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Review

Breast cancer: Current and future endocrine therapies

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ABSTRACT

Endocrine therapy forms a central modality in the treatment of estrogen receptor positive breast cancer. The routine use of 5 years of adjuvant tamoxifen has improved survival rates for early breast cancer, and more recently has evolved in the postmenopausal setting to include aromatase inhibitors. The optimal duration of adjuvant endocrine therapy remains an active area of clinical study with recent data supporting 10 years rather than 5 years of adjuvant tamoxifen. However, endocrine therapy is limited by the development of resistance, this can occur by a number of possible mechanisms and numerous studies have been performed which combine endocrine therapy with agents that modulate these mechanisms with the aim of preventing or delaying the emergence of resistance. Recent trial data regarding the combination of the mammalian target of rapamycin (mTOR) inhibitor, everolimus with endocrine therapy have resulted in a redefinition of the clinical treatment pathway in the metastatic setting. This review details the current endocrine therapy utilized in both early and advanced disease, as well as exploring potential new targets which modulate pathways of resistance, as well as agents which aim to modulate adrenal derived steroidogenic hormones.

Contents

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1. Introduction

Endocrine therapy (ET) is a key treatment modality in the management of estrogen receptor alpha (ER)-positive breast cancer. ET can be given preoperatively (neoadjuvant), post-operatively (adjuvant), and in the metastatic/advanced disease setting (palliative treatment). Historically, ET is the oldest systemic therapy for the treatment of breast cancer, and the notable historical landmarks and studies are laid out in Fig. 1.

Current ET constitutes treatments which modulate or disrupt the process of estrogen production or the function or presence of the ER in breast cancer cells. In pre-menopausal women the majority of estrogen production is from the ovarian follicles. This process is under the control of the anterior pituitary gland which produces luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH acts upon thecal cells to stimulate androgen synthesis, while FSH acts upon granulosa cells to stimulate the production of the enzyme aromatase which then converts testosterone and androstenedione to estradiol and estrone respectively by aromatisation. The pituitary production of LH and FSH is in turn under the control of gonadotrophin releasing hormone (GnRH) (also known as luteinising-hormone-releasing hormone, LHRH) produced in the hypothalamus. In the postmenopausal setting estrogen production is dependent on peripheral aromatisation, predominantly in the liver, adrenal glands, and adipose tissue. Estrogen exerts its effect via binding to ER which in turn directly regulates the transcription of target genes. ET is aimed at modulating and disrupting this process by either blocking pituitary production of LH/FSH (GnRH analogues), blocking ER (tamoxifen), degrading ER (fulvestrant) or by inhibiting the peripheral production of estrogen (aromatase inhibitors). Given their modes of action menopausal status is important in determining the potential endocrine treatment options that can be utilised.

2. Adjuvant endocrine therapy for women with ER positive breast cancer

2.1. Premenopausal

2.1.1. Tamoxifen

Tamoxifen has until recently been the gold standard for the adjuvant treatment of ER positive breast cancer in both pre- and postmenopausal women. The 2011 meta-analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), with a median of 13 years follow up, has shown that 5 years of tamoxifen compared to none reduced recurrence rates by almost half throughout the first 10 years (Rate Ratio (RR) 0.53 [SE 0.03]). Furthermore, yearly breast-cancer mortality was reduced by about a third throughout the first 15 years (RR 0.70 [0.05], $p < 0.00001$). The EBCTCG data also showed that the proportional risk reductions produced by tamoxifen are little affected by age or chemotherapy (EBCTCG, 2011). This overview also explored the effect of ER level as measured by fmol/mg of cytosol protein, on outcome. ER levels were shown to predict for tamoxifen efficacy, with benefit only being shown with ER levels of 10 fmol/mg of cytosol protein and above (EBCTCG, 2011).

2.1.2. Duration of treatment

The EBCTCG meta-analysis also confirmed that 5 years of tamoxifen is superior to 1–2 years (EBCTCG, 2005). Whilst 5 years of tamoxifen has been the standard of care a number of studies have sought to explore whether further prolonging therapy may add additional benefit. These studies have include the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial (Davies et al., 2012) and adjuvant Tamoxifen—To offer more? (aTTom) trial (Gray et al., 2013). These studies both randomised women (pre- and postmenopausal) who had received 5 years of adjuvant tamoxifen

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