The Role of Aromatase Inhibitor (AI) in The Treatment of Breast Cancer

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INTRODUCTION

Discussion on the topic with the same title above would never be separated from rising questions such as ‘why does it need endocrine therapy?’ and ‘What is endocrine therapy?’ Aside from that, it has been widely known that development of breast cancer is estrogen dependent. Thus, reducing estrogen level by medical or surgical treatment will result in tumor regression, mainly in those who have high number of estrogen receptor (ER). Tamoxifen therapy which was classified as selective estrogen receptor modulator (SERM) after 5 years surgical treatment would decrease relapse and mortality rate to 47% and 26%. However, patients who had undergone definitive surgical treatment, chemotherapy and hormonal therapy for 5 years and still ‘disease free’ were still facing significant possibility of recurrent disease. This paper is an overview of the role of estrogen and aromatase inhibitor (AI) as widely accepted standard of care for breast cancer in various cancer centre and its expanding role upon tamoxifen in postmenopausal patients.

ESTROGEN AND BREAST CANCER

It has been widely known that estrogen has great influences on many organ systems. Especially, estrogen stimulates tumor cell growth in breast cancer tissue. In postmenopausal women with breast cancer, concentration of estradiol is found much higher than in the serum due to in situ aromatization process. Many studies had proven that disturbance of hormonal axis of estrogen-estrogen receptor may reduce or even eliminate tumor cell growth.

In breast cancer (BC) cells with positive ER, the estrogen is bonded to ER and undergoes dimerization process, translocation into nucleus and interaction with the estrogen response element in DNA, recruiting co-factor that facilitates estrogen dependent genome transcription and biomolecular protein synthesis supporting tumor cell growth. (figure1).

Endocrine therapy is a modulation of transduction signal pathway through interactions between soluble growth factor and specific cell receptor. Classically, this therapy had been understood as mean to disturb hormonal axis of estrogen-estrogen receptor complex by inhibiting estrogen production (ablation) or inhibiting the interaction between estrogen-estrogen receptor (additive). In wider concept, it includes progesteron – progesteron receptor (pgR), androgen-androgen receptor (AR), insulin like growth factor-insulin like growth factor family (EGFR) which is also known as human epithelial receptor (HER and erb-B) and other various angiogenic factors and other receptor such as VEGF (fibroblast growth factor). Endocrine therapy is divided into 2 mechanisms of strategies; estrogen suppression and estrogen blockade on receptor function by using anti estrogen or ER down regulator.
Aromatase is an enzyme which catalyzes conversion of androgen to estrogen. So, reducing estrogen level by AI is considered a rational approach. Ideally, AI should be selective on aromatase without adverse effect on steroidogenesis and possesses anti tumor effects. After the discovery of first generation of AI such as non selective aminoglutethimide up to third generation like exemstane, letrozole and anastrozole with minimal side effect and aromatase residual less than 5% had suggested that third generation AI was superior than tamoxifen/SERM. Table 1 shows various hormonal therapy used and its influence on estrogen synthesis.

Table 1. Hormonal Therapy Group Based on Ablative and Additive Properties

<table>
<thead>
<tr>
<th>Additive</th>
<th>Ablative surgery</th>
<th>Medical ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogenik</td>
<td>Ethinylestradiol</td>
<td>Oophorektomi</td>
</tr>
<tr>
<td>Androgen</td>
<td>Diethy stilbestrol</td>
<td>Adrenalectomi</td>
</tr>
<tr>
<td></td>
<td>Fluoxymestrone</td>
<td>Hypophysectomy</td>
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<tr>
<td></td>
<td>Methyl testosterone</td>
<td></td>
</tr>
<tr>
<td>SERMs</td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toremifene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Droloxfene</td>
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<tr>
<td></td>
<td>Idoxfene</td>
<td></td>
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<tr>
<td></td>
<td>Raloxifene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EM 800</td>
<td></td>
</tr>
<tr>
<td>Pure antiestrogens</td>
<td>Fulvestrant</td>
<td></td>
</tr>
<tr>
<td>Progestins</td>
<td>Megestrol acetate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medroxyprogesterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetate</td>
<td></td>
</tr>
<tr>
<td>Antiprogestins</td>
<td>Mifepristone</td>
<td></td>
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<tr>
<td></td>
<td>Onapristone</td>
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</table>

Aromatase Inhibitor and Breast Cancer

Next discussion will focus on the role of AI in breast cancer. Aminoglutethimide, the first generation of AI was introduced over 30 years ago. Initially, it was developed as anticonvulsant but then it was found to have inhibitory effects on several cytochrome P-450 enzymes in adrenal steroidogenesis. It was then redeveloped for use as ‘medical adrenalectomy’ in the treatment of advanced breast cancer. Its use on metastasis breast cancer (MBC) for over 20 years showed similar result with tamoxifen. However, neurologic toxicity and skin rash had limited its clinical use and it was drawn from clinical therapy. Second generation of AI like fadrozole (type 2 imidazole) and fermestene (type 1) were not more effective compared to first generation AI except that they have less toxicity. On the other hand, fermestene has disadvantage of requiring injection intramuscularly, while fadrozole can cause adrenal suppression which has limited its use to doses that produce about 90% inhibition. Compared to tamoxifen, fadrozole showed less response rate and lower median response while fermestene has shorter time to progression (TTP). Third generation of AI had been developed since 1990 including the triazoles anastrozole and lestrozole (both are type 2 which means reversible inhibitor of AI) and the steroidal agent exemestane (type 1 irreversible enzyme binding) specifically showed nearly complete specificity at clinical doses with minimal adverse effect on basal level of cortisol and aldosteron. This had
suggested better clinical efficacy of them compared to first and second generation.

**Table 2. Relative Potency of Aromatase Inhibitor Type I and Type II**

<table>
<thead>
<tr>
<th>Aromatase Inhibition (%)</th>
<th>Residual Aromatase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formestane</td>
<td>91.9</td>
</tr>
<tr>
<td>Exemestane</td>
<td>97.9</td>
</tr>
<tr>
<td>Aminoglutethamide</td>
<td>90.6</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>96.7</td>
</tr>
<tr>
<td>Letrozole</td>
<td>98.7</td>
</tr>
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</table>

**CLINICAL ROLE**

**Advanced Breast Cancer**

1. **First line therapy**

Recently, there are three phase III clinical trials (all are multicentre, double blind studies involving patients whose positive or unknown ER status) which shows the role of AI particularly anastrozole and letrozole as first line therapy in MBC. Total number of patients is 1928 involved in 2 clinical trials of anastrozole (1021 patients) and 1 clinical trial of letrozole (907 patients). It appeared that letrozole consistently and anastrozole possibly were superior compared to tamoxifen in post menopausal MBC.

Moridsen et al studied the use of letrozole vs tamoxifen in 907 postmenopausal MBC patients with median follow up 18 months. It indicated that letrozole resulted more tumor regression with had more prolonged TTP (9.4 vs 6.0 months; p value = 0.0001) and TTF (median 40 vs 25 weeks; p value = 0.0001) compared to tamoxifen. On the other hand, although overall RR (ORR) and clinical benefit of letrozole was superior to tamoxifen, but time period was not significantly different. Two other studies conducted by Nabhotz (353 patients) and Bonmatere (668 patients) had anastrozole vs tamoxifen with conflicting results. One of them had shown that anastrozole just like letrozole had prolonged TTP (11.1 vs 5.6 months; p = 0.005) and more tumor regression. But the other study did not confirm this finding. It may be concluded that in postmenopausal MBC, letrozole as first line therapy was superior to tamoxifen, while anastrozole showed contradictive result but confirmed that it was at least as effective as tamoxifen. The clinical trial on exemestane and tamoxifen is currently under way.

The fact that only half of patients with positive ER respond to hormonal therapy had induced the search for other mechanism of autocrine and paracrine developed by tumor cells. Wright et al showed reduced first line hormonal therapy from 48% to 20% due to co-expression on Her2/neu gene in patients with positive ER. Lipton et al also reported second line hormonal therapy giving less favorable response in patients with positive ER and Her2/neu compared to those who were negative Her2/neu. Lipton et al in phase III clinical trial, double blind, multicenter study, compared first line therapy: letrozole 2.5 mg with tamoxifen 20 mg in 562 MBC patients. Positive ER and increased or normal serum of Her/neu as predictive factor. The result showed patients with normal serum Her/neu receiving letrozole had ORR, CB, TTP and TTF significantly better than tamoxifen. While in increased serum Her/neu the difference was not significant except that letrozole showed more prolonged TTP and TTF compared to tamoxifen.

2. **Second line therapy**

Studies which had compared third generation AI to tamoxifen with the results mentioned above had made clinical relevance of second line therapy of AI. However, several studies which compared AI to megestrol acetate as second line therapy after tamoxifen in MBC showed third generation of AI was more effective in controlling disease activity and toxicity.

Research phase IIIB-IV involved 713 patients with MBC, postmenopausal, with positive ER or PR (48%) or unknown; relapsed after given antiestrogen like tamoxifen showed that letrozole had higher OR (19.1 % vs 12.3 %, p=0.014, OR 1.70)No significant difference in TTP, TT and CB between both anastrozole and lestrozole.

**Early Breast Cancer**

1. **Neo adjuvant**

The choice of pre-operative hormonal therapy is an interesting topic to discuss for two reasons; first in effort of down staging to avoid mastectomy and second to observe tumor responsiveness. Study on the use of tamoxifen in elderly women showed tumor regression in short time but weak in long term local control. Eirmann et al on 337 post menopausal patients with primary breast cancer, positive ER/PR, treatment naïve and were not candidates for breast conserving surgery (BCS) and 14% were inoperable. They were given letrozole 2.5 mg and tamoxifen 20 mg for 4 months. The result show letrozole was superior on clinical ORR compare to tamoxifen (55% vs 36%; p=0.042). Secondary
objective such as BCS (45% vs 35%, p=0.022),
response based on USG (35% vs 25%, p = 0.042),
and mammography (34% vs 16%; p=0.001) had
showed similar result. Both drugs were well-
tolerated and similar side effects except for higher
incidence of leucorrhea in tamoxifen group. Ellis et
al on phase III, randomized trial observed 324
patient with primary breast cancer were not
candidates for BSC, positive ER/PR and over
expression erbB-1 and or erbB-2 had been given
letrozole (154 patients) and tamoxifen (170 patients)
for 4 months. The result showed letrozole was
superior with RR were (60% vs 41%; p=0.0041) and
BCS (48% vs 36%; p=0.036). The significant dif-
cence on RR in patients with ErbB-1 and or ErbB-
2 and positive ER (88% vs 21%; p=0.0004). This data
is preliminary report and needs further studies for
confirmation. However, if other studies confirmed
this result, thus, using AI in elderly women with large
tumor size and positive ER would be an alternative
treatment choice to mastectomy.

2. Adjuvant therapy

Discussion on endocrine adjuvant therapy other
than tamoxifen/TAM which is considered standard
therapy in breast cancer is possible regarding side
effect of increased thromboembolism and uterine
cancer. AI as adjuvant therapy had been initiated
over 20 years and showed improved survival. There
are three large clinical trials phase III, double blind,
randomized consisting of three third generation of
AI which are ‘the Arimidex, tamoxifen alone or in
combination’ (ATAC), MA-17 (letrozole) and the
intergroup exemestene study (IES). ATAC was first
published in Lancet 2002 and Cancer 2003 had
divided the patients into 3 groups receiving
anastrozole or tamoxifen or sequential tamoxifen and
anastrozole or the other way around. The
observation was done for 33 months on 9366
patients in which 7839 patients (84%) with positive
ER showed anastrozole had better ‘disease free
survival’ (DFS) that statistically significant (89.4%
vs 87.4%; p=0.013). This effect occurred only in
positive ER patient. Combination therapy was not
better than single therapy of tamoxifen, but the
incidence of contralateral breast cancer was lower
in anastrozole group (p=0.0086) based on 4 years
follow up with 17% reduction. This result supported
pre-clinical research that stated combination of
anastrozole and tamoxifen would increase clearance
of tamoxifen. There was no significant difference
between patients with naïve therapy and involved
more than 4 lymph nodes. MA-17 study reported
randomized trial of letrozole 2.5 mg and placebo for
5 years involving 5187 post menopausal breast
cancer patients after receiving tamoxifen for 4.5-6
years and were still disease free. It was found that

<table>
<thead>
<tr>
<th>References</th>
<th>agents</th>
<th>Number of patients</th>
<th>Response %</th>
<th>Clinical benefit †</th>
<th>Median Time months</th>
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<tbody>
<tr>
<td>Mouridsen et al.</td>
<td>Letrozole</td>
<td>453</td>
<td>30‡</td>
<td>49‡</td>
<td>9.4‡</td>
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<tr>
<td>Nabholtz et al.</td>
<td>Tamoxifen</td>
<td>454</td>
<td>20</td>
<td>38</td>
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<td>Bonnetere et al.</td>
<td>Anastrozole</td>
<td>171</td>
<td>21</td>
<td>59‡</td>
<td>11.1‡</td>
</tr>
<tr>
<td>Eiermann et al.</td>
<td>Letrozole</td>
<td>154</td>
<td>55‡</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ellis et al.</td>
<td>Letrozole</td>
<td>17</td>
<td>88‡</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Dashes indicate not applicable
† Clinical benefits is shown as the total percentage of patients who had a response or whose disease stabilized for at least six months
‡ There was a significant difference from the result with tamoxifen
§ Eiermann et al compared letrozole and tamoxifen as preoperative therapy breast conserving surgery was possible in 45% of the subjects receiving letrozole and 35% of those receiving tamoxifen
¶ The data of Ellis et al refer to a subgroup from the study by Eiermann et al. (Positive for epidermal growth factor receptor positive for HER2) receiving preoperative treatment
207 local recurrent or metastatic or contralateral new lesions consisted of 75 patient receiving letrozole and 132 patients receiving placebo with hazard ratio 0.57 (95%CI 0.43-0.75; p=0.0008), with relative reduction prevalence of contralateral recurrent was 46% in letrozole group. Deaths due to breast cancer showed significant difference between letrozole and placebo groups (9 vs 17 patients but no significant difference on death caused by others. Predicted 4 years survival rate was 93% vs 87% (p=0.001 for DFS comparison) for Letrozole group. However, overall survival was significantly different (p=0.25). Based on this result, the study had been stopped earlier in median 2.4 years from 4 years previously planned. The use of letrozole on post menopausal women with positive ER after 5 years of tamoxifen treatment had to be considered. IES study which involved 4742 patients after receiving tamoxifen for 3 years were replaced by exemestene (2362 patients) and the rest continued receiving tamoxifen showed exemestene increased DFS significantly but no influence on overall survival. Adverse effects like flushing, vaginal bleeding, leucorrhea, uterine cancer, cerebrovascular disease and thromboembolism were found less in AI group than tamoxifen and incidence of fractures was frequently higher in patients receiving anastrozole and letrozole.

CONCLUSION

Estrogen is known to have potential in stimulating breast cancer cell growth. The in situ aromatization process of tumor cell maintains high level of estradiol inside the cell compared to its concentration in the serum. The additive inhibition or decreased production (ablative) of estrogen/estradiol may reduce or negate tumor cell growth.

AI had been developed since first generation over 30 years before. To date, Third generation of AI (type 1: exemestane; type 2 : letrozole and anastrozole) has shown increased clinical efficacy and minimal side effects.

First and second generation of AI had been compared to tamoxifen which was the standard care of hormonal therapy for breast cancer and showed similar result. However, significant adverse effects such as neurologic toxicity, skin rash or adrenal suppression have limited their clinical use and efficacy.

Third generation of AI like letrozole (and possibly anastrozole as well), in several studies suggested better clinical efficacy as first line therapy in MBC compared to tamoxifen and megestrol acetate as second line therapy after being considered inadequate response to tamoxifene.

Two clinical trials phase III had proven letrozole as neoadjuvant therapy and may become an alternative choice to mastectomy in elderly women with large size tumor and positive ER or unknown ER status. However, it still needs further research to confirm this.

As adjuvant therapy, third generation of AI (anastrozole) showed longer ‘disease free survival’ (DFS) comparing to tamoxifen, but its use is limited for positive ER only. Combination therapy with tamoxifen and letrozole as well appears to have no clinical difference compare to tamoxifen alone.

Letrozole given for 5 years in postmenopausal women with breast cancer and positive ER 5 years post tamoxifen therapy would decrease contralateral relapse and increase DFS, thus, such alternative treatment should be considered. Replacement therapy of exemestane after tamoxifene given for 2-3 years would increase DFS.

REFERENCES