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Experience in a UK cancer centre of weekly paclitaxel in the treatment of relapsed ovarian and primary peritoneal cancer

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Abstract

Objectives. Weekly paclitaxel (WP) has been reported to have significant activity in patients with ovarian and primary peritoneal cancer patients while retaining a favorable toxicity profile. This study assessed the current usage of WP in routine clinical practice in a tertiary cancer center.

Methods. We conducted a retrospective audit in 53 patients with recurrent ovarian or primary peritoneal cancer treated with WP (80–100 mg/m^2) over a 2-year period (Nov 2003–Nov 2005). Toxicity was assessed using Common Toxicity Criteria, and response was evaluated using radiological and CA-125 criteria.

Results. Patients had a median age of 69 (36–86) and previously received a median of 3 treatments (range 1–7). A median of 13 weekly doses of paclitaxel (range 1–39) were given. The response rate was 48% by radiological criteria and 69% by CA-125 assessment. Grade 3 toxicities were fatigue (13% of patients), peripheral neuropathy (11%) and neutropenia (8%) and there were no grade 4 toxicities. The median progression-free survival was 4. 8 months and median survival was 13. 5 months. There was no significant difference in efficacy between those 24 patients previously treated with taxanes (radiol. response 43%/CA-125 response 63%) and those 29 patients who had not received prior taxanes (radiol. response 52%/CA-125 response 76%). There was also no difference in efficacy for patients with platinum-free or treatment-free intervals of less than 6 months compared to 6 months or longer.

Conclusions. WP is a well tolerated and active regimen in patients with pre-treated ovarian cancer and its use in recurrent disease is likely to increase. Further studies should aim to assess the importance of the "paclitaxel-free interval" in predicting response in relapsed disease, along similar lines as are now established for platinums.

Keywords: Weekly paclitaxel; Ovarian cancer; Treatment-free interval

Introduction

Ovarian cancer is a chemosensitive disease and has traditionally been treated with platinum agents [1]. More recently paclitaxel in combination with platinum agents has been established as the standard of care for newly diagnosed advanced ovarian cancer following cytoreductive surgery [2,3]. Despite high overall response rate to first line treatment the majority of patients with advanced ovarian cancer will relapse.

There are a number of factors predictive of a response to chemotherapy in relapsed ovarian cancer. These include tumour size (b5 cm), serous histology and a small number of disease sites [4]. There is a well established relationship between the platinum-free interval, PFI (period of time from last treatment with a platinum agent), and the response rate to re-challenge with platinum chemotherapy in relapsed ovarian cancer. In patients who are drug sensitive (PFI ≥ 6 months) response rates of 30–50% are seen to second line chemotherapy whereas in those deemed to be drug resistant (PFI b6 months) the response rate is only 10% [5–7]. The PFI has also been shown to predict response to non-platinum chemotherapy in patients who have relapsed following platinum therapy with response rates varying from 6–35%[8,9].

Strategies to improve the treatment for relapsed ovarian cancer have concentrated on optimising the use of existing cytotoxics and identifying novel targets [8]. There is also interest

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in pursuing new strategies for drug sequencing, incorporating non-cross resistant drugs, in an effort to maximise the platinum-free interval [9].

Paclitaxel is a cytotoxic agent derived from the bark of the Pacific Yew tree. Its major mechanism of action involves inhibition of microtubule depolymerisation during mitosis [10], although an anti-angiogenic effect of paclitaxel, with a reduction of Vascular Endothelial Growth Factor (VEGF) and Interleukin-8 (IL-8), has also been proposed from pre-clinical models and clinical trials [11–13]. Paclitaxel is usually administered on a 3 weekly schedule but interest has more recently centred on weekly paclitaxel as there have been reports of objective responses in patients with ovarian cancer who progressed on the 3 weekly schedule [14,15]. The use of weekly paclitaxel has been given further credence following the results of a phase III trial comparing the two schedules as neoadjuvant treatment in breast cancer. This study recruited 258 patients and reported almost double the number of pathological complete responses in the weekly paclitaxel arm compared to the 3 weekly arm [16]. A trial comparing 3 weekly versus weekly paclitaxel in 208 patients with ovarian cancer previously treated with a platinum agent demonstrated equal efficacy but less toxicity with the weekly arm [17]. The trial was underpowered to demonstrate a difference in response rate, time to progression or survival as accrual stopped due to poor recruitment after 208 of the planned 350 patients. Phase I studies using weekly paclitaxel have experienced dose limiting toxicity at 100 mg/m^2/week and most clinicians recommend a starting dose of 80–90 mg/m^2/week [18,19].

Two groups have conducted phase II trials of weekly paclitaxel in the treatment of recurrent ovarian cancer. Kaern et al. reported an overall response rate of 56% and progression-free survival of 4.3 months in 57 patients with platinum resistant disease [15]. Markman et al. reported an overall response rate of 20.9% and progression-free survival of 3.6 months in 48 patients who were resistant to both platinum agents and paclitaxel (progressed during or within 6 months of treatment) [20]. Both these trials describe favourable toxicity profiles.

Our centre has increasingly adopted the use of weekly paclitaxel in the treatment of recurrent ovarian cancer over the past 4 years. We therefore conducted a single institution audit on the use of weekly paclitaxel in order to investigate whether the results of the phase II trials are reproducible in routine clinical practice. Within the limits of a retrospective audit, we also planned an analysis of predictive factors for response.

Materials and methods

The study had the approval of the Local Audit Committee.

Patients

To be eligible to receive weekly paclitaxel patients had to satisfy the following criteria: histological confirmation of ovarian or primary peritoneal carcinoma, objective and/or symptomatic disease progression after one or more previous chemotherapy regimens that included a platinum agent and the patient should not have received a taxane within the previous 6 months. Patients were required to have adequate renal function, normal haematological indices and no serious co-morbidities.

Treatment

Paclitaxel was given intravenously at a dose of 80–90 mg/m^2 in a 3 weekly cycle receiving treatment on days 1, 8 and 15. Treatment was administered on an outpatient basis unless hospitalisation was necessary for other reasons. Dexamethasone (8 mg) was administered prior to therapy as prophylaxis against paclitaxel-associated hypersensitivity reactions. As there is no proven role for maintenance paclitaxel, 6–8 cycles (18–24 weeks) of therapy was given without breaks at the individual clinician's discretion. Patients who specifically requested continued therapy and had demonstrable benefit in the absence of toxicity were considered for more than 24 weeks treatment. Dose delays and reductions were given for toxicity and in the event of progressive disease or unacceptable toxicity treatment was discontinued.

Dose modifications were performed (reduction by 10–20 mg/m^2) for the following indications: 1) on the day of treatment, absolute neutrophil count $b0.8\times10^3$/ml or platelet count of $b75\times10^3$/ml 2)≥ grade 2 motor or sensory neuropathy 3)≥ grade 2 renal toxicity or 4) any other toxicity ≥ grade 3. Treatment was interrupted in patients experiencing these toxicities until recovery by 1 grade had occurred. The use of colony stimulating factors was discouraged.

Response and toxicity

Response was evaluated by radiological and tumour marker assessments which were defined according to the following criteria:

1) Radiological response on a single scan (by CT-scan, as per the RECIST criteria): Complete response-CR (disappearance of all target lesions), partial response-PR (at least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum of the longest diameters), progressive disease-PD (at least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since the treatment started or any new lesion), or stable disease-SD (neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD).
2) Biochemical response (CA-125): Response was defined as at least 50% reduction in CA-125 levels (if elevated before treatment) that is confirmed and maintained for at least 28 days. Progression was defined as a CA-125 ≥ 2 times the upper limit of normal or ≥ 2 times that of the pre-treatment level, in patients with normal or elevated levels before treatment respectively, documented on two occasions at least one-week apart. The date of progression was regarded as the first date of CA-125 elevation above these limits [21].

Toxicity was assessed using the common toxicity criteria and adverse events (CTCAE) version 3.0.

Statistics

Overall survival was measured from the date of first treatment until death or last follow-up. Progression-free survival was measured from date of first treatment until either progression or death and was censored at last follow-up. Survival curves were generated using the methods of Kaplan and Meier. The relationship between subgroup variables and response to treatment was analysed using the Chi-square test or Fisher's exact test as appropriate.

The dose density of treatment (mg/m^2/week) was calculated for each patient by the following formula: $(D\times n)/N$, where D is the average dose given per week (mg/m^2), n is the total number of doses administered and N is the actual treatment duration (in weeks). Dose intensity is the calculated dose density expressed as a percentage of the scheduled dose density, 90 mg/m^2/week.

Results

Patient characteristics

Between November 2003 and November 2005 53 patients with ovarian or primary peritoneal carcinoma received weekly paclitaxel. All patients had previously been treated with a platinum cytotoxic agent and 24 patients had previous exposure to a