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Carboplatin in Advanced Hormone Refractory Prostatic Cancer Patients

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25 patients with measurable or evaluable metastatic prostate cancer, progressive after hormonal treatment, were treated weekly with carboplatin 150 mg/m² intravenously. The weekly schedule allowed higher dose intensity carboplatin administration with respect to the common monthly cycles. Toxicity was manageable even in elderly patients with extensive bone metastases and consisted primarily of myelosuppression. 4 out of 24 evaluable patients (17%) had a partial response and 12 (50%) had disease stabilisation. The median response duration was 7 months. Prostate-specific antigen and prostatic acid phosphatase serial values showed a correlation with disease response in only 47 and 50% of patients, respectively. These results suggest that carboplatin possesses a moderate but definite activity in prostate cancer patients.
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INTRODUCTION

ALTHOUGH PROSTATE CANCER represents a prime model of an endocrine-dependent tumour, about 30–40% of patients are refractory to the initial endocrine manipulations and the others will develop irreversible resistance during the course of the disease [1]. More effective hormonal agents or alternative therapy are needed. Chemotherapy is of limited value in this disease. In fact, only occasional responses have been reported with a number of cytotoxic agents used alone, while combination therapy has not produced better results but only significantly more side-effects. No single drug or combination has been shown to improve survival [2–5].

Among single agents, cisplatin has demonstrated a limited but definite clinical activity, in the range of 20–40% objective response rate [6–8]. Carboplatin, a second generation cisplatin analogue, has shown in many solid tumours an activity at least comparable to cisplatin with less side-effects [9]. Allen *et al.* showed that a weekly regimen of carboplatin in paediatric tumours achieved a high percentage of objective response associated with low toxicity. The weekly dose schedule allowed higher dose intensity carboplatin administration with respect to the more common monthly schedule [10].

These findings prompted us to test the value of a weekly carboplatin regimen in advanced hormone refractory prostatic cancer patients.

PATIENTS AND METHODS

25 patients with metastatic prostate cancer were studied. Patients were required to fit the following criteria: histological or cytological proof of advanced prostate cancer that was progressive despite first- and second-line hormonal treatment; a performance status of 2 or lower (WHO scale); advanced objectively measurable or evaluable disease; age 80 years or less and a life expectancy of at least 12 weeks. Before treatment all patients had a physical examination with documentation of all signs and symptoms of disease paying particular attention to measurable lesions, blood count, blood chemistry, measurement of serum prostatic acid phosphatase (PAP) and prostatic-specific antigen (PSA), chest radiograph, computer tomography (CT) scan or sonography of the pelvis and abdomen, and bone scan. Bone radiographs were performed to check positive scan-detected lesions. Physical examination, complete blood count and blood chemistry were repeated every week; PSA and PAP determinations were performed monthly. Bone scan, X-ray, CT scan or sonography, when necessary for disease evaluation, were repeated every 2 months. Carboplatin 150 mg/m² was administered intravenously over 30 min once a week on an outpatient basis. Courses were repeated weekly at 100% of the planned dose if leukocyte count was ≥ 4000, platelets ≥ 100 000 and creatinine clearance ≥ 40 ml/min. Drug administration was delayed by 1 week in the case of no full haematological recovery at the scheduled retreatment time. Treatment was administered until progression, severe toxicity or patient's refusal.

Evaluation of response and toxicity were performed according to the National Prostate Cancer Project (NPCP) [11] and WHO [12] critiera, respectively. Patients who received chemotherapy for at least 8 courses were considered evaluable for response. All patients were analysed for toxicity. All patients were required to give informed consent.

RESULTS

The main characteristics of the patients on the study are summarised in Table 1. 24 patients were evaluable for response: 12 presented measurable disease and 12 evaluable disease. 2 patients with measurable disease achieved a partial response (17%), 8 patients (67%) had stabilisation of their disease and 2 (17%) showed progressive disease. In patients with evaluable disease only 2 partial responses (17%) were observed, with 4 patients having stable disease (33%) and 6 progressive disease (50%). Overall, 4 of 24 patients had a partial response so the overall response rate was 17% (confidence interval 2–32%) with a median response duration of 7 months (range 3–15) (Table 2). In the 2 responding patients with measurable disease, a more

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Table 1. Main patients' characteristics

	No. of patients
Total entered	25
Median age (range)	68 years (52–79)
Median ECOG performance status (range)	1 (0–2)
Prior treatment	
Orchidectomy	4
LH-RH analogues alone	2
LH-RH analogues and anti-androgens	17
Anti-androgens alone	4
Extramustine phosphate	10
Lonidamine	2
Mytomicin-C	3
Sites of metastatic disease	
Bone	22
Lymph nodes	10
Liver	3
No. of disease sites	
1	11 (44%)
2	9 (36%)
3	5 (20%)

than 50% reduction in the number of abnormal areas of bone scan and a 50% decrease in the size of abdominal nodes were observed. Of the two responding patients with evaluable lesions, one presented a 50% reduction in liver enlargement due to tumour involvement, and the other had normalisation of PAP levels, stabilisation of bone disease and improvements in pain index.

A correlation between serial values of PSA and PAP and disease response (including indicators of stable disease) was observed in only 47% (7 of 15) and 50% (4 of 8) of patients, respectively. 3 patients showed a reduction of more than 50% with respect to pretreatment assessment in the PSA circulating levels. 1 patient showed PSA reduction associated with clinical progression; in the other 2 patients PSA changes correlated with clinical response.

PAP pretreatment values showed normalisation in 2 patients with stable disease, and more than a 50% reduction in 2 other patients with stable disease and progressive disease, respectively. Median time to progression was 6 months (range 2–15). The median number of cycles delivered to any individual patient was 11 (range 4–28). The dose intensity was quite successfully achieved and maintained. In fact, the median dose intensities delivered during the first four and eight cycles were 83 and 80%, respectively.

All the 25 patients were evaluable for toxicity. The major acute toxicity encountered was myelosuppression. Leukopenia G3–G4 occurred in 4 patients (16%) and thrombocytopenia G3–G4 in 5 patients (20%). All the patients were prophylactically treated with a metoclopramide-based anti-emetic regimen. No clinically apparent infections were encountered. Only 4 patients (16%) experienced G1 nausea. Alopecia and renal toxicity were never observed. No deaths related to toxicity were recorded.

Table 2. Tumour response

	Measurable disease (n = 12)	Evaluable disease (n = 12)
Partial response	2 (17%)	2 (17%)
Stable disease	8 (67%)	4 (33%)
Progressive disease	2 (17%)	6 (50%)

DISCUSSION

Chemotherapy trials have failed to demonstrate convincing evidence of meaningful survival advantages for patients with advanced prostate cancer [2]. However, objective responses, palliation of symptoms and maintenance of acceptable levels of quality of life have often been achieved by using cytotoxic chemotherapy [2–4].

In this study, carboplatin has been shown to be moderately active in a group of heavily pretreated prostate cancer patients. These patients were pretreated with a median of two treatment modalities and 50% of them also received previous cytotoxic therapy. Responses were seen in soft tissue, viscera and bone metastatic lesions. Hormone refractory prostatic cancer is often reported as a heterogenous disease at different metastatic sites, with bone metastasis more resistant to medical treatment. In our study two out of 20 bone metastases showed a partial response.

The evaluation of chemotherapeutic agents in prostatic cancer has always been complex because of the characteristic clinical manifestations of this disease, with prevalent bone osteoblastic metastatic lesions that are extremely difficult to evaluate [13–15]. This explains the large variability in response rates reported by different investigators for a given drug.

Moreover, serum tumour markers have always been considered in the evaluation of response to hormone treatment, and have also been expected to help in the evaluation of clinical courses during chemotherapy. While markers' changes parallel the clinical course of disease in patients with hormone-sensitive disease treated with androgen deprivation, few data are available on sequential markers' changes in patients with hormone refractory disease, although they do not seem to be correlated with the response to chemotherapy [16–20]. No correlation between PSA and PAP serum levels and disease response to chemotherapy has been observed in our study.

In an attempt to improve carboplatin activity, we used a weekly dose schedule allowing higher dose intensity. Several studies showed increased response rates and longer survival, with increasing average chemotherapy dose intensity per unit time in solid tumours [21, 22]. Our results show that weekly administration of carboplatin was quite well tolerated with acceptable haematological toxicity, in terms of thrombocytopenia and leukopenia, despite the old age and extensive bone involvement in many patients.

The results of our study suggest that carboplatin possesses a moderate but definite activity in a subgroup of patients generally resistant to cytotoxic chemotherapy, associated with a reasonable tolerance and acceptability.

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Radioimmunoscintigraphy Using [^{111}In]Antimyosin Fab Fragments for the Diagnosis and Follow-up of Rhabdomyosarcoma

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Between 1987 and 1992, 39 radioimmunoscintigraphic studies using ^{111}In-labelled antimyosin Fab fragments were performed in 27 patients with rhabdomyosarcoma (RMS), 2 patients with leiomyosarcoma (LMS) and 1 with alveolar soft tissue sarcoma. 21 patients were children aged 3–14 years. These patients, who had histologically proven myosarcoma, were examined scintigraphically to search for local recurrences or metastases and to determine the response to treatment. The results of immunoscintigraphy were compared with histopathological parameters and other imaging modalities. The sensitivity of antimyosin scintigraphy in this series was 82% and the specificity was 73%. Although the technique appears to be not highly specific for RMS, it was found to be useful for the early detection of local recurrence and metastases, as well as for the evaluation of the response to therapy.
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INTRODUCTION

RHABDOMYOSARCOMA (RMS) is a tumour arising from primitive mesenchymal tissue, that mimics normal striated muscle [1]. Pathologically, the tumour is thought to develop from primitive rhabdomyoblasts or pluripotential mesenchymal cells. It is the most common soft tissue sarcoma in children, representing approximately 10% of all pediatric tumours. In children, the primary tumour site is distributed over the head and neck region, the pelvis, the orbit and the limbs. There are two peaks in the incidence, one at the age of 2–6 years and a second at the age of 18 years [2].

By histopathological classification nearly all of these tumours are of the embryonal type. RMS may become markedly enlarged before ever being discovered. Like all soft tissue sarcomas, RMS may infiltrate local structures and may invade both the lymphatics and the blood stream. Metastases to regional lymph nodes are common. Haematogenous metastatic sites are the lungs, bone and bone marrow. Bone scintigraphy is regarded as useful for the detection of RMS skeletal metastases [3]. Wein-

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