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Treatment of Advanced Breast Cancer with Miconazole: a Potential Inhibitor of Peripheral Oestrogen Synthesis

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MICONAZOLE is an orally absorbable antifungal drug which inhibits steroid biosynthesis in mammals and aromatase activity in breast cancer cells *in vitro* [1–3]. Our previous successful use of other aromatase inhibitors and the long half-life (24 h), allowing once daily dosing, led us to test miconazole in advanced breast cancer.

20 post-menopausal women, median age 62 years (39–80), with progressive advanced breast cancer and assessable disease were treated with miconazole 750 mg daily increasing, if tolerated, to 1.5 g daily (Table 1). Treatment was continued for at least three months provided there was no evidence of progressive disease. Patients with life-threatening disease or hepatic/renal dysfunction were excluded. Most patients were pretreated with a median of 3 (0–7) treatments per patient but had not received systemic treatment for at least 4 weeks. 14 patients had responded to previous endocrine treatment.

Serum oestradiol was measured before and during treatment according to previously published methodology [4]. Patients were seen monthly and a reassessment was made at the time of maximum response and/or progression. Response was assessed by standard UICC criteria.

There were no complete responses, but 2/20 (10%) patients achieved a partial response (PR) and there was stable disease in 6 patients (30%) for at least 3 months (Table 2). 1 patient achieving PR was previously untreated and the other had been treated with TAD (tamoxifen, aminoglutethimide and danazol in combination). The duration of response was 13 months for 1 patient and greater than 9 months for the other. This gives an overall response rate of 13% (95% confidence limits 0–31%) in endocrine therapy responders and patients naive to therapy. Responses occurred in skin and nodal metastases but not with bone or visceral disease. 17 patients had pre- and post-treatment oestradiol levels (Table 2). On treatment oestradiol levels fell by more than 50% in 4 patients, were largely unaltered in 12 patients and in 1 patient oestradiol rose (19.8–40.5 pmol/l). The 2 patients with PR had no change in oestradiol level.

Toxicity was manifest by nausea (6 patients) and pruritic skin rash (3 patients). 3 patients discontinued treatment within 4 weeks because of toxicity. There were no disturbances in liver function tests during treatment.

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Table 1. Patients' characteristics

Previous treatment	Endocrine	14
	Chemotherapy	5
	None	1
Sites of disease (median number/patient = 2)	Soft tissue	19
	Lung	3
	Liver	2
	Bone	4
	Pleura	2

Table 2. Response to treatment

		Oestradiol		
Tumour	Response*	Decrease (>50%)	No change (<50%)	Increase (>50%)
CR	0	—	—	—
PR	2	0	2	—
NC	6	2	3	—
PD	8	2	5	—
NA	4	—	2	1

*3 patients not assessable for changes in oestradiol.

Previous use of miconazole in breast cancer has been reported only in premenopausal women, a situation in which aromatase inhibitors have found little application [3]. Although miconazole is an inhibitor of aromatase [1–3], only 4/17 patients in this study had a fall in oestradiol levels: despite using an oestradiol assay which has been well validated for this use [4]. This may be related to the known variability in absorption which was not controlled for in this study. The response rate was low in these heavily pretreated patients and less than reported with other aromatase inhibitors [5], although *in vitro* inhibition of aromatase miconazole was reported as 70 fold greater than by aminoglutethimide [3]. Response was not related to changes in oestradiol. Toxicity was confirmed to nausea and pruritus but was limiting in 3 patients.

Although miconazole can alter oestradiol levels in postmenopausal women, the effects are not consistent. The low response rate and toxicity suggest that it is unlikely to have a role in the management of advanced breast cancer.

1. Mason JI, Murrg BA, Olcott M, Sheets JJ. Imidazole antimycotics: inhibitors of steroid aromatase. *Biochem Pharmacol* 1985, **34**, 1087–1092.
2. Sheets JJ, Mason JI, Wise CA, Estabrook RW. Inhibition of rat liver microsomal cytochrome P-450 steroid hydroxylase reactions by imidazole antimycotic agents. *Biochem Pharmacol* 1986, **35**, 487–491.
3. Yamamdo T, Fukuoka M, Yasumura T, Okada H. *In vivo* and *in vitro* effects of the antifungal agent miconazole on estrogen biosynthesis in human breast cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 1493–1497.
4. Dowsett M, Goss PE, Powles TJ, *et al.* Use of the aromatase inhibitor 4-hydroxyandrostenedione in post-menopausal breast cancer: optimization of therapeutic dose and route. *Cancer Res* 1987, **47**, 1957–1961.
5. Harris A, Powles TJ, Smith IE. Aminoglutethimide in the treatment of advanced post-menopausal breast cancer. *Cancer Res* 1982, **42** (Suppl.), 34055–34085.