Critical Reviews in Oncology/Hematology 100 (2016) 57–68

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

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

Endocrine therapy in post-menopausal women with metastatic breast cancer: From literature and guidelines to clinical practice

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ARTICLE INFO

Article history:
Received 17 November 2015
Accepted 15 February 2016

ABSTRACT

Current international guidelines recommend endocrine therapy as the initial treatment of choice in hormone receptor positive advanced breast cancer. Endocrine therapy has been a mainstay of hormone responsive breast cancer treatment for more than a century. To date it is based on different

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http://dx.doi.org/10.1016/j.critrevonc.2016.02.008

Keywords:
Advanced breastcancer
Endocrine therapy
Hormone receptor positive
Postmenopausal
Treatment
Maintenance
Endocrine resistance

approaches,such as blocking the estrogen receptor through selective receptor estrogen modulators, depleting extragonadal peripheral estrogen synthesis by aromatase inhibitors or inducing estrogen receptor degradation using selective down-regulators. Despite estrogen and/or progesterone receptor positive status, up to a quarter of patients could be either primarily resistant to hormone therapies or will develop hormone resistance during the course of their disease. Different mechanisms, either intrinsic or acquired, could be implicated in endocrine resistance.
In the present work available endocrine therapies and their appropriate sequences have been reviewed, and the most promising strategies to overcome endocrine resistance have been highlighted.

1. Introduction

About 70% of breast cancers express the hormone receptor (HR). Hormonal manipulation has been a mainstay of hormone responsive breast cancer treatment for more than a century, and often represents the first of several lines of treatment in the metastatic setting.

To date endocrine therapy is based on different approaches, such as blocking the estrogen receptor (ER) through selective ER modulators (SERMs), reducing estrogen levels by depleting extragonadal peripheral estrogen synthesis by aromatase inhibitors (AIs) or inducing ER degradation using selective ER down-regulators (SERDs).

A substantial proportion of patients, up to one-quarter, despite ER and/or progesterone receptor (PgR) positive status, could be either primarily resistant to hormone therapies or will develop hormone resistance during the course of their disease.

ER maintains active in tumor with acquired resistance to endocrine therapy, and continued endocrine therapy in combination with other agents are effective in such patients.

Other available therapies, such chemotherapy or combinations of endocrine and target therapies, as PI3K-mTOR inhibitors, could have a key role in primary or secondary resistant HR+ metastatic breast cancer.

Also, a proper view of available endocrine therapies, related studies, their appropriate sequences and relative strategies to overcome endocrine resistance, could help our daily clinical practice.

2. Certainties and new approaches in the treatment of estrogen receptor positive metastatic breast cancer

Sites and extent of disease, related symptoms, ER levels and human epidermal growth factor-2 (HER2) status, disease-free and treatment-free intervals, and performance status are key factors in the choice of treatment in metastatic HR+ breast cancer.

While hormone-unresponsive or life-threatening disease requires chemotherapy, HR+ metastatic breast cancer patients are usually candidate to endocrine therapy. Indeed while initial treatment with chemotherapy rather than endocrine therapy may be associated with a higher response rate, the two initial treatments had a similar effect on overall survival(OS) (Wilcken et al., 2003). No studies directly compared endocrine and chemotherapy in this setting.

Main international guidelines recommend endocrine therapy as the treatment of choice in HR+ advancedbreast cancer:

- NCCN Guidelines: Many women with hormone-responsive breast cancer benefit from sequential use of endocrine therapy at disease progression. Therefore, women with breast cancer who respond to endocrine therapy with either tumor shrinkage or long-term disease stabilization should receive additional endocrine therapy at disease progression (NCCN, 2015).

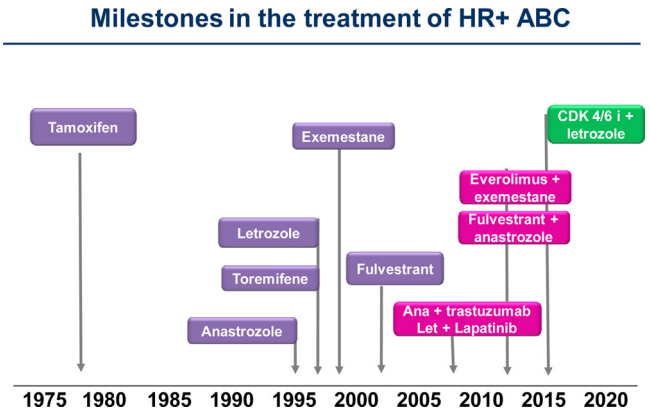

Fig. 1. Endocrine therapy involves many agents.

- ABC1 Guidelines: Endocrine therapy is the preferred option for HR + disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or there is disease needing a fast response (Cardoso et al., 2012a).
- ESMO Guidelines: Endocrine therapy is the preferred option except if clinically aggressive disease mandates a quicker response or if there are doubts regarding endocrine responsiveness of the tumor (Cardoso et al., 2012b).

To date endocrine therapy involves many agents (Fig. 1). For many years tamoxifen, a selective ER modulator (SERM) which antagonises estrogen signaling in HR+ breast cancer,has been the mainstay in the treatment of HR+ breast cancer. Tamoxifen became the standard therapy for advanced breast cancer after having demonstrated first-line efficacy and more favorable toxicity profile when compared with a range of other endocrine agents in this setting (Fossati et al., 1998). A systematic review, on 35 randomized controlled trials (RCTs), comparing tamoxifen witha range of other endocrine therapies, including ovarectomy, megestrol acetate, aromatase inhibitors (AIs), medroxyprogesterone acetate, SERMs, goserelin and fluoxymesterone, reported an overall response rate (ORR) of 30% withtamoxifen versus 29% with the other agents and an OS hazard ratio of 1.02 [confidence interval (CI) 0.94–1.10], without gross statistical heterogeneity between trials ($p = 0.48$) or differences hormonal categories ($p = 0.60$) (Fossati et al., 1998).

2.1. Tamoxifen versus megestrol acetate

In at least five RCTs (Allegra et al., 1985; Gill et al., 1993; Ingle et al., 1982; Morgan, 1985; Muss et al., 1988; Paterson et al., 1990) tamoxifen demonstrated to have comparable efficacy with megestrol acetate, that acts by inhibiting pituitary function and thus suppressing luteinizing hormone and the subsequent production of estrogen, in terms of ORR and OS, with a better side-effect profile.