Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Steroid Biochemistry & Molecular Biology 95 (2005) 113–119
The Journal of Steroid Biochemistry & Molecular Biology
www.elsevier.com/locate/jsbmb

Aromatase inhibitors for therapy of advanced breast cancer☆

James N. Ingle[a,*], Vera J. Suman[b]

[a] *Division of Medical Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA*
[b] *Cancer Center Statistics, Mayo Clinic, Rochester, MN 55905, USA*

Abstract

In postmenopausal women with advanced breast cancer, numerous phase III trials have been performed comparing the third-generation non-steroidal aromatase inhibitors (NS-AIs) anastrozole and letrozole and the steroidal AI (S-AI) exemestane in the "first-line" setting against tamoxifen and in the "second-line" setting against megestrol acetate. In both settings, the AIs were at least as efficacious or superior in some endpoints with a preferable toxicity profile including a lower incidence of thrombotic events. Relatively small differences in potency between the three AIs have been identified and it has not been demonstrated that these differences have clinical implications. The recent establishment of the value of AIs in the adjuvant setting for postmenopausal women will impact on their utilization in advanced disease. In premenopausal women the third-generation AIs have not been studied as monotherapy and there is a paucity of data in combination with ovarian function suppression in the advanced disease setting. The main area of future investigations for the AIs in premenopausal women will be in the adjuvant therapy setting in combination with suppression of ovarian function.

Keywords: Aromatase inhibitors; Anastrozole; Exemestane; Letrozole; Tamoxifen; Clinical trials

1. Introduction

Tamoxifen emerged as the endocrine agent of choice for postmenopausal women with metastatic breast cancer in the decade of the 1970s receiving approval for this indication by the United States Food and Drug Administration (FDA) in 1977. The following decade saw the emergence of tamoxifen as therapy for premenopausal women with metastatic breast cancer with FDA approval granted in 1989. It was in this setting of tamoxifen dominance by that the third-generation aromatase inhibitors (AIs), viz., the non-steroidal agents anastrozole and letrozole and the steroidal agent exemestane, were evaluated with virtually all of the clinical research being conducted in postmenopausal women.

The study of the third-generation AIs began with their evaluation in postmenopausal women in the setting of tamoxifen-resistant disease. Phase III clinical trials in this setting comparing these agents with megestrol acetate demonstrated not only improved tolerability but also improved efficacy in outcome parameters for the three AIs. Based on these phase III studies the third-generation AIs replaced megestrol acetate as the agent-class of choice in postmenopausal women who had experienced disease progression on tamoxifen and either a non-steroidal AI (NS-AI) or a steroidal AI (S-AIs) could be chosen. Investigation of AIs subsequently moved into the metastatic disease settings where the patient either had not had prior exposure to tamoxifen or the patient's disease did not recur within 12 months of discontinuing tamoxifen and as such was not considered tamoxifen-resistant. Again, the AIs emerged as superior with improved tolerability and efficacy. The primary purpose of this review was to examine the main body of evidence addressing the therapeutic value of the third-generation AIs relative to both megestrol acetate and tamoxifen in postmenopausal women metastatic disease. There was much less data for AIs in the metastatic setting for premenopausal women but this will also be reviewed.

2. Materials and methods

The materials reviewed include the findings from the randomized phase III clinical trials comparing third-generation

☆ Presented at the VIIth International Aromatase Conference: AROMATASE 2004, Edinburgh, Scotland, UK, 6–8 September 2004.

* Corresponding author. Tel.: +1 507 284 2511; fax: +1 507 284 1803.
E-mail address: ingle.james@mayo.edu (J.N. Ingle).

0960-0760/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2005.04.014

AIs with megestrol acetate and with tamoxifen. The AI:megestrol acetate comparison includes two trials that compared anastrozole with megestrol acetate [1,2] and were then combined into a single analysis by Buzdar et al. [3], two trials that compared letrozole with megestrol acetate [4,5] and a trial that compared exemestane with megestrol acetate [6]. The AI:tamoxifen comparison includes two trials that compared anastrozole with tamoxifen [7,8] and were then combined into a pre-planned single analysis by Buzdar and co-workers [9], a trial that compared letrozole with tamoxifen [10,11], and a trial that compared exemestane with tamoxifen with published phase II data [12] but phase III data that has thus far been reported in abstract form only [13].

The unadjusted progression hazard ratio (AI:megestrol acetate or AI:tamoxifen) and its corresponding two-sided 95% confidence interval (CI) were taken from the publication of the trial results. A point and interval estimate of the difference in overall response rates, defined as complete response (CR) plus partial response (PR) rates, and clinical benefit rates, defined as CR plus PR plus stable disease for at least 24 weeks, among treatment groups within a given trial were calculated by using the properties of the binomial distribution.

3. Pivotal trials of aromatase inhibitors in postmenopausal women with advanced breast cancer

3.1. Anastrozole versus megestrol acetate

The two phase III multi-center trials [1,2] that were included in the combined analysis [3] involved a randomization between anastrozole (1 mg/day), anastrozole (10 mg/day) and megestrol acetate (40 mg four times daily). The trials were double blind for the anastrozole arms but open label for the megestrol acetate arm. The total number of women on the two studies was 764. The focus of this review will be to examine the comparison of megestrol acetate (253 patients) with the anastrozole arm utilizing the 1 mg dose (263 patients) as this is the dose currently used in clinical practice. The estrogen receptor (ER) was known to be positive in 68% and 73% of patients on these treatment arms, respectively.

3.2. Letrozole versus megestrol acetate

Two double blind phase III multi-center trials [4,5] involved a randomization between letrozole (2.5 mg/day), letrozole (0.5 mg/day) and megestrol acetate (160 mg/day). The first trial to be reported was that of Dombernowsky et al. [4] and involved 551 patients. The focus of this review will be to examine the comparison of megestrol acetate (189 patients) with the letrozole arm utilizing the 2.5 mg dose (174 patients) as this is the dose currently used in clinical practice. The ER and/or progesterone receptor (PgR) were known to be positive in 59% and 58% of patients on these treatment arms, respectively. In the second study by Buzdar et al. [5], 602 patients were randomized with 201 patients allocated megestrol acetate and 199 patients allocated letrozole at 2.5 mg/day. The ER and/or PgR were known to be positive in 80% of patients on both treatment arms.

3.3. Exemestane versus megestrol acetate

A double blind phase III multi-center trial [6] involved a randomization between exemestane (40 mg/day) and megestrol acetate (40 mg four times daily). The total number of patients randomized was 769 with 366 randomized to exemestane and 403 randomized to megestrol acetate. The ER and/or PgR were known to be positive in 67% and 68% of patients on these treatment arms, respectively.

3.4. Anastrozole versus tamoxifen

The two double blind phase III multi-center trials [7,8] that were included in the combined analysis [9] involved a randomization between anastrozole (1 mg/day) and tamoxifen (20 mg daily). The combined analysis involved a total of 1021 patients with 511 randomized to anastrozole and 510 randomized to tamoxifen. The ER and/or PgR were known to be positive in 60% of patients on both treatment arms.

3.5. Letrozole versus tamoxifen

A double blind phase III multi-center trial [10,11] involved a randomization between letrozole (2.5 mg/day) and tamoxifen (20 mg/day). The total number of patients randomized was 907 with 453 randomized to letrozole and 454 randomized to tamoxifen. The ER and/or PgR were known to be positive in 65% and 67% of patients on these treatment arms, respectively. This trial differed from the others noted in this review in that an optional crossover to the alternative treatment upon disease progression was available with maintenance of the double-blind feature.

3.6. Exemestane versus tamoxifen

The multi-center trial comparing exemestane and tamoxifen differs from the other trials under consideration in that it was conducted as a phase II/III trial. The randomized phase II portion has been published [12] but the phase III trial findings have been reported in abstract form only [13]. The trial was open label and involved a randomization to exemestane (190 patients) or tamoxifen (192 patients). Thus, the sample size is substantially smaller in this trial than in those with the other two AIs noted above. The “hormone receptor status” was said to be balanced between the two treatment arms but the proportions of ER positive patients were not provided in the abstract.