As in postmenopausal women with early breast cancer, the sequencing of hormonal therapies in women with metastatic disease has become a topic of considerable interest. Postmenopausal women may now receive not only tamoxifen but also aromatase inhibitors in the adjuvant setting, and the optimal sequencing of hormonal agents for the treatment of metastatic disease is unknown. Fulvestrant, an estrogen receptor downregulator, is a recent addition to the hormonal therapy armamentarium. As second-line therapy in postmenopausal women with advanced breast cancer, fulvestrant and anastrozole have similar efficacy. Fulvestrant has also been compared to tamoxifen, as first-line therapy in women with advanced ER/PR-positive disease, and the benefits were comparable. Retrospective analyses of subsequent hormonal agents administered following fulvestrant have demonstrated significant response rates. Future clinical trials are required to determine the optimal sequencing of hormonal therapy options.

**CONSIDERED ANALYSER OF TWO PHASE III MULTICENTER TRIALS COMPARING FULVESTRANT TO ANASTROZOLE AS SECOND-LINE THERAPY IN PATIENTS WITH ADVANCED BREAST CANCER**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete response rate</th>
<th>Partial response rate</th>
<th>Objective response rate</th>
<th>Clinical benefit rate</th>
<th>Median duration of response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant</td>
<td>8.0%</td>
<td>16.5%</td>
<td>24.5%</td>
<td>39.5%</td>
<td>27.0 months</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>6.5%</td>
<td>11.5%</td>
<td>18.0%</td>
<td>27.5%</td>
<td>27.4 months</td>
</tr>
</tbody>
</table>

**RESPONSE TO SUBSEQUENT ENDOCRINE THERAPY IN PATIENTS ENROLLED IN TWO PHASE III TRIALS COMPARING FULVESTRANT TO ANASTROZOLE AS SECOND-LINE THERAPY: RETROSPECTIVE ANALYSIS**

<table>
<thead>
<tr>
<th>Response</th>
<th>Fulvestrant (68 patients)</th>
<th>Anastrozole (65 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease control</td>
<td>55 (81%)</td>
<td>49 (75%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>23 (34%)</td>
<td>16 (25%)</td>
</tr>
</tbody>
</table>

**SEQUENCING HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN**

I generally use an aromatase inhibitor in a postmenopausal patient progressing after tamoxifen and an aromatase inhibitor; however, clinical trials have shown that fulvestrant is equivalent to anastrozole after tamoxifen failure, and in a recently published European study comparing front-line fulvestrant to tamoxifen, I did not view fulvestrant as inferior to tamoxifen. In addition, a Phase II study is underway comparing fulvestrant to exemestane for second-line therapy. I use third-line fulvestrant, but rarely use it first-line. In particular in women who can’t afford an aromatase inhibitor, in addition I would estimate that approximately 40 percent of my patients prefer a monthly injection to taking a pill every day.

— Daley D. Braddock, MD

The overall results of Trials 20 and 21 showed no significant difference between anastrozole and fulvestrant, but differences occurred in survival analyses. The duration of response was seen to be longer in patients who responded to fulvestrant, and who had visceral disease seemed to respond better than those who did not. I think the key message is that they’re equally efficacious; there may be subsets of patients in whom you might prefer to use fulvestrant. Surprisingly the magnitude of benefit from fulvestrant who remained sensitive to further endocrine therapy may be an issue or those with visceral disease.

The other important point is anecdotal studies arguing that you can use one and switch to the other. Third-line aromatase inhibitors are efficacious after fulvestrant and vice versa.

— Gershoni Becker, MD

In postmenopausal women whose disease recedes while on adjuvant tamoxifen, I use fulvestrant because I’ve seen very some very long remissions with it. I will use an aromatase inhibitor later because data indicate that patients with disease that progresses on fulvestrant can still respond to other endocrine treatments (eg, aromatase inhibitors and registered acuates).

A few reports have evaluated the response to fulvestrant in patients who received an aromatase inhibitor. A small Swiss study reported that about one third of patients driven clinical benefit from fulvestrant after treatment with tamoxifen or an aromatase inhibitor. At ASCO 2003, a compassionate-use trial reported data from about 60 patients treated with fulvestrant as second-line therapy. Fulvestrant provided more than a 50 percent clinical benefit rate in those patients.

— Stephen S. Jones, MD

Women with breast cancer whose disease fails while on tamoxifen can usually respond to fulvestrant, and the response rate is equivalent to that seen with aromatase inhibitors. Also, in women with disease that has failed an aromatase inhibitor, subsequent therapy with fulvestrant leads to a substantial clinical benefit rate of approximately 40 percent. Those patients who use fulvestrant and an aromatase inhibitor also show response rates of approximately 40 percent. Support for the feasibility of benefit from fulvestrant does not predict whether the cancer will respond to a subsequent hormonal maneuver. One of the risks that have surfaced in the past has been the magnitude and duration of response to the most recent hormonal therapy practiced for the likelihood of response to subsequent hormonal therapies. A small retrospective study suggests that not the case with fulvestrant.

— Robert W. Carlson, MD

**SELECT PUBLICATIONS**


Lee Y-2. Postmenopausal tamoxifen (“fulvestrant”) is a hormonal therapy in postmenopausal patients with advanced breast cancer (ABC): progesterone receptor (PR) and/or estrogen receptor (ER) positive ABC. Breast Cancer Res Treat 2005; 92:361-369.


Lee Y-2. Postmenopausal tamoxifen irreversible disturbance of the metabolism of advanced breast cancer (ABC) with hormonal therapy (HT): progesterone receptor (PR) and/or estrogen receptor (ER) positive ABC. Breast Cancer Res Treat 2005; 92:401-409.