As evident from publication of the NSABP P-1 chemoprevention trial, NSABP B-24 DCIS trial and the ATAC trial, endocrine agents are being utilized in earlier stages of breast cancer. This trend will result in a more heavily pretreated population of patients with advanced breast cancer. The availability of the novel agent fulvestrant raises the issue of the optimal sequencing of endocrine agents in the management of postmenopausal women with metastatic breast cancer, and specifically the sequence of fulvestrant, tamoxifen and aromatase inhibitors. Data presented at the San Antonio Breast Cancer Symposium demonstrate responsiveness to subsequent endocrine therapy in patients treated with fulvestrant.

RESPONSE TO ENDOCRINE THERAPY AFTER FULVESTRANT OR TAMOXIFEN: A RETROSPECTIVE EVALUATION

**Responsive patients**

- **CB** = Clinical Benefit; **nCB** = no Clinical Benefit

<table>
<thead>
<tr>
<th>Progression or Withdrawal</th>
<th>Further Therapy</th>
<th>Further Therapy</th>
<th>Further Therapy</th>
<th>Further Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant 350 mg IM at a monthly interval</td>
<td>Endocrine therapy 20/35</td>
<td>Endocrine therapy 15/35</td>
<td>Endocrine therapy 10/31</td>
<td>Endocrine therapy 12/21</td>
</tr>
<tr>
<td>Anastrozole 0.5/10</td>
<td>Anastrozole 7/12</td>
<td>Anastrozole 9/16</td>
<td>Anastrozole 7/9</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen 1/5</td>
<td>Tamoxifen 1/3</td>
<td>Tamoxifen 4/18</td>
<td>Tamoxifen 3/6</td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate 1/5</td>
<td>Megestrol acetate 1/2</td>
<td>Megestrol acetate 2/3</td>
<td>Megestrol acetate 2/3</td>
<td></td>
</tr>
<tr>
<td>Other 1/5</td>
<td>Other 2/6</td>
<td>Other 0/1</td>
<td>Other 2/6</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Response Rate to Fulvestrant or Tamoxifen**

<table>
<thead>
<tr>
<th>Number of patients with clinical benefit</th>
<th>PR</th>
<th>SD ≥24 weeks</th>
<th>Progression</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd generation AIs</td>
<td>3</td>
<td>12</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

**Possible Locations for Fulvestrant in the Endocrine Cascade for Postmenopausal Women**

![Diagram showing possible locations for fulvestrant in the treatment of metastatic breast cancer]

**Other options for very advanced disease**

**Retrospective Evaluation of Endocrine Therapy after Fulvestrant**

“These data represent the first evaluation of responses to treatment after fulvestrant in patients with advanced disease previously untreated with endocrine therapy…Patients who respond to initial fulvestrant or tamoxifen may retain sensitivity to subsequent endocrine therapy...Aromatase inhibitors such as anastrozole or letrozole produce similar response rates in patients who have progressed on fulvestrant or tamoxifen. The proportion of post-fulvestrant responses reported here are similar to those previously described for second-line aromatase inhibitor therapy in patients who failed on first-line tamoxifen treatment. For example, CB was observed in 99/248 patients treated with anastrozole and in 65/377 patients receiving exemestane...The addition of fulvestrant to the choice of endocrine therapies may extend the opportunity for use of endocrine regimens before reliance upon cytotoxic chemotherapy is necessary.

Fulvestrant is effective in patients progressing on tamoxifen and these data show that after receiving fulvestrant, patients remain sensitive to treatment with other endocrine agents, including tamoxifen and AIs. Fulvestrant therefore provides an additional treatment option that may extend the period of effectiveness of endocrine therapy, before cytotoxic chemotherapy needs to be considered."

— Howell A. Breast Cancer Res Treat 2002; Poster/Abstract 251.

**Post-Fulvestrant Responses to Endocrine Therapy**

Sequencing of fulvestrant is a key issue to be addressed. We have data that you can see responses to aromatase inhibitors after fulvestrant and vice versa. Fulvestrant resistance is not hormone insensitivity. We do not yet know the mechanism by which cancer becomes resistant to fulvestrant. We do not believe it is an agonistic property. We can see ER expression on patients fulvestrant — even at the time of resistance. We are studying mechanisms of resistance with sequential biopsies, examining specimens both when patients are responding and when they become resistant.

— John Robertson, FRCS

**Emergence of Fulvestrant**

“The most recent entrant into the new pantheon of drugs for the treatment of breast cancer is the pure antiestrogen fulvestrant. …Preclinical data suggest fulvestrant may be more effective than tamoxifen, and it might work in patients who are initially resistant to tamoxifen. It is possible that combinations of fulvestrant and aromatase inhibitors will be effective, in contrast to the outcome of the ATAC trial, where there was no advantage to combining tamoxifen and aromatase blocker.”

— I Craig Henderson, MD

**Fulvestrant and the Sequencing of Endocrine Therapy in Postmenopausal Women**

Fulvestrant is equivalent as second-line therapy to our best drugs — the aromatase inhibitors. We now have a choice between treatments that are clearly equivalent. In postmenopausal women, I believe first-line therapy for advanced disease — even in those who have not had adjuvant tamoxifen — is an aromatase inhibitor. I see fulvestrant being used after the aromatase inhibitors.

— Anthony Howell, FRCP

Currently, this agent is used after aromatase inhibitors, but there are data demonstrating equal or perhaps greater efficacy than aromatase inhibitors for the management of metastatic breast cancer. The different route of administration for fulvestrant is a good thing for some patients, because they won’t have to remember to take a tablet on a daily basis. On the other hand, they will have to come to the clinic once a month to receive an intramuscular injection.

— Edith Perez, MD

**SELECT PUBLICATIONS**


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