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Letrozole's superiority over progestins and tamoxifen challenges standards of care in endocrine therapy for metastatic breast cancer

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Endocrine therapy (ET) was the first and is still the number one targeted systemic therapy available to treat breast cancer. Its history in advanced disease, summarised in Table 1, shows that tamoxifen has been the gold standard first-line ET for 20 years, while progestins such as megestrol acetate (MA) and aminoglutethimide (AG) have competed for the position of second-line ET in the marketplace for 15 years.

The third generation aromatase inhibitors (AI) including letrozole (L), anastrozole (A) and exemestane (E) have challenged our assumptions of the therapeutic limitations of second-line hormonal therapy [1], while letrozole has demonstrated for the first time clear superiority over tamoxifen as first-line ET [2].

The contribution of L to these recent and profound mutations in 'optimal ET' for advanced breast cancer is analysed in more detail below.

1. Letrozole superiority over MA

Two randomised clinical trials, one published in 1998 and used for L registration [3] and the other published in 2001 [4], compared the efficacy and tolerability of L given at two dose levels (0.5 mg daily or 2.5 mg daily) versus MA (160 mg daily). Their most important results are summarised in Tables 2 (efficacy) and 3 (tolerability). While L demonstrated clear superiority over MA in the two trials, we are faced with one trial showing an advantage for the higher L dose and another showing advantage for the lower L dose. Because the higher dose showed a trend of superiority over the lower dose in a trial of L versus AG, it was the higher dose that was selected for further development in the first-line setting.

1.1. Letrozole superiority over tamoxifen

The largest ever endocrine therapy trial for advanced breast cancer compared L 2.5 mg daily with tamoxifen [2]. This study's strengths include, besides its large size, its double-blind design and its cross-over extension phase: in other words, patients progressing on first-line ET with L or tamoxifen had the option of crossing over to second-line therapy. This trial, therefore, reflects the needs of daily clinical practice, in which the main goal remains the longest possible control of the disease with an optimal *sequence* of endocrine therapies. While this trial showed comparable tolerability of the two agents, it demonstrated clear superiority of L as first-line ET for all four of the key efficacy endpoints: time to progression, time to treatment failure, overall response rate and clinical benefit rate (Table 4). Results of the extension phase and, importantly, results in terms of overall survival (OS) are eagerly awaited.

Table 1
Endocrine therapy (E.T.) of advanced breast cancer in post-menopausal women

Before 1975	Diethyistilboestrol (DES) first-line standard Progestins second-line
1975–1980	Randomised trials show superiority of tamoxifen over DES
1981	Aminogentethimide (AG) introduced
From 1980	Tamoxifen first-line standard Progestins/AG second-line
From 1995 onwards	Third generation aromatase inhibitors (A.I) challenge: (1) AG or megestrol acetate (MA) as second-line E.T (2) tamoxifen as first line E.T.

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Table 2
Overview of efficacy data from phase III trials of letrozole versus megestrol acetate in tamoxifen failures

	European trial			US02 trial		
	Letrozole[a]		MA[a]	Letrozole[b]		MA[b]
	0.5 mg ($n=188$)	2.5 mg ($n=263$)	160 mg ($n=253$)	0.5 mg ($n=202$)	2.5 mg ($n=199$)	160 mg ($n=253$)
Median follow-up		33 months			37 months	
Median TTP[c] (months)	5.1	5.6	5.5	5.6 $P=0.044$	3.2	3.4
Median survival (months)	21.5	25.3	21.5	33.1	28.8	26.2
Objective response (%)	12.8	23.6 $P=0.04$	16.4	20.8	16.1	14.9

[a] Ref. [3].
[b] Ref. [4].
[c] TTP; time to progression.

Table 3
Most frequent adverse experiences reported in women treated with letrozole (L) or Megestrol acetate (MA)

	European trial			North American trial		
	L 0.5 mg%	L 2.5 mg%	MA%	L 0.5 mg	L 2.5 mg	MA
Any adverse experience[a]	78.2	85.1	89.9	47.5	45.2	57.7
Nausea	19.1	10.9	9.0	12.9	10.6	9.5
Weight increase	2.1	2.3	8.5	2.5	3.0	11.9
Headache	13.3	12.6	9.0	2.5	10.6	4.5
Fatigue	5.9	10.9	11.1	3.5	5.5	8.5
Peripheral oedema	8.0	8.6	7.9	3.5	2.5	7.0
Musculoskeletal pain	25.5	27.0	30.2	2.5	4.5	1.0
Dyspnoea	11.2	9.2	16.4	2.0	1.5	8.5
Alopecia/hair thinning	–	–	–	3.5	6.0	0.5
Vaginal bleeding	–	–	–	2.0	0.5	6.0
Thrombo-embolic events	$n=2$	$n=0$	$n=15$	–	–	–

[a] Reported in at least 5% of women in the European trial and 3% of women in the North American trial.

Table 4
Superior efficacy of letrozole overl tamoxifen as first-line ET for advanced breast cancer

	Letrozole	Tamoxifen	Ratio (95% CI)	*P* value
TTP (median)	9.4 m	6.0 m	0.70[a] (0.60–0.81)	0.0001
TTF (median)	9.1 m	5.8 m	0.71[a] (0.61–0.82)	0.0001
Objective response	30%	20%	1.71[b] (1.26–2.31)	0.0006
Clinical benefit	49%	38%	1.55[b] (1.19–2.01)	0.001

CI, Confidence Interval; TTF, time to treatment failure; m, months.
[a] Hazard ratio.
[b] Odds Ratio.

2. Conclusions

L has performed particularly well versus the two 'standard' therapies, MA and tamoxifen. Together with anastrozole [5] and exemestane [6], the other two potent third-generation AI, it has led to a new standard of care for second-line ET of metastatic breast cancer, displacing MA to the third-line setting. In first-line treatment, third generation AI are gaining increasing attention from the oncology community; however, a claim for 'definitive' superiority over tamoxifen awaits mature and confirmatory data from the ongoing exemestane versus tamoxifen trial, as well as survival results.

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