive breast cancer [3] and testing of selective oestrogen receptor modulators (SERMs) to prevent breast cancer, osteoporosis and coronary heart disease.

ER = oestrogen receptor; HRT = hormone replacement therapy; SERM = selective oestrogen receptor modulator.

We will also discuss the effect of hormone replacement therapy (HRT) on breast cancer. Large clinical studies have demonstrated that there is a significant reduction in osteoporotic fractures and, paradoxically, colon cancer in women who use oestrogen plus progestin replacement (HRT), but there is an unacceptable increase in breast cancer, dementia, cardiovascular disease and clotting episodes [4,5]. The discovery of new designer oestrogens or SERMs has now become a priority in medicine, and there are opportunities to develop new progestins. The goal is to improve quality of life without carcinogenic potential.

Another review may look at the new trend in antihormone or SERM therapy and endocrine drug resistance. The use of SERMs to prevent breast cancer, osteoporosis or coronary heart disease will not necessarily be limited to 5 years of treatment, but long-term use may increase the potential to develop endocrine-resistant breast cancer. Thus, the challenge for the future is fast becoming how to address endocrine drug resistance and the identification of novel targets to treat tumours resistant to SERMs. Not surprisingly, extended endocrine therapy eventually results in drug resistance but, uniquely, SERM-stimulated breast tumour growth continues to depend on the ER in the signal transduction pathway. A pure antioestrogen, that retargets and destroys the ER, is already available as a new second line treatment for tamoxifen-resistant breast cancer [6,7].

Remarkable and certainly worth some scrutiny is the newly emerging information showing that the oestradiol–ER complex may not only control the survival of the breast cancer cell but also induce its death following exhaustive endocrine therapy. Until now, the only remaining option for the patient developing antihormonal resistance has been cytotoxic chemotherapy. Clinical studies [8] demonstrate that the reintroduction of high-dose oestrogen following exhaustive endocrine therapy results in dramatic tumour responses. Laboratory studies also demonstrate that tumour regression can occur if physiological levels of oestrogen are used to treat long-term SERM resistance, and the few tumours that regrow are again responsive to tamoxifen treatment [9]. The clinical question could soon become, 'Can low-dose oestrogen therapy be incorporated into the clinical treatment plan, cause tumour regression and reactivate antihormonal sensitivity?'

If the mechanism of ER-mediated apoptosis is discovered, then this could improve response rates in breast cancer. Women with antihormone-resistant ER-positive tumours may respond to a cocktail of agents targeted at tyrosine kinases so that the ER becomes more central to survival. In other words, the aim would be to create multiple blocks to survival so that oestrogen-induced death becomes the only cellular option. Success here would double the response rate for endocrine treatment of breast cancer. If that were not enough, it would not be unreasonable to suggest that if the mechanism of ER-mediated apoptosis was discovered then it could open the door to innovation in targeted drugs for the death pathway of all cancer cells.

Obviously, there is much to be done before we can begin to target the treatment of all ER-negative tumours, and it is reasonable to predict that issues of selectivity and systemic toxicity will be central to success. Nevertheless, who would have believed, when the principle of SERM action was established first in the laboratory and translated to the clinic, that this would act as the catalyst for the development of selective modulators for each member of the steroid receptor superfamily. Knowledge in one discipline can today be rapidly exported to enhance advances in other areas.

The goal of *Breast Cancer Research*'s new section on endocrinology and hormone therapy is not to replicate existing reviews in the endocrinology of breast cancer but to invigorate a new generation of investigators to take the lessons learned, whether they were good or bad, and apply the knowledge to new areas of investigation. The section will not necessarily provide answers but will instead aim to challenge our readers with novel concepts that might result in enhanced survival in breast cancer.

Competing interests

None declared.

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