New directions in hormone therapy for metastatic breast cancer

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Introduction
Metastatic breast cancer is incurable. Hormone therapy, which maintains quality of life, is well adapted to this situation. Current directions in hormone therapy are related to the introduction of new drugs, refinement of selection criteria and the development of new strategies.

New drugs

Blockade of ovarian function
This is achieved medically by luteinizing hormone-releasing hormone (LH-RH) analogs. The efficacy of this therapy resembles that obtained by castration [1].

Anti-estrogens
These agents are divided into two classes: nonsteroidal anti-estrogens, such as tamoxifen (Tam), which have both antagonist and agonist activity, and steroidal ‘pure’ anti-estrogens such as fulvestrant, which lack agonist activity.

Anti-aromatases
These drugs inhibit the action of aromatase, resulting in a reduction in circulating estrogens. Two classes of agent exist.
• Nonsteroidal, type II (reversible) anti-aromatases, termed aromatase inhibitors. The first clinically available drug, aminoglutethimide (AG), belongs to this class. Aminoglutethimide is nonspecific and requires patients to associate a corticosteroid. Two newer, more specific agents that are administered orally and act solely on aromatase have been tested: letrozole (Let) (2.5 mg/day) and anastrozole (Ana) (1 mg/day).
• Steroidal, type I (reversible) anti-aromatases, also known as aromatase inactivators. The major representative of this class is exemestane (Exe), which is administered per os (25 mg/day).

Parameters reflecting hormone sensitivity
When a metastasis is diagnosed, selection of first-line therapy is based on parameters reflecting hormone sensitivity.

Classical parameters of hormone sensitivity, Hormone receptor (HR) positivity, histological grade, disease-free interval and site of the metastasis.

More recent parameters of hormone sensitivity. More recent parameters of hormone sensitivity linked to expression of the HER2 receptor assayed in the tumor or the circulating blood.
• Tumor HER2 concentration: retrospective analysis of various trials and meta-analysis of results [2] have revealed that the objective response rate (ORR) obtained by hormone therapy is lower in patients whose tumor overexpresses HER2 than in patients without such overexpression.
• Circulating HER2 concentration: Lipton et al. [3] measured the circulating HER2 concentration in the serum of 719 patients enrolled in second-line clinical trials comparing megestrol acetate with fadrozole or letrozole. The HER2 concentration was <15 ng/ml in 500 patients and >15 ng/ml in 219 patients. Hormone therapy was more effective in the group with a low level of circulating HER2: ORR (20% versus 7%); time to progression (TTP) (180 versus 90 days; \( P <0.0001 \)); time to failure (175 versus 93 days, \( P <0.0001 \)); duration of remission (17.4 versus 11.7 months, \( P <0.0001 \)) and median duration of survival (29.6 versus 17.2 months, \( P <0.0001 \)).

New strategies

First-line hormone therapy
The approach depends on the patient’s menopausal status.
• Premenopausal patients: a combination of two treatments, such as castration and tamoxifen, is more effective than either of the treatments used alone, as demonstrated by a meta-analysis [4] (Table 1). The standard hormone therapy for metastatic premenopausal patients is thus an association of medical or surgical castration and tamoxifen.
• Postmenopausal patients: in the early 1990s, tamoxifen was the hormone therapy of reference in this situation.

Comparison of tamoxifen with anastrozole. Three trials compared anastrozole and tamoxifen in this situation. The percentage of HR-positive patients was 89% in the American study [5], 45% in the European study [6] and 100% in the Spanish trial [7]. The improvement in the TTP achieved with anastro-
Zole was found to be related to the percentage of HR+ patients, and ranged from 0 in the European study to 7 months in the Spanish study. If we combine all of the patients in the first two trials who were HR+ [8], the improvement in the TTP achieved with anastrozole was 4 months (Table 2).

Comparison of tamoxifen with letrozole.

A randomized trial compared tamoxifen and letrozole in 907 patients, 67% of whom were HR+ [9] (Table 2). This trial called for cross-over after the initial core phase when resistance to therapy occurred. Only 50% of patients were able to benefit from cross-over. Analysis of core phase results revealed that letrozole improved the TTP by 57% and the ORR by 50%. The risk of progression was reduced by 30%. These benefits were observed whether or not adjuvant hormone therapy was given and regardless of the site of metastases (bone or visceral). The survival of those patients who did not benefit from cross-over increased from 19 to 33 months. Drug tolerance was identical.

Comparison of tamoxifen with exemestane.

A preliminary randomized phase II trial [10] demonstrated an ORR in favor of exemestane (40.9% versus 13.6%). A phase III trial is in progress.

In conclusion, anti-aromatase agents appear to be more effective than tamoxifen as first-line therapy. These drugs are better tolerated, and can be considered the new standard for postmenopausal HR+ patients.

Second-line hormone therapy for tamoxifen-resistant patients

At the moment of progression of metastatic disease treated by hormone therapy, the question is whether to prescribe second-

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**Table 1.** Meta-analysis of trials comparing LH-RH with LH-RH plus tamoxifen

<table>
<thead>
<tr>
<th></th>
<th>LH-RH</th>
<th>LH-RH plus Tam</th>
<th>Relative risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (%)</td>
<td>30%</td>
<td>39%</td>
<td>0.67</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to progression (months)</td>
<td>5.4</td>
<td>8.7</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean survival duration (years)</td>
<td>2.6</td>
<td>2.9</td>
<td>0.76</td>
<td>0.002</td>
</tr>
</tbody>
</table>

LH-RH, luteinizing hormone-releasing hormone; OR, objective response, Tam, tamoxifen.

**Table 2.** Anti-aromatase agents versus tamoxifen as first-line therapy

<table>
<thead>
<tr>
<th></th>
<th>American trial (J.M. Nabholz)</th>
<th>European trial (J. Bonneterre)</th>
<th>Spanish trial (A. Milla-Santos)</th>
<th>Letrozole trial (H. Mouridsen)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tam</td>
<td>Ana</td>
<td>Tam</td>
<td>Ana</td>
</tr>
<tr>
<td>Number</td>
<td>182</td>
<td>171</td>
<td>328</td>
<td>340</td>
</tr>
<tr>
<td>HR+ (%)</td>
<td>88.4</td>
<td>88.2</td>
<td>45.3</td>
<td>43.5</td>
</tr>
<tr>
<td>Adj HT (%)</td>
<td>18.1</td>
<td>21.1</td>
<td>10.7</td>
<td>12.0</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>17.0</td>
<td>21.1</td>
<td>32.6</td>
<td>32.9</td>
</tr>
<tr>
<td>CB (%)</td>
<td>45.6</td>
<td>59.1</td>
<td>55.5</td>
<td>56.1</td>
</tr>
<tr>
<td>TTP (months)</td>
<td>5.6</td>
<td>11.1</td>
<td>8.2</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Ana, anastrozole; Adj HT, adjuvant hormone therapy; CB, clinical benefit; ORR, objective response rate; Tam, tamoxifen; TTP, time to progression.

**Table 3.** New generation aromatase inhibitors versus megestrol acetate

<table>
<thead>
<tr>
<th></th>
<th>Ana 1 mg vs MA (A. U. Buzdar)</th>
<th>Let 2.5 mg vs MA (P. Dombernowski)</th>
<th>Exe 25 mg vs MA (M. Kaufmann)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>263 vs 253</td>
<td>174 vs 189</td>
<td>366 vs 403</td>
</tr>
<tr>
<td>OR (CR + PR) (%)</td>
<td>12.6 vs 12.2</td>
<td>23.6 vs 16.4*</td>
<td>15 vs 12</td>
</tr>
<tr>
<td>Clinical benefit (%)</td>
<td>42.2 vs 40.3</td>
<td>34.5 vs 31.7</td>
<td>37 vs 35</td>
</tr>
<tr>
<td>Progression (%)</td>
<td>57.4 vs 59.3</td>
<td>53.4 vs 56.1</td>
<td>35 vs 36</td>
</tr>
<tr>
<td>MTTP (months)</td>
<td>4.9 vs 4.9</td>
<td>5.6 vs 5.5*</td>
<td>4.7 vs 3.8*</td>
</tr>
<tr>
<td>MSD (months)</td>
<td>27 vs 23*</td>
<td>25 vs 21.5</td>
<td>NA vs 28.4*</td>
</tr>
</tbody>
</table>

*aStatistically significant difference.

Ana, anastrozole; CR, complete response; Exe, exemestane; Let, letrozole; MA, megestrol acetate; MSD, median survival from diagnosis; MTTP, median time to progression; OR, objective response; PR, partial response.
line hormone therapy or to offer chemotherapy. Parameters in favor of second-line hormone therapy include achievement of an objective response (OR) with first-line therapy, HR positivity of the metastasis (when this can be determined), duration of remission obtained with first-line therapy and a low concentration of circulating HER2. These patients have usually progressed while being treated with tamoxifen and are referred to as tamoxifen-resistant.

- **Premenopausal patients**: ovariectomy after progression while on tamoxifen has proved successful in some cases. When first-line therapy consisted of a combination of an LH-RH analog and tamoxifen, replacement of tamoxifen by anastrozole [11] induced an OR in 73% of patients.

- **Postmenopausal patients**: aromatase inhibitors anastrozole [12], letrozole [13] and exemestane [14] were compared with megestrol acetate (MA) in three phase III clinical trials. The results (Table 3) reveal that letrozole improved the ORR ($P=0.04$) and the duration of remission ($P=0.0009$). The TTP was longer with exemestane ($P=0.037$). Survival was improved with both anastrozole ($P<0.0025$) and exemestane ($P=0.039$).

In light of these results, anti-aromatase agents have become the standard second-line treatment for tamoxifen-resistant patients.

**Second-line hormone therapy: strategy development**

In a trial using letrozole as first-line therapy, this drug had markedly better effects on parameters such as ORR and TTP than tamoxifen. Patients who did not cross-over the hormone treatment had their survival prolonged by 14 months [19 versus 33]. After cross-over, analysis of the overall increase in survival by the Wilcoxon test revealed that patients who started with letrozole died later. The benefit was significant after 6, 12, 18 and 24 months.

A similar analysis was made during the follow-up of trials comparing first-line therapy with anastrozole and tamoxifen [15]. In patients who relapsed while on anastrozole, tamoxifen induced an OR in 8% and a clinical benefit in 60.8%.

**Conclusions**

Hormone therapy of metastatic breast cancer is currently undergoing profound modifications.

- As first-line therapy for premenopausal patients, a combination of an LH-RH analog and tamoxifen is currently the standard approach. In postmenopausal patients, use of an aromatase inhibitor appears more effective than tamoxifen, especially with respect to TTP and sometimes the ORR or survival. These benefits are especially seen in patients with positive hormone receptors.

- As second-line therapy, in cases of resistance to tamoxifen, aromatases are the standard, but fulvestrant may play the same role. Prescription of tamoxifen after progression while on first-line anti-aromatase therapy can induce a useful clinical benefit.

**References**
