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Short Communication

A Pilot Study to Evaluate Paclitaxel (Taxol™) as Primary Medical Treatment for Patients with Inoperable Stage III and IV Breast Carcinoma

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The activity of paclitaxel has been extensively investigated in previously treated patients with metastatic breast carcinoma. We evaluated the activity of paclitaxel as primary medical therapy in patients with stage III and IV breast carcinoma. 6 female patients were recruited with no previous history of surgery, radiotherapy or chemotherapy. Paclitaxel was administered as a 3-h infusion at a dose of 225 mg/m^2 repeated every 3 weeks weekly to a maximum of 10 cycles. 2 patients achieved a complete response, one of whom had a normal trucut biopsy of the affected breast 6 months after discontinuation of chemotherapy and radiotherapy and a normal mammogram at 17 months. 3 patients achieved a partial response and one stabilised. The patients received between four and ten cycles of chemotherapy. Paclitaxel at this dose was associated with toxicity including alopecia, stomatitis, nausea and diarrhoea. Moderately severe neutropenia occurred in 4 patients, 2 requiring antibiotics but was of short duration and did not necessitate a dose reduction for subsequent courses. Paclitaxel has shown activity as primary medical therapy in patients with inoperable breast carcinoma at presentation at this dosage and schedule. One patient achieved a complete response and avoided surgery altogether and all 6 patients had their primary tumour downgraded. It may be indicated as a single agent in this context or in combination with other drugs with proven activity in breast carcinoma.

Key words: breast carcinoma, paclitaxel, primary medical treatment

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INTRODUCTION

PACLITAXEL (TAXOL™) is a taxane which affects the G2/M phase of the cell cycle and interferes with microtubule assembly which is essential for the formation of the mitotic spindle apparatus and for maintaining cell shape [1]. It was first identified in 1971 as a cytotoxic agent [2].

Paclitaxel has been shown to have antitumour activity against several forms of cancer [3]. It has activity in patients with previously treated metastatic breast cancer [4, 5] and Spielman and associates [6] demonstrated an overall response rate of 27% in a multinational randomised study. Reichman and associates [7] administered paclitaxel as initial chemotherapy for metastatic breast cancer and achieved objective responses in 62% of patients including complete responses in 12%.

We carried out a pilot study to evaluate the use of paclitaxel as a primary medical therapy for breast carcinoma.

MATERIALS AND METHODS

All patients had either histologically or cytologically confirmed stage IIIa, IIIb or IV breast carcinoma according to UICC criteria, an ECOG performance of 0, 1, 2 and were between 18 and 75 years of age. They were newly diagnosed and had received no prior surgery, radiotherapy or chemotherapy. They had bidimensionally measurable disease as determined by physical examination or radiological investigation. All patients had adequate haematological, renal and hepatic function. Pre- and postmenopausal patients were eligible.

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Table 1. Outcome following paclitaxel as primary medical therapy

Patient	Age	Stage pretreatment	Stage post-treatment	No. of cycles	Response	Management	Pathology	Outcome following chemotherapy
1	38	T4c N1 M1 (bone and liver metastases)	T0 N0 M0	10	CR	Radiotherapy to breast and axilla. Tamoxifen		Relapsed at 7 months with distant metastases and died 18 months later
2	51	T4c N0 M0	T0 N0 M0	4	CR	Radiotherapy to breast. Tamoxifen		Remains well at 19 months
3	37	T4c N1 M0	T2 N1 M0	6	PR	Refused mastectomy. Radiotherapy to breast, axilla and supraclavicular fossa. Goserelin		Relapsed at 5 months with local recurrence and distant metastases and died 16 months later
4	34	T4c N2 M1 (supraclavicular node)	T1 N0 M0	5	PR	Radical mastectomy and axillary clearance. Radiotherapy to supraclavicular fossa. Goserelin	1.5 cm invasive carcinoma 17/21 nodes	Disease stable at 17 months
5	51	T4c N2 M0	T4 N0 M0	8	PR	Refused mastectomy. Radiotherapy to breast and axilla. Tamoxifen		Disease stable at 16 months
6	51	T4b N0 M0	T3 N0 M0	7	NC	Mastectomy and axillary clearance. Radiotherapy to supraclavicular fossa. Tamoxifen	3 cm invasive carcinoma 16/21 nodes	Disease stable at 20 months

CR, complete response; PR, partial response; NC, no change.

Paclitaxel was given as a 3-h infusion at a dose of 225 mg/m^2 repeated every 3 weeks. All patients were premedicated with dexamethasone 20 mg, 12 and 6 h prior to chemotherapy and chlorpheniramine, 10 mg, and cimetidine, 300 mg, 30 min prior to chemotherapy.

Patients were evaluated for response after two cycles of paclitaxel and for toxicity after one cycle using WHO criteria to a maximum of 10 cycles. Patients were assessed for response according to UICC criteria.

RESULTS

6 female patients were recruited, all with advanced local disease. Patient 1 had a liver metastasis on ultrasound examination and a single hot spot on bone scan. Patient 4 had a supraclavicular lymph node involvement. The other patients had no evidence of metastatic disease on chest X-ray, liver ultrasound or bone scan (Table 1).

The patients received between four and 10 cycles of paclitaxel. 5 patients showed evidence of response in terms of reduction of the primary breast carcinoma. The breast carcinoma in the sixth patient was downstaged to T3 but due to insufficient reduction in size was classified as no change (NC) according to UICC criteria.

The first 2 patients showed a complete response clinically. During follow-up, both exhibited good local control, but patient 1 died of distant metastases 18 months later. Patient 2 had a normal trucut biopsy of the affected breast 6 months after discontinuation of chemotherapy and radiotherapy and a normal mammogram at 17 months. The next 3 patients achieved a partial response. 2 of the patients refused mastectomy, one of whom, patient 3, relapsed locally and with distant metastases at 5 months and died at 16 months. Patient 4 had a radical mastectomy and axillary clearance for a 1.5 cm moderately differentiated carcinoma with 17/27 nodes involved. Patients 4 and 5 remain well at 17 and 16 months, respectively. Patient 6 had a mastectomy and axillary clearance for a 3 cm invasive ductal carcinoma with 16/21 nodes involved and remains well at 20 months.

Paclitaxel at a dose of 225 mg/m^2 was associated with significant toxicity, graded according to WHO criteria. All patients suffered from grade 3 alopecia and fatigue. 3 patients developed grade 1 or 2 stomatitis. Diarrhoea

occurred in 3 patients, grades 1, 2 and 3, respectively, and nausea in 3, two grade 1 and one grade 2. Two patients developed a skin rash, one grade 1 and one grade 2. Moderately severe neutropenia ($<1.0 \times 10^9/l$) occurred in 4 patients, two requiring antibiotics. However, neutropenia was of short duration and did not require dose reduction on subsequent courses.

DISCUSSION

In this pilot study, paclitaxel has shown activity as primary medical therapy in patients with inoperable breast carcinoma at presentation. Patient 2 who achieved complete remission with chemotherapy avoided surgery altogether. All 6 patients had their primary tumour downgraded making them more amenable to surgery, although only 2 patients went on to have mastectomy and axillary clearance. Patient 1 relapsed with distant metastases, but maintained local control which is of considerable importance considering that the patient was T4c at presentation. Patient 2 also had a T4c tumour at presentation and so far, following radiotherapy, has no disease recurrence locally or elsewhere.

Paclitaxel is active in patients with locally advanced breast carcinoma at this dosage and schedule and may be indicated as a single agent in this context. Paclitaxel at this dosage did not cause life-threatening myelosuppression or hypersensitivity.

Seidman and associates [8] administered paclitaxel to patients with stage IV breast carcinoma, some of whom had been extensively pretreated with other chemotherapeutic agents including anthracyclines. Paclitaxel was more active in the previously untreated group, but activity was also seen in the treated group suggesting non-cross-resistance with anthracyclines. Further trials are underway to investigate the combination of paclitaxel and other drugs with known activity in breast carcinoma and also to assess its activity in other malignancies.

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