Exploring the lack of cross-resistance between aromatase inhibitors: evidence for a difference?

Per Eystein Lønning[a,b]

A lack of cross-resistance between the aromatase inhibitors (AIs) provides evidence to suggest that there are clinical differences between these agents. Available data from clinical trials indicate that patients exposed to nonsteroidal AIs may benefit from a steroidal compound of similar biochemical potency, and durable stable disease can be achieved in a significant proportion of patients. To date, there is little evidence suggesting specific pharmacokinetic/pharmacodynamic resistance for individual tumours to particular compounds. To clarify fully this issue, a head-to-head comparative trial in the adjuvant setting is needed and the results of the MA.27 trial randomizing patients to the steroidal AI exemestane vs. the nonsteroidal AI anastrozole will be invaluable in this regard. *Anti-Cancer Drugs* 19 (suppl 2):S11–S13 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Section of Oncology, Institute of Medicine, University of Bergen and [b]Department of Oncology, Haukeland University Hospital, Bergen, Norway

Currently, there is no head-to-head comparison of aromatase inhibitors (AIs) in the adjuvant treatment of breast cancer and therefore any attempt to compare the efficacy and/or toxicities of the AIs must be drawn from data from the metastatic setting. Clinical trials evaluating sequential treatment with AIs in advanced disease show that there is a partial lack of cross-resistance between the steroidal and nonsteroidal AIs (Table 1) [1–7]. In these clinical trials, patients responded to treatment with formestane, anastrozole or exemestane after failing treatment with aminoglutethimide, formestane or a nonsteroidal AI.

Data from *in vivo* studies evaluating aromatase inhibition cannot explain the observed lack of cross-resistance between nonsteroidal and steroidal AIs. Third-generation AIs inhibit aromatase to a greater degree than first-generation and second-generation compounds, but there are only small differences seen in noncomparative studies between the third-generation AIs [7]. For example, there is a difference between total body aromatase inhibition for the first- and second-generation inhibitors aminoglutethimide and fadrozole and formestane versus exemestane (80–90 vs. 97.9%) [8–11], but there seems to be no difference between exemestane and anastrozole (97.9 vs. 98.1%) and exemestane and letrozole (97.9 vs. 98.9%) [11–13].

In a third-line study of exemestane 25 mg/day in patients who had failed treatment with tamoxifen and a nonsteroidal AI, a substantial proportion of patients achieved durable stable disease for a period of more than 6 months; 24.3% of patients had complete response, partial response or stable disease [4]. Subgroup analyses of patients who had previous exposure to aminoglutethimide and those who had prior exposure to a third-generation nonsteroidal AI demonstrated similar response rates (complete response + partial response + stable disease ≥ 24 weeks: 27.2 vs. 20.0%) between the two groups.

The question remains: if there is a class difference, what is the evidence that there can be responses both ways (i.e. that patients may benefit from a nonsteroidal AI subsequent to a steroidal compound)? HarperWynne and Coombes demonstrated SD on anastrozole following failure to formestane [5]. Bertelli *et al.* [14] evaluated the sequence of various AIs: patients who had no prior AI therapy were given exemestane, patients receiving exemestane were given anastrozole or letrozole, and those on anastrozole or letrozole received exemestane. The results demonstrated that a nonsteroidal AI provides some clinical benefit following treatment with exemestane as well as effects of exemestane after non-steroidal compounds (Table 2). The number of patients in each group, however, was small.

The findings from the Spanish Breast Cancer Research Group 2001–2003 study [15], in those patients whose disease became resistant to exemestane 25 mg/day and were then treated with anastrozole 1 mg/day, demonstrated that none of these patients achieved an objective response to therapy, or durable stable disease. Conversely, those patients treated with exemestane following failure on anastrozole had a significantly longer median TTP (4.4 months; $P = 0.017$).

Although the results from the Bertelli *et al.*, and Spanish Breast Cancer Research Group studies should be interpreted with care due to the small number of patients in each, an interesting observation is that all patients who

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Table 1 Trials evaluating sequential treatment with aromatase inhibitors/inactivators in patients with metastatic breast cancer

	Treatment and results						
First drug	AG	AG	AG	AG	nAI	For	nAI
Second drug	For	For	Exe	Exe	Exe	Ana	For
No. of patients	112	10	78	136	105	21	20
RR second drug (%)	20.5	20.0	25.6	8.1	4.8	0	0
RR + SD ≥ 6 months	42.9	50.0	60.3	27.2	20.0	62	55
Reference	[1]	[2]	[3]	[4]	[4]	[5]	[6]

AG, aminoglutethimide; Ana, anastrozole; Exe, exemestane; For, formestane; nAI, nonsteroidal third-generation aromatase inhibitors (anastrozole, letrozole and vorozole); RR, response rate; SD, stable disease.

Table 2 Efficacy of various treatment sequences on clinical outcomes

Response			
	Group A exemestane	Group B letrozole/ anastrozole after exemestane	Group C exemestane after letrozole/anastrozole
Patients	40	18	236
Response, *n* (%)			
Complete response	0	2 (11.1)	0
Partial response	11 (27.5)	2 (11.1)	2 (8.7)
Stable response	18 (45.0)	9 (50.0)	9 (39.1)
Progressive disease	11 (27.5)	5 (27.8)	11 (47.8)
Not evaluable	0	0	1 (4.3)
SD ≥ 24 weeks	16 (40.0)	6 (33.3)	8 (34.8)
Clinical benefit	27 (67.5)	10 (55.6)	10 (43.5)

CR, complete response; PR, partial response; SD, stable disease.
Clinical benefit, CR + PR + SD ≥ 24 weeks.

benefited from a nonsteroidal AI subsequent to exemestane were exposed to treatment with letrozole. Notably, a study in 12 postmenopausal patients with oestrogen-receptor positive (ER +) metastatic breast cancer – where patients were first exposed to anastrozole 1 mg/day and then letrozole 2.5 mg/day or the reverse – demonstrated that in both groups letrozole consistently resulted in more complete total body aromatase inhibition ($P = 0.0022$) [13]. The answer to the issue – whether more aggressive aromatase inhibition is actually translated into improved clinical efficacy – will be settled in an ongoing, large, randomized trial.

The evaluation of fulvestrant vs. exemestane clinical trial randomized patients who failed prior nonsteroidal AI therapy to fulvestrant or exemestane [16]. The objective response rate (7.4 vs. 6.7%), clinical benefit (32.2 vs. 31.5%), and median TTP (3.7 vs. 3.7 months) were similar between the two treatment arms. The data are interesting, inasmuch as they indicate a similar degree of cross-resistance between anastrozole and exemestane as seen for anastrozole vs. fulvestrant, a compound with a different mechanism of action. On the basis of these data, exemestane is a good therapeutic option in patients with breast cancer who have failed treatment with a nonsteroidal AI.

In conclusion, patients exposed to nonsteroidal AIs may benefit from a steroidal compound of similar biochemical potency. Although the objective response rate is low, durable stable disease is achieved in about 20% of patients treated for up to 6 months. A response to anastrozole was demonstrated after formestane and to letrozole after exemestane, but these observations were based on small studies.

To date, there is little evidence suggesting specific pharmacokinetic/pharmacodynamic resistance for individual tumours to individual compounds.

No difference is observed regarding the efficacy of exemestane and fulvestrant in patients with metastatic breast cancer failing nonsteroidal AIs, substantiating previous findings of a lack of complete cross-resistance between nonsteroidal AIs and exemestane. A head-to-head comparison of exemestane and anastrozole in the adjuvant setting will be needed to clarify the issue of whether exemestane actually is superior to anastrozole or whether the two compounds may be effective in different patient subpopulations. The results of the comparative trial (MA.27) of exemestane vs. anastrozole are awaited with interest.

Conflicts of interest: PE Lønning received speaker's honoraria and compensation for participation in Advisory Boards for Pfizer, Novartis and AstraZeneca.

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