Docetaxel and cisplatin combination chemotherapy in advanced carcinoma of the urothelium: A multicenter phase II study of the Hellenic Cooperative Oncology Group

M. A. Dimopoulos,1 C. Bakoyannis,2 V. Georgoulia,3 C. Papadimitriou,1 L. A. Moulopoulos,1 C. Deliveliotis,1 A. Karayannis,1 I. Varkarakis,1 G. Aravantinos,4 A. Zervas,1 D. Pantazopoulos,1 G. Fountzilas,5 A. Bamias,6 Z. Kyriakakis,1 A. Anagnostopoulos,1 A. Giannopoulos1 & P. Kosmidis2
1Department of Clinical Therapeutics, Urology and Radiology, University of Athens School of Medicine, Athens; 2Department of Medical Oncology, Metaxa Cancer Hospital, Piraeus; 3Department of Medical Oncology, University of Crete, Heraklion, 4Agi Anargiri Cancer Hospital, Athens; 5Department of Medicine, Aristotle University of Thessaloniki, Thessaloniki; 6Department of Medical Oncology, University of Ioannina, Ioannina, Greece

Summary

Purpose: Both docetaxel and cisplatin have moderate activity in patients with advanced urothelial cancer. We performed a multicenter phase II study in order to assess the efficacy and toxicity of the combination of these two agents in patients with advanced carcinoma of the urothelium.

Patients and methods: Sixty-six patients not amenable to curative surgery or irradiation were enrolled onto this cooperative group study and treated on an outpatient basis with docetaxel 75 mg/m² followed by cisplatin 75 mg/m², both administered intravenously. Granulocyte-colony stimulating factor was administered subcutaneously at a dose of 5 µg/kg daily from day 5 until resolution of neutropenia. The chemotherapy was administered every three weeks for a maximum of six courses in patients without evidence of progressive disease.

Results: Thirty-four of sixty-six patients (52%, 95% confidence interval 40%-64%) demonstrated objective responses, with eight achieving clinical complete responses and twenty-six partial responses. A multivariate logistic regression analysis indicated that the patients most likely to respond were those without lung metastasis and without weight loss before treatment. The median duration of response was 6.1 months and the median times to progression and survival for all patients were 5 and 8 months, respectively. Absence of anemia, of liver metastases and of weight loss correlated with longer survival. Grade > 3 toxicities included granulocytopenia in 33% of patients, anemia in 14%, diarrhea in 13% and emesis in 7% of patients.

Conclusion: The combination of docetaxel and cisplatin appeared relatively well tolerated and moderately active in patients with advanced urothelial cancer. The patients most likely to benefit were those without weight loss and without lung or liver metastases.

Key words: cisplatin, docetaxel, urothelial cancer

Introduction

Cisplatin-based combination chemotherapy induces responses in 40%-75% of patients with advanced urothelial carcinoma, and the combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) is considered to be one of the most active regimens [1-3]. However, only 3% of the patients treated with MVAC are still without disease at six years [4]. Thus, new therapies are needed. The taxanes, paclitaxel and docetaxel, have shown activity in this disease [5-8]. The development of chemotherapy regimens which combine these new agents with other active drugs is relevant. Because docetaxel and cisplatin have single-agent activity and different dose-limiting toxicities, we combined these two agents and performed a multicenter phase II study for the treatment of advanced urothelial carcinoma.

Patients and methods

Patient selection

Patients with metastatic or locally advanced (incurable by surgery or radiotherapy) carcinoma of the urothelium were included in the study. Patients who had received neoadjuvant or adjuvant chemotherapy were eligible if recurrent disease had been diagnosed more than six months after the last course. All patients had measurable disease and an ECOG performance status (PS) of 0-3. Other eligibility criteria included normal blood counts, serum creatinine <1.6 mg/dl, bilirubin level ≤1.5 times the upper normal limit and alkaline phosphatase and transaminases ≤3 times the upper normal limit provided that these abnormalities were due to the presence of liver metastases. The study was approved by each Hospital Ethics Committee and informed consent was obtained from each patient.
Evaluation

All patients underwent a baseline physical examination, assessment of PS, and appropriate imaging studies. A numerical-scale pain score and any weight loss were recorded [9]. The pattern of metastases was defined as local-regional when the disease involved local-regional structures, and as distant when splenic, organs, bones or distant lymph nodes were affected [2]. Complete blood counts were determined on day 10 and at the start of each cycle. Physical examination, PS, pain and toxicity evaluations, urinalysis, electrolytes and serum chemistries were repeated before each chemotherapy course. Response to treatment was assessed by repeating all abnormal imaging modalities after the third and sixth courses of treatment or whenever the patient was taken off study because of toxicity or evidence of progressive disease.

Docetaxel and cisplatin were given on an outpatient basis every 21 days for a maximum of 6 cycles. Chemotherapy was discontinued in cases of progressive disease or unacceptable toxicity. Docetaxel was administered at a dose of 75 mg/m² as a one-hour i.v. infusion followed by cisplatin 75 mg/m² in 1000 ml 0.9% NaCl i.v. over two hours. Appropriate premedication for docetaxel, antiemetics and at least three liters of 0.9% NaCl which contained potassium and magnesium were also administered. All patients received dexamethasone 4 mg p.o. b.i.d. for four consecutive days after each dose of chemotherapy. Granulocyte-colony stimulating factor (G-CSF) was administered subcutaneously daily at a dose of 5 μg/kg from day 2 until the total WBC count exceeded 10,000/μl. The dose of docetaxel was reduced by 25% if febrile neutropenia occurred. In instances of neurotoxicity or fatigue WHO grade > 2, treatment was delayed by one or two weeks and both drugs were reduced by 25%. Cisplatin was reduced by 50% for a creatinine level > 2 times baseline and withheld for a creatinine level > 3 times baseline. If treatment was delayed for > 3 weeks the patient was taken off the study.

WHO criteria for response and toxicity were used [10]. Even patients receiving just one course were considered evaluable for response and toxicity assessment. Toxic deaths were rated as no response.

Results

Between March 1995 and September 1997, 66 patients were treated; their characteristics are shown in Table 1. Thirty-four patients (52%, 95% confidence interval (95% CI): 40%-64%) achieved objective responses including eight CRs (12%) and twenty-six PRs (40%), fourteen were rated as having stable disease and eighteen experienced early disease progression. We observed responses in all sites but all CRs occurred in the bladder or the lymph nodes. Variables such as age, gender, PS, pain score, metastatic pattern, lung, liver or bone metastases, weight loss, histology, primary site, hemoglobin, WBC count, platelet count, prior adjuvant or neoadjuvant chemotherapy and prior radiotherapy were assessed for their possible association with response. Table 2 shows the variables associated with a probability of response to treatment. A logistic regression model was used to evaluate the simultaneous effect of those variables [11]. Backward stepwise procedure revealed that an absence of lung metastases and weight loss was associated with an increased likelihood of response.

The median time to progression for all patients was 5 months (range 1-33+ months) and that of responders 9 months (range 4-33+ months); the median response duration was 6 months (range 2-31+ months). The median overall survival was 8 months (range 1-33+ months). Several parameters were analyzed for their possible association with survival. Neither age, gender, tumor histology, primary site, WBC count, platelet count, bone metastases, prior chemotherapy nor radiotherapy correlated with survival. Parameters such as pain score 2-5, weight loss, PS 2 or 3, lung or liver metastases, and anemia correlated with inferior survival (P < 0.05). A multivariate Cox proportional hazards model indicated that patients without weight loss, without liver metastases and without anemia had a higher probability of survival [11].

Therapy was relatively well tolerated. A total of 293 courses of chemotherapy were administered. A least 70% of the intended dose of docetaxel and cisplatin was administered to 94% of patients. Detailed toxicity data are shown in Table 3. Two patients died after the first course of treatment and both were rated as non-responders. Twelve patients (18%) had generalized fatigue which caused them to be temporarily unable to perform normal activities. Skin and/or nail changes were recorded in 40% of patients. Docetaxel infusion-related hypersensitivity reactions were seen in three patients and discontinuation of treatment was required in one. Mild leg edema occurred in eight patients. Grade 3 or 4 neutropenia occurred in 33% of patients. There were 10 episodes of neutropenic fever.

Discussion

We administered the combination of docetaxel and cisplatin to a large number of patients with advanced...
urothelial cancer. The chemotherapy was administered to outpatients and was relatively well tolerated without incidents of significant renal impairment. Despite the routine administration of G-CSF for a median of 5 days, the incidence of significant neutropenia was 33% and there were 10 episodes of neutropenic fever. Moderate or significant neurotoxicity, mucositis or diarrhea occurred in a small number of patients and were usually reversible.

Several patients with poor-prognosis factors, including advanced age, impaired performance status, pain, weight loss and prior adjuvant or neoadjuvant chemotherapy or radiotherapy, were treated. On an intent-to-treat basis, 52% of patients achieved objective responses, including 8 CRs and 26 PRs. The multivariate analysis indicated that patients without weight loss and without lung metastases were more likely to respond to treatment. Our response data are similar to those reported by Sengelov et al, who observed objective responses in 60% of their patients; however, the CR rate in our study was lower (12% versus 26%) [12]. This may be due to differences in patient selection.

The median time to progression for all patients was 5.4 months and 8.5 months for those who achieved objective responses. The median duration of response was 6.1 months. Four patients with local-regional disease who achieved a CR have remained without evidence of disease for at least 24 months. The median survival of all patients was 8.4 months, which is shorter than that of recent phase II studies performed in single institutions or referral centers [12, 13]. This is likely due to the multi-institutional nature of our study and to the inclusion of several patients who may not have been included in many phase II studies. Our multivariate analysis indicated that patients without anemia, no liver metastases and no weight loss had a significantly longer survival. The median survival of patients without any of these adverse prognostic factors was 15 months but only 5 months when all three variables were present.

We conclude that the combination of docetaxel and cisplatin was relatively well tolerated, with objective responses noted in one-half of the treated patients. To further elucidate the role of this combination we have initiated a multicenter prospective randomized study comparing this regimen to MVAC.

Acknowledgement

We are grateful to G. Kouvatseas and D. Gika for the statistical analysis and data management.

References

9. Moore MJ, Osoba D, Murphy K et al. Use of palliative endpoints to evaluate the effects of mitoxantrone and low-dose prednisone


Received 23 June 1999; accepted 20 September 1999.

Correspondence to:
M. A. Dimopoulos, MD
227 Kifissias Avenue
14561 Kifissia, Athens
Greece