Sequencing of Hormonal Therapies in Metastatic Disease

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. In addition, these agents have similar times to response, despite differences in their route of administration and pharmacokinetics. 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 of US Oncologists, September 2005. (n = 50)

TIME TO RESPONSE (TTR) WITH FULVESTRANT AND ANASTROZOLE IN PHASE III CLINICAL TRIALS

Data source	Median TTR (months)	Range (months)
Trial 0020		
Fulvestrant (n = 46)	3.15	0.9 - 24.9
Anastrozole (n = 36)	3.10	0.7 - 9.4
Trial 0021		
Fulvestrant (n = 36)	3.02	0.9 - 33.1
Anastrozole (n = 34)	2.96	0.8 - 20.2
Combined data (trials 0020 and 0021)		
Fulvestrant (n = 82)	3.10	0.9 - 33.1
Anastrozole (n = 70)	2.99	0.7 - 20.2

Supporting TTR data were subsequently collected from three other randomized Phase III trials of fulvestrant, anastrozole and tamoxifen in advanced breast cancer.

Conclusions and future directions:

- Median TTR was similar between fulvestrant and oral endocrine agents, such as anastrozole and tamoxifen, despite differences in their route of administration and pharmacokinetics.
- These data suggest that patients without rapidly progressive disease should be kept on endocrine treatment for at least three months to allow a response to be achieved prior to considering changing treatments.

SOURCE: Pippen JE. Poster. San Antonio Breast Cancer Symposium 2005; Abstract 5092.

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.

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%	—

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

"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."

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

SELECT PUBLICATIONS

Carlson RW, Henderson IC. **Sequential hormonal therapy for metastatic breast cancer after adjuvant tamoxifen or anastrozole.** *Breast Cancer Res Treat* 2003;80(Suppl 1):19-26.

Howell A. **Postmenopausal women with advanced breast cancer who progress on fulvestrant or tamoxifen retain sensitivity to further endocrine therapies.** Poster. San Antonio Breast Cancer Symposium 2002;Abstract 251.

Iaffaioli RV et al. **Phase II study of sequential hormonal therapy with anastrozole/exemestane in advanced and metastatic breast cancer.** *Br J Cancer* 2005;92(9):1621-5.

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.

Jones SE et al. **A retrospective analysis of the proportion of patients responding for ≥1, 1.5 and 2 years in two Phase III studies of fulvestrant vs anastrozole.** *Proc SABCS* 2004;Abstract 6047.

Perey L et al. **Fulvestrant (Faslodex™) as hormonal treatment in postmenopausal patients with advanced breast cancer (ABC) progressing after treatment with tamoxifen and aromatase inhibitors: Update of a Phase II SAKK trial.** *Breast Cancer Res Treat* 2004;Abstract 6048.

Pippen JE. **Similar time to response between fulvestrant and anastrozole: Comparison from two Phase III trials.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 5092.

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38.

Vergote I et al. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79(2):207-11.

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 experience disease 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)

The trials of fulvestrant conducted to date do not provide a clear indication as to where we should be using this drug. 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)