ORIGINAL ARTICLE

Pilot Study of Formestane in Postmenopausal Women with Breast Cancer

J K Joseph, MRCP, A K H Lim, FRCR, Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur, Jalan Pahang, Kuala Lumpur, Malaysia

Summary

A pilot study of Formestane or 4-Hydroxyandrostenedione (Lentaron®), a new endocrine agent, was conducted on 18 postmenopausal patients with locally advanced and metastatic breast cancer. 16 patients were evaluable for response and objective responses were seen in 4 patients (25%). Stabilisation of disease was seen in 5 patients (32%). Out of 17 patients evaluable for toxicity, 3 (18%) reported adverse effects including hot flushes, lethargy and myalgia. Adverse effects were mild, transient and no patient required discontinuation of drug.

Our study confirms that Formestane is a well tolerated endocrine agent with low toxicity and reasonable efficacy in postmenopausal patients with locally advanced and metastatic breast cancer.

Key Words: Formestane, Aromatase inhibitor, Postmenopausal women, Metastatic breast cancer

Introduction

In 1995, breast cancer was the leading cause of cancer deaths in women in Malaysia. About 40% of patients with breast cancer present with locally advanced and metastatic disease. The great majority of these patients have incurable disease[1]. Palliation of symptoms is therefore the prime goal of treatment in this group. Endocrine treatments have an excellent tolerability when compared to cytotoxic chemotherapy regimens. They are considered as 1st line treatment particulary in those with ER positive tumours and those with unknown receptor status unless they have rapidly progressive disease[2]. Since the first report by Beatson in the Lancet 100 years ago, endocrine treatments have a long and established track record in the treatment of breast cancer[3]. Formestane or 4-hydroxyandrostenedione (Lentaron®), a selective aromatase inhibitor is a recent addition to the armamentarium of endocrine agents available to the oncologist for the treatment of advanced breast cancer.

In this paper the authors share their experience of a pilot study using Formestane in postmenopausal patients with advanced breast cancer at the Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur. The aims of the study were to assess the toxicity, tolerability and efficacy of Formestane at the standard dose and schedule.

Patients and Methods

Between August 1994 and December 1995, 18 patients attending the Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur were enrolled in the study.

Inclusion Criteria

1) Patients had to be postmenopausal. (Postmenopausal status being defined as no menses for a minimum of 12 months prior to entry.)
2) Histologically proven diagnosis of invasive carcinoma of the breast.
3) All patients had metastatic disease or locoregional recurrence.
4) Patients had to have prior treatment with Tamoxifen.
5) Patients were unselected for estrogen receptor status.

Exclusion Criteria

Patients with documented pulmonary lymphangitis, overt brain and liver metastases were excluded from this study.

Informed consent was obtained from all patients. Approval to treat patients on a named patient basis (as the drug was unregistered at the time of study) was obtained from the Drug Control Authority, Ministry of Health, Malaysia.

Treatment Schedule

Formestane was administered in a dose of 250 mg by intra-muscular injection every 2 weeks. Patients were required to attend the Institute of Radiotherapy and Oncology every 2 weeks. Formestane was continued until there was objective evidence of disease progression at which point it was discontinued.

Clinical Evaluation

Prior to entry into study a clinical assessment including medical history, physical examination, complete blood count, chest x-ray and serum biochemistry was performed.

Dimensions of measurable skin and soft tissue lesions were noted. Patients with bone metastases were assessed by serial plain x-rays 2 monthly and Isotope bone scans 6 monthly. Patients with intrathoracic (lung, pleura or mediastinal nodes) metastases were assessed by serial chest x-ray 2 monthly and/or computerised tomograms 3 monthly.

Response Assessment

Response was assessed according to standard UICC criteria (Union Internationale Contre le Cancer) of response.

Complete response was defined as the complete disappearance or resolution of all tumour masses that was confirmed on 2 separate occasions at least 4 weeks apart.

Partial Reponse was defined as a 50% or greater decrease in the sum of products of all measurable lesions. Measurable disease refers to bidimensionally measurable lesions in 2 planes perpendicular to each other. Stable disease or "No change" was defined as patients with metastatic lesions that did not show disease progression or development of new lesions for at least 10 weeks.

In patients with bone lesions only i.e. evaluable but non-measurable (lytic areas in bone are not bidimensionally measurable), no partial response assessment was allowed. Patients were judged to have either stable disease or progressive disease. Stable disease was defined as static osteolytic lesions and improvement of bone pain.

Disease progression was defined as the development of new lesions or an increase of more than 25% in established lesions within 8 weeks of initiating therapy. Adverse effects experienced (if any) were noted at each visit.

Results

The total number of patients entered was 18. 2 patients defaulted, the first after one dose and the other after 3 doses.

The median age of the patients was 54 years (range 45-86 years). Out of 18 patients, 16 (89%) had unknown oestrogen receptor tumours. One (6%) had a positive oestrogen receptor tumour and one (6%) had a negative oestrogen receptor tumour.

All patients had prior systemic treatment with Tamoxifen. Most patients were heavily pretreated with 9 (50%) having received prior systemic treatment both in the adjuvant and metastatic setting.

9 patients (50%) had prior treatment with chemotherapy in the metastatic setting. (Table I)

Sites of disease involvement were as follows:
12 patients had multiple sites of disease involvement and 7 patients had intrathoracic involvement (lung, pleura or mediastinal node). 4 patients had soft tissue involvement only. 9 patients had bone involvement of which 2 had only bone involvement. (Table II)

Adverse Effects

17 patients were evaluable (out of 18 entered) for

adverse effects. One patient defaulted after the first dose. 3 patients (18%) reported adverse effects. All adverse effects reported were mild, transient and self-limiting. No patient required discontinuation of Formestane due to toxicity. (Table III)

Response to Therapy

16 patients were evaluable for response (2 defaulted follow up). There were 4 patients who had an objective response. The objective response rate for the evaluable patients was 25%. A further 5 patients had stabilisation of disease (stabilisation defined as freedom from disease progression for 10 weeks or more) or 31% of evaluable patients had disease stabilisation.

The total number of evaluable patients in this study who experienced either stabilisation of disease or objective response was 9 patients or 56% of evaluable patients. No patient had complete response to Formestane.

Table I
Prior systemic treatment

	No. of Patients	%
Adjuvant Tamoxifen	14	78
Prior Endocrine Rx For Advanced Disease	4	22
Adjuvant Chemotherapy	10	56
Prior chemotherapy For Advanced Disease	9	50

Table II

Sites of Disease Involvement	No. of Patients	%
Soft Tissue	10	56
Bone	9	50
Intrathoracic Involvement	7	39
Soft Tissue Only	4	22
Bone Only	2	11
Mixed Sites	12	67

The time to progression (defined as the interval between start of treatment to the time of documented disease progression) was also assessed. The median time to progression for all evaluable patients was 10 weeks (range 2 to 90+ weeks).

The median time to progression for objective responders (4 patients) was 32 weeks (range 30-44 weeks).

The median time to progression for patients with stabilisation of disease was 20 weeks (range 10-90+ weeks). (Table IV)

All patients have progressed at the time of reporting except one who continues on Formestane and has disease stabilisation for more than 90 weeks.

Discussion

Metastatic breast cancer remains an incurable disease[4]. Among postmenopausal women with metastatic disease, a recent trial comparing the sequence of initial chemotherapy followed by endocrine therapy on disease progression with the sequence of endocrine therapy

Table III

Side Effects*	Number
Hot Flushes	2
Lethargy	2
Muscle Ache	2
Pain at injection site	2

** Multiple symptoms possible in individual patients.*

Table IV
Response to therapy

Median Time to Progression (TTP)	Weeks (Range)
All Evaluable	10 (2-90+)
Responders	32 (30-44)
Stable Disease	20 (10-90+)

first followed by chemotherapy showed no survival advantage for initial chemotherapy[5]. Thus in postmenopausal patients likely to respond to endocrine therapy, this should be used initially.

Tamoxifen is the most widely used agent as first line endocrine therapy both in the metastatic and adjuvant settings particularly in postmenopausal women[6]. This has led to an increasing need for second and third line endocrine agents upon relapse of disease. The current second and third line endocrine therapy for postmenopausal women in Malaysia are medroxyprogesterone acetate (a progestin) and aminoglutethimide. Medroxyprogesterone acetate is significantly more toxic than Tamoxifen as shown in randomised comparative trials[7,8]. Aminoglutethimide, an early aromatase inhibitor (AI) is also disadvantaged by considerable side effects occcuring in approximately 35% of patients. Furthermore, it requires coadministration of glucocorticoid at therapeutic doses due to adrenal suppression[9].

Formestane is a newer steroidal aromatase inhibitor. It is a selective aromatase inhibitor and has significant advantages over aminoglutethimide. Formestane is a substrate analog that blocks the aromatase enzyme which mediates the final step in the synthesis of oestrogens. It is about 60 times more potent than Aminoglutethimide[11].

Unlike Aminoglutethimide there is no requirement for coadministration of corticosteroids as Formestane does not interfere with the synthesis of other corticosteroids.

The pilot study of Formestane at our Institute confirms that this drug has a low toxicity profile and is well tolerated in our patients. In addition although the response rates and median time to progression were modest in these patients, several factors have to be borne in mind.

Firstly response rates alone are not the best way to evaluate endocrine agents in metastatic breast cancer. Stabilisation of disease especially for periods of months may translate into improved survival and is equivalent to an objective response[12].

Most of the patients included were heavily pretreated with 2 or more lines of treatment. This group is less likely to respond to another endocrine agent.

Finally the vast majority of patients in this series were unselected for endocrine therapy as they had tumours of unknown oestrogen receptor status.

Our local study confirms the results of reported phase II and phase III studies that Formestane has a low toxicity profile and is well tolerated with efficacy almost equivalent to Tamoxifen[13-14]. The response rate of 25% in this study concurs with the response rates of 20-25% obtained in other reported studies on Formestane.

Conclusions

Formestane is a well tolerated endocrine agent with a low toxicity profile. It has reasonable efficacy in postmenopausal women with advanced breast cancer as confirmed in this series of patients.

Further evaluation including pharmacoeconomic and quality of life issues are being addressed in multicentre prospective randomised trials comparing Formestane with second-line endocrine agents in metastatic breast cancer. It is likely that in the future Formestane and other newer selective aromatase inhibitors will be utilised as second line endocrine agents in postmenopausal patients with hormone responsive breast cancer.

Acknowledgement

The authors wish to acknowledge the support of Ciba-Geigy (M) Sdn. Bhd. in providing the drug to our patients.

The authors wish to thank the Director General of Health of Malaysia for his permission to publish the findings of this study.

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