Critical Reviews in Oncology/Hematology 107 (2016) 82–89

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

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

Aromatase inhibitors in premenopause: Great expectations fulfilled?

Rosalba Torrisi (MD)[a,*,1], Selene Rota (MD)[a], Agnese Losurdo (MD)[a], Monica Zuradelli (MD)[a], Giovanna Masci (MD)[a], Armando Santoro (MD)[b]

[a] Dept of Oncology and Hematology, Humanitas Cancer Center, Humanitas Clinical and Research Hospital, Viale Manzoni 56, 20089 Rozzano, Italy
[b] Dept of Oncology and Hematology, Humanitas Cancer Center, Humanitas Clinical and Research Hospital, Humanitas University, Viale Manzoni 56, 20089 Rozzano, Italy

Contents

ARTICLE INFO

Article history:
Received 12 January 2016
Received in revised form 14 July 2016
Accepted 23 August 2016

Keywords:
Aromatase inhibitors
Premenopause
Breast cancer
Ovarian suppression
Circulating estradiol

ABSTRACT

Tamoxifen and GnRH analogues (GnRHa) represent the mainstay of endocrine manipulations in premenopausal women. The estrogen blockade obtained by aromatase inhibitors (AIs) plus GnRHa suppresses circulating estrogens more deeply than tamoxifen plus GnRHa. Retrospective and prospective evidence confirm a substantial activity for AIs and GnRHa in locally advanced and metastatic breast cancer. In early breast cancer inconsistent evidence emerged from 2 large randomized studies with anastrozole performing as tamoxifen in terms of DFS, but significantly worse as of OS while exemestane outperformed tamoxifen as of DFS particularly in very young and high-risk women. These findings support the use of AIs plus GnRHa in advanced breast cancer while long term efficacy and safety data are expected to define the appropriate indication of AIs in early breast cancer. In addition the clinical significance of persistent circulating estrogens and long term effects of estrogen deprivation in young women need further clarification.

© 2016 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

About two-thirds of breast cancers at any age express some degree of estrogen receptors (ER) (Anderson et al., 2002). Thereby endocrine therapy represents an approach of utmost relevance for a large proportion of premenopausal women with breast cancer.

The antiestrogen Tamoxifen ± ovarian suppression by means of a GnRH analogue (GnRHa) represent the standard treatment of premenopausal breast cancer patients. Despite the number of published clinical trials, the optimal combination, timing and duration of these two agents in early disease are still debated, while in advanced disease the combination of the two agents is established as the standard treatment (Jankowitz et al., 2013; Klijn et al., 2001).

As a matter of fact, after failure on an initial endocrine agent most tumors still maintain expression of ER suggesting that a further endocrine manipulation may be effective (Johnston, 2010). However in premenopausal women the exploitment of persistent

* Corresponding author.
E-mail addresses: rosalba.torrisi@humanitas.it (R. Torrisi), selene.rota@humanitas.it (S. Rota), agnese.losurdo@humanitas.it (A. Losurdo), monica.zuradelli@humanitas.it (M. Zuradelli), giovanna.masci@humanitas.it (G. Masci), armando.santoro@humanitas.it (A. Santoro).

[1] Rosalba Torrisi is a medical oncologist who has focused her clinical and research activity on breast cancer. She is author and co-author of about 80 manuscripts published in peer reviewed and indexed journals.

http://dx.doi.org/10.1016/j.critrevonc.2016.08.009
1040-8428/© 2016 Elsevier Ireland Ltd. All rights reserved.

endocrine sensitivity after tamoxifen failure has been limited by the lack of other endocrine active agents.

The development of aromatase inhibitors (AIs) has substantially changed the algorithm of endocrine therapy in postmenopausal women (Santen and Harvey, 1999; Smith and Dowsett, 2003; Winer et al., 2005). The availability of these agents could theoretically depict new opportunities also for premenopausal breast cancer patients.

In the present review we will summarize data about the use of AIs in premenopausal breast cancer, highlight potential concerns and finally briefly discuss other potential use of aromatase inhibitors in premenopausal women.

2. Endocrinology of aromatase inhibitors in premenopause

Aromatase is a cytochrome P-450 enzymes which catalyzes the synthesis of estrogens from the androgen precursors (Santen and Harvey, 1999). Aromatase expression occurs in many organs, including ovary, placenta, hypothalamus, liver, muscle, adipose tissue, and breast cancer itself (Santen and Harvey, 1999). Aromatase catalyzes three separate steroid hydroxylations which are involved in the conversion of androstenedione to estrone or testosterone to estradiol. In premenopausal women the major source of aromatase is represented by ovaries, its expression being induced by follicle stimulating hormone (FSH) during puberty (Santen and Harvey, 1999). However, extraglandular aromatization of adrenal substrates in peripheral tissues which represents the major source of aromatase in postmenopausal women, substantially contributes to estrogen levels also in premenopause (Santen and Harvey, 1999).

Both circulating and locally synthesized estrogens exert a negative feedback on gonadotropin release (Smith and Dowsett, 2003). Inhibition of aromatase activity leads to a decrease of estrogens and releases the hypotalamic/pituitary axis from negative estrogen feedback finally resulting in a stimulation of gonadotropin synthesis which in turn stimulates estrogens and aromatase (Smith and Dowsett, 2003). Although AIs block also ovarian aromatase, earlier attempts with aminoglutheimide were not effective in suppressing circulating estrogens of premenopausal women to the postmenopausal range (Santen et al., 1980; Harris et al., 1982; Wander et al., 1986). Similarly, there was no decrease in estradiol after short term treatment with the more potent second generation steroidal AI, formestane (Stein et al., 1990). Conversely, when formestane was given in patients receiving GnRHa, estradiol and other estrogen levels fell below the levels reached with medical ablation alone (Stein et al., 1990; Celio et al., 1999), suggesting that formestane was effective in suppressing peripheral conversion of androgens which may be responsible of the persistent detectable levels of estrogens after ovarian ablation. As a consequence, serum estradiol levels measured in premenopausal women treated with combined therapy were close to the lower limits measured in postmenopausal women treated with formestane (Stein et al., 1990).

The third generation triazole derivatives anastrozole and letrozole induced a greater suppression of aromatase activity as compared to formestane in postmenopausal women (Smith and Dowsett, 2003). Significant differences in the extent of aromatase inhibition, and suppression of circulating estrone, estradiol and estrone sulphate favoring letrozole on anastrozole have been reported (Geisler et al., 2002; Dixon et al., 2008).

The hypothesis that the combination of AIs plus GnRHa was able to induce a more complete estrogen blockade than tamoxifen plus GnRHa was investigated both in head-to-head –comparison and in sequence therapy (Rossi et al., 2008; Forward et al., 2004; Cheung et al., 2010). A 6-month treatment of letrozole plus triptorelin significantly suppressed plasma estradiol and estrone as compared with tamoxifen and triptorelin in premenopausal women treated within a randomized phase III adjuvant trial (Rossi et al., 2008). On the other hand, Forward showed that anastrozole further decreased estradiol levels by 76% in 16 premenopausal patients previously treated and progressing on tamoxifen; this observation was not confirmed in another smaller sample of 6 women (Forward et al., 2004; Cheung et al., 2010).

The profound suppression of circulating estrogens obtained by GnRHa plus AIs provided a strong rationale for evaluating whether this blockade might translate in a clinical benefit beyond that of standard therapy with tamoxifen plus GnRHa.

3. Studies with aromatase inhibitors in metastatic and locally advanced disease

The results of studies with 3rd generation AIs in advanced breast cancer are summarized in Table 1 (Forward et al., 2004; Cheung et al., 2010; Carlson et al., 2010; Park et al., 2010; Yao et al., 2011; Nishimura et al., 2013; Liu et al., 2013; Wang et al., 2015).

Forward reported a retrospective small series of 16 women who received anastrozole plus goserelin after tamoxifen failure for advanced disease (Forward et al., 2004). A clinical benefit (CB) was observed in 75% of patients with a median duration of response of 17+ months (Forward et al., 2004). All patients had previously obtained objective response (OR) and/or very prolonged CB with tamoxifen thus featuring a truly endocrine sensitive population. This study albeit very limited, represented the first report of a significant disease control with a second line endocrine treatment in premenopausal women (Forward et al., 2004).

A second series was reported by Cheung who retrospectively collected data about 36 premenopausal women administered anastrozole and goserelin as first-line endocrine therapy for metastatic and locally advanced disease (Cheung et al., 2010). Sixty-seven percent of patients obtained a CB with a OR rate of 36% and a longer duration of response (24+ months) as compared with that previously observed as second line (Cheung et al., 2010).

A few phase II studies have investigated the combination of an AI and goserelin as 1st line treatment in premenopausal women with advanced disease (Carlson et al., 2010; Park et al., 2010; Nishimura et al., 2013). The first study enrolled 32 premenopausal women who received goserelin + anastrozole (Carlson et al., 2010). More than two-third of patients received the combination as first endocrine treatment. Objective responses and CB were obtained in 37.5% and 72% of patients, respectively and time to progression (TTP) was 8.3 months (Carlson et al., 2010).

In the second study Park compared the activity of goserelin and letrozole in 36 premenopausal patients with a parallel series of postmenopausal women treated with letrozole (Park et al., 2010). Results in terms of CB and TTP were comparable while objective response rate was significantly higher in premenopausal women (Park et al., 2010).

Nishimura investigated the activity of goserelin and anastrozole in a group of 36 patients all previously treated with GnRHa and TAM either in adjuvant or metastatic (70%) setting (Nishimura et al., 2013). Only 1 out of 7 responses was obtained in a patient progressing on or shortly after adjuvant tamoxifen (Nishimura et al., 2013).

Age seems not to affect the activity of AIs. Liu reported the results of a retrospective series of 35 women aged <35 yrs old treated with goserelin and letrozole as 1st line therapy for advanced disease (Liu et al., 2013). Ovarian suppression was assessed through the study. Outcome in terms of OR, CB and progression free survival (PFS) was similar to that observed in "older" premenopausal women (Liu et al., 2013).

More limited data are available with the steroidal AI exemestane. In the retrospective series by Cheung, 13 patients received

Download English Version:

https://daneshyari.com/en/article/3328519

Download Persian Version:

https://daneshyari.com/article/3328519

Daneshyari.com