Adjuvant hormone therapy in early breast cancer: aromatase inhibitors and the perimenopausal status

Luca Moscetti
Fabrizio Nelli
Enzo Maria Ruggeri

UOC of Oncology, Ospedale Belcolle, AUSL Viterbo, Viterbo, Italy

Address for correspondence:
Luca Moscetti
UOC of Oncology, Ospedale Belcolle, AUSL Viterbo
Strada Sammartinese
00110 Viterbo, Italy
E-mail: l.moscetti@asl.vt.it

Summary

In postmenopausal status the aromatase inhibitors (AIs) represent a standard treatment whereas not recommended in the pre- and perimenopause status. The medical oncology community has to be warned about use of AIs in the perimenopausal status due to the paradoxical increase in the both gonadotropin and of estrogen serum levels induced by these agents. Moreover, AIs are not recommended for women who report cessation of menses after chemotherapy due to the possible resumption of ovarian function. Although several clinical trials have been conducted in the adjuvant setting of postmenopausal status, few data are available on the endocrine safety of AIs in the perimenopausal setting. Defining of the menopausal status of a woman who will be treated with adjuvant hormone therapy is essential to avoid unexpected increase of estrogen levels that could promote tumor regrowth.

KEY WORDS: adjuvant hormone therapy; premenopausal status; aromatase inhibitors.

Introduction

The diagnosis of early stage breast cancer in premenopausal women under 50 years of age is currently increasing. The vast majority of these malignancies are hormone receptor positive and represent the main group of patients in which the treatment can reduce the cancer-related events. Current guidelines for hormone adjuvant treatment of endocrine sensitive breast cancer are well defined. For postmenopausal women the American society of clinical oncology (ASCO) guidelines recommend the choice of treatment with either tamoxifen or aromatase inhibitors (AIs). The AIs are not indicated in the premenopausal setting and, even though they may stimulate ovarian function their use is not uncommon in the medical oncology community (1-3).

Aromatase inhibitors and perimenopausal status

AIs are classified as steroidal (irreversible, type I) and nonsteroidal (reversible, type II). The currently AIs available are represented by the steroidal AI exemestane and the nonsteroidal AIs anastrozole and letrozole (4, 5). These agents determine a deep suppression of the 98% of the circulating estrogens (6-9). The role of AIs is not clear in the adjuvant setting of the perimenopausal status and for women who are premenopausal at diagnosis and appear to have a cessation of menses after adjuvant chemotherapy. The clear definition of meno-pausal status is essential for all of the patients undergoing a hormone therapy. The World Health Organization (WHO) defines the menopause as follow: menopause is the permanent cessation of menstruation that results from loss of ovarian follicular activity. The perimeno-pause corresponds to the period before the menopause and at least to the first year after the menopause. The postmenopause dates from the menopause, although it cannot be definitively determined until a period of 12 months of spontaneous amenorrhea has occurred (10). According to the WHO definition, the perimenopause could be restricted only to a one year period but this definition cannot be strictly applied to women with a chemotherapy-induced amenorrhea because of the likelihood menses resumption ranges from 4 to 29 months (11). The National Comprehensive Cancer Network (NCCN) guidelines define the menopause as follow: prior bilateral oophorectomy, age >60 years, age ≤60 years and amenorrhea for at least 12 months in absence of chemotherapy, tamoxifen, toremifene or ovarian suppression, or age ≤60 years and FSH and estradiol in the postmenopausal range in case of therapy with tamoxifen or toremifene (12). With regard of the definition of menopause for the use of AIs in randomized trials, the five available clinical studies don't help us to find a explicit description (Tab. 1). The lack of menses induced from chemotherapy in a premenopausal woman, even induced 5 years before, is not a certainty of a real menopausal status. The serial monitoring of serum estradiol, FSH and LH currently represent the only standardized method to determine the menopausal status. New markers are now developing as reported by Anders et al. (13). These authors investigated the role of inhibin B and anti-Müllerian hormone and reported that the risk of chemotherapy related amenorrhea increased among women with lower pre-chemotherapy Inhibin B (RR = 1.67, p = 0.15) and anti-Müllerian hormone (AMH) (RR = 1.83, p = 0.05). Among patients whose prechemotherapy Inhibin B and AMH values were below the medi-

Table 1 - Definition of menopause in the main clinical trials of aromatase inhibitors in adjuvant treatment of early breast cancer.

Study	Definition of menopause
ATAC trial	Surgical oophorectomy; age > 60 ys; if age 45-59 amenorrhea >12 months or if amenorrhea < 12 months: postmenopausal range of FSH
BIG 1-98	Amenorrhea > 60 ys (age > 50 ys) or 12 (age <50ys) months, Surgical oophorectomy or Chemotherapy induced amenorrhea and age > 45 ys and FSH/LH/estradiol postmenopausal range
IES	Age > 55 ys with amenorrhea > 24 months or amenorrhea > 12 months at time of diagnosis
ARNO ABCSG	Amenorrhea > 12 months, Surgical oophorectomy or postmenopausal range FSH and LH
MA 17	Age > 50 ys at start of tamoxifen, postmenopausal at start of tamoxifen, Surgical oophorectomy. Age < 50 ys with CT or tamoxifen induced amenorrhea or postmenopausal range FSH and LH

Table 2 - Association of LHRH and AIs in the metastatic settings.

Author	Treatment	#pts	17b Estradiol	FSH	LH
Stein 18	Goserelin ⇨ Goserelin + Formestane at PD	6	Reduced by Formestane	Unaffected	Unaffected
Dowsett 19	Goserelin 4 weeks ⇨ Goserelin + Vorozole 12 weeks	10	Reduced by Vorozole	Unaffected	Reduced
Forward 20	Goserelin + TAM ⇨ Goserelin + Anastrozole at PD	16	Reduced by Anastrozole	Increased	Unaffected
Carlson 21	Goserelin + Anastrozole	35	Suppressed	Increased	Not Reported
Celio 22	Triptorelin vs Triptorelin + Formestane	21	Suppressed	Not Reported	Not Reported

an, the incidence of CRA was 87.5%. These results indicate that prechemotherapy Inhibin B and AMH are lower among women experiencing CRA and may be predictive of CRA among premenopausal women undergoing chemotherapy for early stage breast cancer.

In the postmenopause the serum estrogen levels are maintained at a modest steady state through the conversion of androgen into estrogen by the aromatase enzyme. The inhibition of estrogen levels, as the result of the aromatase-induced block, could stimulate an increase of the gonadotropin release, which could in turn stimulate the ovarian production of estrogen. The absence of menses after chemotherapy does not translate in absence of ovarian function and premenopausal consistent levels of estradiol were found in some women with chemotherapy-induced amenorrhea (14). In healthy premenopausal women an estradiol suppression has been observed with the use of anastrozole as a single agent (15). The resultant of this action is the increase in serum of gonadotropin levels which stimulate follicular growth and estradiol production through a mechanism of feedback. The use of an AI for induction of ovulation, such as letrozole, at the standard dose 2.5 mg per day, was explored and has been shown to induce an effective ovulation (16). Hargis et al. reported the case of a 40 years old woman who presented, after five years of tamoxifen, the resumption of menses soon after the initiation of letrozole. Several similar cases are reported in literature and, taken together, these reports point out the substantial biologic differences in the pre- and postmenopausal status (3, 4). Smith et al. reported the effects of treatment with AIs in 45 premenopausal women who became amenorrheic after chemotherapy. The median age was 47 years (range 39 to 52) and 33 had biochemically confirmed ovarian suppression before starting treatment. Eighteen (40%) had the recovery of ovarian function with 1 patient becoming pregnant without prior menstruation, whereas eight patients had the recovery of ovarian function, which was biochemical confirmed, with a median plasma estradiol of 252 pmol/L (range, 47 to 461 pmol/L). Twenty-four of the remaining 33 patients (73%), who remained clinically postmenopausal, also had a biochemical ovarian function check and all of them maintained postmenopausal plasma estradiol levels (17).

LHRH agonists may be used in association with aromatase inhibitors?

Preliminary experiences in the metastatic settings showed the feasibility of combining LHRH agonists and AIs (Tab. 2) (18-22) and the Hoboe trial currently explores the role of this association in the adjuvant treatment of premenopausal women (23). The preliminary results showed that letrozole in combination with trip-

torelin induced a more intense suppression of estradiol levels compared to the tamoxifen group. In both groups of patients FSH and LH levels were suppressed but FSH levels were higher and LH levels were lower with letrozole than with tamoxifen. These effects may be due to the potent suppression of E2 levels produced by letrozole. There are no other data supporting the use of an AI in combination with LHRH agonists but two large, ongoing, randomized trials are addressing the value of AIs in premenopausal women (24, 25).

Recent data in premenopausal setting

The trial by Gnant et al. explored the endocrine treatment in combination with zoledronic acid in the premenopausal setting. No differences emerged between tamoxifen and anastrozole and the trial generates hypothesis to test the association of LHRH agonists and anastrozole in the adjuvant setting but no data are available on the endocrine safety (26).

The recent update of the trial shows similar disease free survival between anastrozole and tamoxifen, but patients treated with tamoxifen had significantly higher overall survival compared to anastrozole (27).

An update of the MA 17 trial showed that the efficacy of AIs in women who are premenopausal at diagnosis and become menopausal during tamoxifen, is more pronounced than postmenopausal women, but no data are available on safety in this subset population (28).

Conclusions

AIs represent the standard of care for adjuvant hormone therapy of postmenopausal women with early breast cancer and current guidelines recommend its use as upfront therapy, as switching strategy after 2-3 years of tamoxifen, or as extended treatment after 5 years of tamoxifen. In premenopausal women tamoxifen represents the drug of choice with or without the association of LHRH agonists. Owing to the potential of ovary stimulation and probability of resumption menses, AIs should no to be offered in this setting. The women who became amenorrheic after chemotherapy should not be considered postmenopausal. The cessation of menses is not synonymous of true ovarian failure because the estrogens levels can remain in a premenopausal range in spite of one year or longer of chemotherapy-induced amenorrhea and the AIs might determine the resumption of ovarian function. The monitoring of estradiol, FSH and LH values should be performed before prescribing an AI. In summary women aged younger than 40 years should not receive an AIs and perimenopausal women who developed chemotherapy-induced amenorrhea should be offered tamoxifen as the preferable option. The role of AIs is defined in the postmenopause, the results of the large ongoing clinical trials will address the issue in the pre- and perimenopausal setting.

References

1. Winer EP, Hudis C, Burstein HJ. American Society of Clinical Oncology Technology Assessment on the Use of Aromatase Inhibitors As Adjuvant Therapy for Postmenopausal Women With Hormone Receptor-Positive Breast Cancer: Status Report 2004. J Clin Oncol 2005; 23:619-629.
2. Hargis JB, Nakajima JD. Resumption of Menses with Initiation of Letrozole After Five Years of Amenorrhea on Tamoxifen: Caution Needed When Using Tamoxifen Followed by Aromatase Inhibitors. Cancer Investigation 2006; 24:174-177.
3. Burstein HJ, Mayer E, Partridge AH, et al. Inadvertent use of Aromatase Inhibitors in patients with breast cancer with residual ovarian function: cases and lessons. Clinical Breast Cancer 2006; 7, 2:158-161.
4. Brueggemeier RW. Aromatase inhibitors-mechanisms of steroidal inhibitors. Breast Cancer Res Treat 1994; 30:31-42.
5. Vanden Bossche HV, Moereels H, Koymans LM. Aromatase inhibitors mechanisms for non-steroidal inhibitors. Breast Cancer Res Treat 1994; 30:43.
6. Geisler J, King N, Anker G, et al. In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. Clin Cancer Res 1998; 4:2089-2093.
7. Geisler J, King N, Dowsett M, et al. Influence of anastrozole (Arimidex), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in postmenopausal women with breast cancer. Br J Cancer 1996; 74:1286-1291.
8. Demers LM. Effects of fadrozole (CGS 16949A) and letrozole (CGS 20267) on the inhibition of aromatase activity in breast cancer patients. Breast Cancer Res Treat 1994; 30:95-102.
9. Buzdar AU. Pharmacology and pharmacokinetics of the newer generations aromatase inhibitors. Clin Cancer Research 2003; 9:468s-472s.
10. World Health Organization. Technical Report Series 670: Research on the Menopause. Geneva, Switzerland, WHO, 1991.
11. Bianco AR, Del Mastro L, Gallo C, et al. Prognostic role of amenorrhea induced by adjuvant chemotherapy in premenopausal patients with early breast cancer. Br J Cancer 1991; 63:799-803.
12. NCCN Clinical practice guidelines in oncology. Breast Cancer V.I. 2010.
13. Anders C, Marcom PK, Peterson B, et al. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest, Apr-May 2008; 26(3):286-95.
14. Braverman AS, Sawhney A, Tendler A, et al. Premenopausal serum estradiol levels may persist after chemotherapy-induced amenorrhea in breast cancer. Proc Am Soc Clin Oncol 2002; 21:42.
15. Tredway DR, Buraglio M, Hemsey G, et al. A phase I study of the pharmacokinetics, pharmacodynamics, and safety of single-and multipledose anastrozole in healthy, premenopausal female volunteers. Fertil Steril 2004; 82:1587-1593.
16. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001; 75: 305-309.
17. Smith IE, Dowsett M, Yap Y, et al. Adjuvant Aromatase Inhibitors for Early Breast Cancer After Chemotherapy-Induced Amenorrhoea: Caution and

Suggested Guidelines. J Clin Oncol 2006; 24:2444-2447.
18. Stein RC, Dowsett M, Hedley A. The clinical and endocrine effects of 4-hydroxyandrostenedione alone and in combination with goserelin in premenopausal women with advanced breast cancer. Br J Cancer 1990 Oct; 62(4):679-83.
19. Dowsett M, Doody D, Miall, et al. Vorozole results in greater oestrogen suppression than formestane in postmenopausal women and when added to goserelin in premenopausal women with advanced breast cancer. Breast Cancer Res Treat 1999 Jul; 56(1):25-34.
20. Forward DP, Cheung KL, Jackson L, Robertson JF. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. Br J Cancer 2004 Feb 9; 90(3):590-4.
21. Carlson W, Schurman CM, Rivera E, et al. Goserelin plus anastrozole in the treatment of premenopausal hormone receptor positive, recurrent or metastatic breast cancer. J Clin Oncol (Meeting Abstracts) 2007; 25:1030.
22. Celio L, Martinetti A, Ferrari. Premenopausal breast cancer patients treated with a gonadotropin-releasing hormone analog alone or in combination with an aromatase inhibitor: a comparative endocrine study. Anticancer Res 1999 May-Jun; 19(3B):2261-8.
23. Rossi E, Morabito A, De Maio E, et al. Endocrine effects of adjuvant letrozole + triptorelin compared with tamoxifen + triptorelin in premenopausal patients with early breast cancer. J Clin Oncol 2008; 26:264-270.
24. Phase III Randomized Study of Ovarian Function Suppression in Combination With Tamoxifen Versus Ovarian Function Suppression in Combination With Exemestane Versus Tamoxifen Alone in Premenopausal Women With Endocrine-Responsive Breast Cancer. Registered in ClinicalTrials.gov NCT00066690.
25. Phase III Randomized Study of Triptorelin and Exemestane Versus Triptorelin and Tamoxifen in Premenopausal Women With Endocrine-Responsive Breast Cancer. Registered in ClinicalTrials NCT 00066703.
26. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009 Feb 12; 360(7):679-91.
27. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy, alone or in combination with zoledronic acid, in premenopausal patients with endocrine-responsive early breast cancer: subgroup analyses of ABCSG-12. Ann Oncol 2010; 21(suppl 8):viii79.
28. Goss P, Ingle J, Martino S, et al. Outcomes of women who were premenopausal at diagnosis of early stage breast cancer in the NCICCTG MA17 Trial. Presentation at 32nd San Antonio Breast Cancer Symposium 2009.