Abstract. Background: The present exploratory phase II study was performed to evaluate the activity and tolerability of adding a second agent (gemcitabine) to the well-tolerated mitoxantrone/prednisone regimen in patients with locally advanced or metastatic prostate cancer no longer responsive to hormonal treatment. Patients and Methods: Forty-three patients with hormone-refractory prostate cancer (HRPC) were included in the study from May 2000 to April 2004. Their median age was 71 years (range, 56-81) and their median Karnofsky performance status (KPS) was 90 (range, 70-100). The treatment schedule consisted of intravenous (i.v.) mitoxantrone (8 mg/m² on day 1), i.v. gemcitabine 800 mg/m² on days 1 and 8, recycled every 21 days and oral prednisone administered at a dose of 10 mg per day. Hormonal treatment with LHRH was continued in all patients. Up to six cycles of treatment were planned in the absence of progressive disease. Results: Sixteen patients had measurable disease (six patients only measurable disease, ten patients bone disease plus measurable disease) and 27 patients had only bone disease. Concerning the PSA levels, a partial response (PR) was observed in 15 patients (38%), stable disease (SD) in 16 patients (41%) and progressive disease (PD) in eight patients (21%). The objective response was evaluable in 16 patients; one patient was not evaluable because he had received only one cycle. Ten patients (63%) had SD and five patients (31%) PD. In the ten evaluable patients with objective SD, depending upon the PSA response, three PR, six SD and one PD were observed. Among the five patients who progressed, three PD and two SD were observed as a PSA response. Pain remission was recorded in 15/41 patients (36%) and the KPS remained stable in most patients. The median overall survival was 15 months (range, 1-41) (95% CI: 10-20 months). The 1-year survival rate was 61%. Hematological toxicity was mild: G 3-4 neutropenia was observed in five (12%) patients. There were no neutropenic fevers. No significant non-hematological toxicity was observed. Conclusion: The mitoxantrone, gemcitabine and prednisone combination, in accordance with the present regimen, was feasible, had a palliative effect, good tolerance and antitumor activity. Nonetheless, our results do not seem to be superior to those previously described for mitoxantrone plus prednisone.

Prostate cancer is a significant health problem throughout the world and is the most common male malignancy and the most frequent cause of male cancer mortality, second to lung cancer (1). The American Cancer Society estimates that, during 2005, approximately 232,090 new cases of prostate cancer will be diagnosed in the United States and 30,350 men will die of metastatic disease (2). In Europe, the incidence rate is 55 cases per 100,000 and the mortality rate 22.6 per 100,000. About 10-20% of men with prostate cancer present metastatic disease and, in many others, metastases develop despite treatment with surgery.
or radiotherapy. Androgen deprivation is the standard therapy for newly-diagnosed metastatic cancer and produced symptomatic improvements in 60-70% of patients, but resulted in only a slight prolongation of both progression-free survival (PFS) and overall survival (OS) (3). Despite initially effective hormonal ablation therapy for patients with metastatic prostate carcinoma, the vast majority of these patients progress to a hormone-refractory state. Hormone-refractory adenocarcinoma of the prostate continues to be a major cause of morbidity and mortality among American men. Low response rates and significant toxicity have led to understandable scepticism concerning the use of chemotherapy in the treatment of this disease (4, 5). This scepticism has been challenged by new developments resulting from trials guided by the description of the action mechanisms of several new antineoplastic agents, the definition of appropriate study end-points and a better understanding of the biology of prostate cancer.

For the clinician, the number of potential therapeutic options narrows at a certain point in patients with metastatic hormone-refractory prostate cancer. For those patients, irrespective of the interventions, the median survival is only 8-12 months (6).

When patients with symptomatic hormone-resistant prostate cancer (HRPC) are treated with chemotherapy, the treatment goals are an improvement in survival duration and quality. Tumor response is not an end-point of patient benefit and its determination has been hampered by the relative infrequency of measurable disease to which standard response assessments can be applied (7). The difficulties in determining the activity of new agents in HRPC are mainly related to the fact that only about 20% of patients have a bi-dimensionally measurable disease (8). Metastases, typically occurring in the bone, are hard to evaluate by bone scan, so the standardised response criteria commonly used in other solid tumors are inadequate. Chemotherapeutic agents have shown, given these limits, a response rate ranging from 15-30%. Clearly, survival remains the most important goal, but none of the cytotoxic agents used to date has been shown to have a significant impact on survival (9, 10). Therefore, surrogate end-points were developed in the 1990s, such as changes in the PSA serum levels and palliation (11, 12).

Clinical response has been increasingly accepted as an alternative means for assessing activity in HRPC. Mitoxantrone has been used as a single agent in several phase II studies and has shown minimal activity in terms of response with a significant improvement in the symptoms of chemotherapy-naïve patients. The combination of mitoxantrone with prednisone demonstrated a significant palliative benefit in a multicenter phase II study with improvement in social and emotional functioning, as well as improved pain scores (13).

Two phase III studies were started in the early 1990s addressing the question of whether the addition of mitoxantrone to corticosteroids, at that time considered the standard treatment, was better than corticosteroids alone. The first study compared low-dose prednisone alone (P) with mitoxantrone in combination with low-dose prednisone (MP). The primary end-point of the trial was a palliative response, defined as changes in the patient symptom scores and analgesic requirements. The palliative response rate was 38% for the MP arm and 21% for the P arm, with a longer duration of response for patients randomly assigned to receive chemotherapy. The patients in the combination arm achieved a better and longer duration of palliation. The patients who received mitoxantrone plus hydro-cortisone achieved a maximum serum PSA decrease of ≥50% compared with 22% of 116 patients who received hydrocortisone alone (p=0.008) (15). Consistent benefits of mitoxantrone plus a corticosteroid were observed in other randomised trials, but none found that this approach improved survival. On the grounds of the two studies above, the United States Food and Drug Administration approved mitoxantrone for use in HRPC (16). These trials established mitoxantrone plus a corticosteroid as the treatment of reference for HRPC.

Gemcitabine (G) demonstrated activity in experimental prostatic tumors. Both alone and in combination with other chemotherapeutic agents, gemcitabine showed a powerful capacity to inhibit the in vitro and in vivo growth of several prostate cancer cell lines (17). Furthermore, gemcitabine has shown some positive results in such patients as well: in a phase II trial, 43 patients with HRPC were treated with gemcitabine and three (RR: 7%) showed a PSA response: one CR and three PR with time-to-treatment failure of 8.7, 6.6 and ≥9.3 months. Seven patients (16%) had stable disease for a median duration of 7.1 months (range 6.1-11.7 months). There was one case with objective regression of lymph node metastases. Despite its limited activity in terms of PSA response, gemcitabine showed a significant beneficial impact on pain (18).

On the basis of these data, the present exploratory phase II trial was conducted to evaluate the feasibility of the mitoxantrone, gemcitabine and prednisone combination in patients with locally-advanced or metastatic prostate cancer no longer responsive to hormonal treatment.
Patients and Methods

Patients were eligible for the study if they had a histological diagnosis of adenocarcinoma of the prostate with clinical or radiological evidence of metastatic disease and a progressive disease after standard hormonal therapy. All the patients previously treated with an anti-androgen agent were required to undergo anti-androgen withdrawal. The patients were required to be off anti-androgens for at least 4 weeks with further evidence of disease progression after stopping the anti-androgen. The patients were also required to have a performance status of ≥70 on the Karnofsky scale, with a life expectancy of at least 12 weeks, no prior treatment with cytotoxic agents and adequate bone marrow (absolute neutrophil count ≥1,500/mm³, hemoglobin level ≥10.0 g/dl and platelet count ≥100,000/mm³), renal (creatinine ≤1.5 mg/dl) and hepatic function (bilirubin ≤1.6 mg/dl, serum alanine aminotransferase and aspartate aminotransferase ≤3 times the upper limit of the normal range). The patients were required to have measurable soft tissue disease, or assessable disease manifested as bone disease with a rising PSA level, or locally-advanced disease with a rising PSA level. Patients with PSA increase as a sole manifestation of recurrent disease were excluded. Patients with a history of another cancer within the previous 5 years (except basal or squamous cell skin cancer) were excluded from the study. Patients with any history of recent myocardial infarction or ongoing ischemia requiring anti-anginal agents, arrhythmia requiring anti-arrhythmics, or a history of ischemic disease with documented compromise of the left ventricular function were excluded from the study. Similarly, patients were also excluded from the study if they had uncontrolled hypertension, known brain metastases, or spinal cord compression. All the patients gave their written informed consent.

Assessment. Pre-treatment evaluations consisted of a medical history and physical examination with assessment of performance status and laboratory studies, including complete blood count, serum chemistry profile, PSA level, radionuclide bone scan, ultrasound of the abdomen and pelvis, chest X-ray, electrocardiography and bone scan. Complete blood counts, including differential and platelet counts, were monitored weekly and chemistry profiles and PSA assessments were repeated every 3 weeks. Electrocardiography, cardiac examination and a reassessment of the metastatic sites, if present at baseline, were repeated every 9 weeks (three treatment cycles). Electrocardiography, cardiac examination, radionuclide bone scan, ultrasound of the abdomen and pelvis, chest X-ray and bone scan were repeated after six cycles of treatment. The evaluation of subjective symptoms (pain, asthenia, anorexia, dyspnea) was performed at baseline and just before starting each treatment cycle.

Dose adjustments. The gemcitabine dose was omitted for a granulocyte count <1,500/µl and platelet count <100,000/µl on day 8. The administration of therapy on day 21 was delayed by a week and re-evaluated for a granulocyte count <1,500/µl and platelet count <100,000/µl. The gemcitabine and mitoxantrone doses were reduced by 25% for a grade 4 granulocyte count lasting more than 3 days, febrile neutropenia and grade 4 thrombocytopenia. The gemcitabine and mitoxantrone doses were reduced by 25% for a creatinine level of 1.3–1.5 mg/dl. The gemcitabine and mitoxantrone doses were reduced by 50% for a creatinine level of 1.5–2.0 mg/dl. The treatment was delayed by a week and re-evaluated after opportune hydration for a creatinine level >2.0 mg/dl.

Treatment. The treatment schedule was as follows: M 8 mg/m² i.v. 30-min infusion on day 1, G 800 mg/m² i.v. 30-min infusion on days 1 and 8, recycled every 21 days; P was administered at the dose of 10 mg orally per day. Hormonal treatment with the LHRH analog continued in all patients. Up to six cycles of treatment were planned in the absence of progressive disease.

Response criteria and toxicity. The therapeutic effect was assessed using the standard WHO criteria for measurable disease (objective response), if present, or change in serum PSA level (PSA response) and pain evaluation. Toxicity was evaluated by means of the WHO criteria (19). Objective responses were assessed using the standard WHO criteria for patients with at least one bi-dimensionally measurable lesion, if present. A complete response (CR) was defined as the total disappearance of all clinically detectable disease measured by physical examination and/or radiographic studies for a period of at least 4 weeks. A partial response (PR) was defined as a ≥50% decrease in the sum of the products of the two longest perpendicular diameters of all measurable lesions for a period of at least 4 weeks, without an increase >25% in the size of any area known to contain a malignant disease and without the appearance of any new areas of malignancy. Stable disease (SD) was defined as a regression not satisfying the above criteria for an objective response. Progressive disease (PD) was defined as an increase of at least 25% in the size of measurable lesions. The PSA response was evaluated in patients with measurable or non-measurable (i.e., bone metastases) disease and elevations in serum PSA. CR required the disappearance of all measurable and non-measurable but assessable lesions, with a decrease in serum PSA to less than 1.0 ng/ml for a duration of at least 4 weeks. PR was defined as a ≥50% decrease in any measurable lesions and/or at least 50% decrease in serum PSA for two consecutive measurements taken more than 2 weeks apart without progression of the non-measurable disease. PD was defined as the appearance of new lesions or an increase in PSA of 50% over the baseline or nadir value. SD was defined by a decrease in PSA level <50% without progression of measurable or non-measurable lesions. Survival was measured from the start of therapy to death, otherwise the patient was censored at the date of last follow-up. Pain was evaluated according to a three-grade coding system based on the consumption of analgesics (20).

Statistical considerations. The study was designed to explore the efficacy of the combination of mitoxantrone, gemcitabine and prednisone in patients with locally-advanced or metastatic prostate cancer no longer responsive to hormonal treatment. The primary end-points of the study were to evaluate the PSA response to chemotherapy and pain remission. The secondary end-point was overall survival. A PSA response ≥40% in a series of about 40 consecutive patients was considered an interesting result that could justify the enlargement of the study. The response rates were assessed using PSA criteria for all patients and classic criteria for those with measurable disease. Patients not assessable for response were included in the denominator unless otherwise stated, providing a conservative estimate. Estimates of overall survival were obtained using the Kaplan-Meier method (21).

Results

Forty-three patients were enrolled in the study from May 2000 to April 2004. The patient characteristics are listed in Table I. The median age was 71 years (range, 56–81) and the
The median Karnofsky performance status (KPS) was 90 (range, 70-100). Sixteen patients had measurable disease (six patients only measurable disease, ten patients bone disease plus measurable disease) and 27 patients had only bone disease. A total of 248 treatment cycles were delivered to the 43 patients. The median number of cycles was six (range, 1-13).

The data regarding the PSA treatment responses are listed in Table II. The PSA plasma levels during the treatment were evaluable in 39 patients, but not evaluable in four patients who only received one cycle. With regard to the PSA levels, a PR was observed in 15 patients (38%), SD in 16 patients (41%) and PD in eight patients (21%). The objective response was evaluable in 16 patients who had measurable disease; one patient was not evaluable because he had only received one cycle. Ten patients (63%) had SD and five patients (31%) PD (Table III). In the ten evaluable patients with objective SD, according to the PSA response, three PR, six SD and one PD were observed. Among the five patients who progressed, three PD and two SD were observed as a PSA response. Pain remission was registered in 15/41 evaluable patients (36%) and the KPS remained stable in most patients. The median overall survival was 15 months (range, 1-41) (95% CI: 10-20 months) (Figure 1). The 1-year survival rate was 61%.

All the patients were evaluable for toxicity. The hematological toxicity was mild: G 3-4 neutropenia was observed in five (12%) patients. There were no neutropenic fevers (Table IV), nor was significant non-hematological toxicity observed.

**Discussion**

Several clinical trials have evaluated the role of both single-agent and combination chemotherapy in the treatment of HRPC. Recent clinical trials have shown encouraging results in disease control and in the improvement of the quality of life. The combination of mitoxantrone and low-dose corticosteroids has been shown to improve the quality of life in phase III trials without, unfortunately, prolonging disease-free survival or overall survival when compared with steroids alone. In these trials, the PSA response was 33-38% (14, 15).

Many chemotherapeutic combinations have been reported in published studies with promising results. Among the cytotoxic combinations, including mitoxantrone, the combination of estramustine and mitoxantrone was investigated by the Hellenic Cooperative Oncology Group in 29 patients with HRPC in a phase II feasibility study. Twenty-seven per cent of patients with measurable soft-tissue disease showed an objective response, which included one CR and six PR. Thirteen patients (50%) had a ≥50% reduction in serum PSA level. The median duration of response was 9.2 months and the median survival for all patients was 15 months (22).

In a subsequent phase II feasibility study, the same Hellenic Group investigated the combination of estramustine, vinorelbine and mitoxantrone in 52 patients with HRPC. Thirty-one per cent of patients with measurable soft-tissue disease showed an objective response, which included one CR and six PR. Thirteen patients (50%) had a ≥50% reduction in serum PSA level. The median duration of response was 9.2 months and the median survival for all patients was 15 months (22).

In a subsequent phase II feasibility study, the same Hellenic Group investigated the combination of estramustine, vinorelbine and mitoxantrone in 52 patients with HRPC. Thirty-one per cent of patients with measurable soft-tissue disease showed an objective response, which included one CR and six PR. Thirteen patients (50%) had a ≥50% reduction in serum PSA level. The median duration of response was 9.2 months and the median survival for all patients was 14.5 months (23).
The MVD regimen (mitoxantrone, vinorelbine, prednisone) in a phase II study in 28 patients produced a significant PSA level decline in eleven patients (46%) for a median duration of 11.4 months. Eight patients (33%) achieved a PR in terms of pain, while seven (29%) showed symptom stabilisation. The median duration of the response was 9.5 months (24).

To date, no studies have reported the combination of mitoxantrone and gemcitabine. The present exploratory phase II study was designed to evaluate the activity and tolerability of the addition of a second agent (gemcitabine) to the well-tolerated regimen mitoxantrone/prednisone. Our combination produced a ≥50% reduction in serum PSA level in 38% of patients and pain remission in 36% of patients. We observed no objective response in patients with measurable disease: ten patients (63%) had SD and five patients (31%) PD. The median overall survival was 15 months (range, 1-38+) (95% CI: 11-19) and the 1-year survival rate was 61%. The hematological toxicity was mild: G 3-4 neutropenia was observed in five patients (12%).

The mitoxantrone, gemcitabine and prednisone combination, in accordance with the present regimen, was feasible, had a palliative effect, good tolerance and anti-tumor activity and allowed us to obtain a PSA level reduction in patients with hormone-resistant prostate cancer. The PSA response observed and pain response were similar to those observed in two clinical trials with mitoxantrone and prednisone (14, 15). The results obtained did not seem to indicate that gemcitabine adds any beneficial effect to those described for the mitoxantrone and prednisone combination.

Recently, a phase III trial (1006 patients) demonstrated that docetaxel every 3 weeks plus prednisone was superior in terms of survival (18.9 vs. 16.4), objective response (45 vs. 32%) and pain response rate (35 vs. 22%), as compared to mitoxantrone and prednisone (25). Another study (SWOG trial) (770 patients) demonstrated that docetaxel plus extramustine was superior when compared to mitoxantrone and prednisone: PSA declined in at least 50% in 50 vs. 27% (p<0.001); pain relief was similar in both groups (26). Given these results obtained with docetaxel and the similarity of the results observed in the present phase II pilot trial to those afforded by the mitoxantrone and prednisone regimen, the combination of mitoxantrone, gemcitabine and prednisone would not appear to warrant further studies.

References


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