Sequencing of Hormonal Therapies in Metastatic Disease

28TH ANNUAL San Antonio Breast Cancer Symposium 20

The preferred sequence for hormonal therapies in postmenopausal women with metastatic disease has become a topic of considerable interest. As more postmenopausal women are being treated with aromatase inhibitors instead of tamoxifen in the adjuvant setting, the optimal therapy to use at initial relapse is not well defined. As first-line therapy, aromatase inhibitors are superior to tamoxifen, but the efficacy of fulvestrant — an estrogen receptor downregulator — is comparable to tamoxifen. As second-line therapy, fulvestrant and anastrozole have similar efficacy. A retrospective analysis of the proportion of patients with a prolonged duration of response suggests a benefit for fulvestrant over anastrozole. Future clinical trials are required to determine the optimal sequencing of the current hormonal therapy options.

SEQUENCING HORMONAL THERAPIES

How do you normally sequence endocrine therapy in postmenopausal patients with metastases and *no prior endocrine therapy*?

	1st-line	2nd-line	3rd-line
Tamoxifen	12%	18%	12%
Anastrozole	56%	12%	—
Letrozole	30%	14%	2%
Exemestane	2%	18%	26%
Fulvestrant	—	38%	34%
Megestrol acetate	—	—	10%
High-dose estrogen	—	—	4%
No endocrine therapy	—	—	12%

How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed adjuvant tamoxifen *one year previously*?

	1st-line	2nd-line	3rd-line
Tamoxifen	4%	4%	10%
Anastrozole	54%	8%	2%
Letrozole	38%	14%	—
Exemestane	4%	18%	34%
Fulvestrant	—	54%	26%
Megestrol acetate	—	—	12%
High-dose estrogen	—	—	4%
No endocrine therapy	—	2%	12%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

RETROSPECTIVE ANALYSIS OF PATIENTS RESPONDING IN TWO PHASE III STUDIES OF FULVESTRANT VERSUS ANASTROZOLE

Response	Fulvestrant 250 mg (n = 428)	Anastrozole 1 mg (n = 423)	*p*-value
Total patients with OR	19.2%	16.5%	0.3070
Patients with OR ≥1y	10.0%	7.1%	0.1627
Patients with OR ≥1.5y	4.0%	3.1%	—
Patients with OR ≥2y	0.9%	0.5%	—
Total patients with CB	43.5%	40.9%	0.5059
Patients with CB ≥1y	19.2%	13.9%	0.0692
Patients with CB ≥1.5y	7.5%	5.7%	—
Patients with CB ≥2y	1.4%	0.9%	—

"This analysis suggests that fulvestrant has benefits over anastrozole in terms of the number of patients with prolonged duration of response. These data support the initial DOR findings in these trials. Fulvestrant is an important new endocrine agent in breast cancer."

OR = objective response; CB = clinical benefit (complete response + partial response + stable disease ≥24 weeks); DOR = duration of response

SOURCE: Jones SE et al. *Proc SABCS* 2004;Abstract 6047.

PHASE III RANDOMIZED TRIAL COMPARING FULVESTRANT TO TAMOXIFEN AS FIRST-LINE ENDOCRINE THERAPY IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER

	All patients		Patients with ER/PR-positive tumors	
	Fulvestrant (n = 313)	Tamoxifen (n = 274)	Fulvestrant (n = 247)	Tamoxifen (n = 212)
Complete response rate	9.6%	6.9%	8.9%	5.7%
Partial response rate	22.0%	27.0%	24.3%	25.5%
Stable disease ≥24 weeks	22.7%	28.1%	23.9%	31.6%
Objective response rate*	31.6%	33.9%	33.2%	31.1%
Clinical benefit rate†	54.3%	62.0%	57.1%	62.7%

* Objective response indicates a complete or partial response; $p = 0.45$ for all patients; $p = 0.64$ for patients with ER/PR-positive tumors.

† Clinical benefit indicates a complete or partial response or stable disease ≥24 weeks; $p = 0.026$ for all patients; $p = 0.22$ for patients with ER/PR-positive tumors.

Median time to progression‡	6.8 months	8.3 months	8.2 months	8.3 months
Estimated median survival§	36.9 months	38.7 months	39.3 months	40.7 months

‡ $p = 0.088$ for all patients (upper limit of 95% confidence interval did not satisfy predefined criterion for concluding noninferiority of fulvestrant compared to tamoxifen); $p = 0.39$ for patients with ER/PR-positive tumors.

§ $p = 0.04$ for all patients; $p = 0.30$ for patients with ER/PR-positive tumors (upper limit of 95% confidence interval did not satisfy predefined criterion for concluding noninferiority of fulvestrant compared to tamoxifen).

SOURCE: Howell A et al. *J Clin Oncol* 2004;22(9):1605-13.

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

	Patients who derived clinical benefit from fulvestrant (n = 54)	Patients who did not derive clinical benefit from fulvestrant (n = 51)
Partial response	4 (7%)	1 (2%)
Stable disease ≥24 weeks	21 (39%)	17 (33%)
Disease progression	29 (54%)	33 (65%)

* More than 80 percent received an aromatase inhibitor as subsequent endocrine therapy.

SOURCE: Vergote I et al. *Breast Cancer Res Treat* 2003;79(2):207-11.

SELECT PUBLICATIONS

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Ingle JN et al. **Evaluation of fulvestrant in women with advanced breast cancer and progression on prior aromatase inhibitor therapy: A Phase II trial of the North Central Cancer Treatment Group.** *Breast Cancer Res Treat* 2004;Abstract 409.

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SEQUENCING HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN

Most clinicians consider fulvestrant a third-line therapy for patients who have failed 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. I use third-line fulvestrant, but I also use it first line, particularly with 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.

— *Adam M Brufsky, MD, PhD.* Breast Cancer Update *2004 (7)*

The overall results of Trials 20 and 21 showed no significant difference between anastrozole and fulvestrant, but differences occurred in subset analyses. The duration of response seemed to be longer in patients who responded to fulvestrant, and patients who had visceral disease seemed to respond better than those who did not. I think the takeaway message is that they're equally efficacious; however, there may be subsets of patients in whom you might prefer to use fulvestrant, particularly those for whom compliance may be an issue or those with visceral disease.

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

— *Gershon Locker, MD.* Meet The Professors *2004 (2)*

Generally, patients are either going to relapse on tamoxifen or after adjuvant tamoxifen. In that setting and in the fulvestrant versus anastrozole clinical trials, evidence exists that a proportion of women have a longer response to fulvestrant than to anastrozole when given right after tamoxifen. I've had patients with long responses to fulvestrant.

I prefer fulvestrant to an aromatase inhibitor after tamoxifen because approximately 20 percent of patients have long responses with it in this setting. However, 99 percent of oncologists will choose an aromatase inhibitor after tamoxifen. Fulvestrant is generally being used as third-line therapy. Despite Trials 20 and 21, most physicians start with anastrozole rather than fulvestrant because of the way the data have been presented.

We are just beginning to see patients who have been treated with two or three years of adjuvant anastrozole and then relapsed. Currently, there are few data on treatment options in this setting. It's somewhat of a "dealer's choice" because there are no hard and fast rules. There are multiple options including fulvestrant, exemestane and even tamoxifen — if the patient hasn't seen it — because it's obviously still a useful drug. So the sequence is going to be all over the map for most folks.

— *Stephen E Jones, MD.* Patterns of Care *2005 (1)*

In the up-front study, tamoxifen and fulvestrant were essentially equivalent. As second-line therapy, fulvestrant seemed to perform equally as well as anastrozole. At this point in time, the sequencing and timing for fulvestrant are unclear. I think it's reasonable to use the drug — maybe not up front, but as second- or third-line therapy. This is when you might consider the patient's preferences in terms of an intramuscular or an oral drug. A recent study of 261 women with metastatic breast cancer demonstrated that about one third preferred a monthly intramuscular injection. I've always assumed that oral drugs were preferable, if they were equally effective. Therefore, I was surprised to see that many patients preferred an intramuscular injection. I need to query my patients more when I start evaluating these options.

— *Debu Tripathy, MD.* Breast Cancer Update *2005 (5)*