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Exploring sequenced chemotherapy regimens in the treatment of transitional cell carcinoma of the urothelial tract

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Abstract

This phase I trial evaluated the two-drug regimen doxorubicin and gemcitabine (AG) every other week for six cycles followed by ifosfamide, paclitaxel and cisplatin (ITP) every 3 weeks for four cycles in patients with transitional cell carcinoma of the urothelial tract. 15 patients were treated at five AG dose levels ranging up to doxorubicin 50 mg/m^2 and gemcitabine 2000 mg/m^2. The dose and schedule of ITP were constant at ifosfamide 1500 mg/m^2 on days 1–3 and paclitaxel 200 mg/m^2 and cisplatin 70 mg/m^2 on day 1. Granulocyte colony-stimulating factor was self-administered between all cycles of therapy. The trial determined that AG given at alternating weeks at doses of doxorubicin 50 mg/m^2 and gemcitabine 2000 mg/m^2 was feasible. After completion of the AG–ITP sequence, 9 of 14 (64%) evaluable patients had a major response (3 complete responses and 6 partial responses). Phase II investigation at the highest dose level is ongoing.

Keywords: Urothelial tract cancer; Transitional cell carcinoma; Sequenced chemotherapy; Gemcitabine; Doxorubicin; Ifosfamide; Paclitaxel; Cisplatin; Clinical trials

1. Introduction

Transitional cell carcinoma (TCC) of the urothelial tract is a chemosensitive disease in which cure is possible with multi-agent regimens. The combination of methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) is standard treatment for unresectable or metastatic TCC [1]. In phase III trials, M-VAC demonstrated a response and survival advantage relative to single-agent cisplatin and the three-drug regimen CISCA (cisplatin, cyclophosphamide and doxorubicin) [2,3]. Despite promising overall response proportions, the median survival for patients receiving M-VAC is consistently reported to be only 12–13 months and a recent update of the Intergroup Trial emphasised the infrequency of long-term relapse-free survival, with 3.7% of M-VAC patients continuously relapse free at 6 years [4]. Improved therapy is needed in this disease.

Current research in TCC focuses on new drugs with single-agent activity and subsequent development of novel combinations. Several new drugs have been identified as active in TCC, including the taxanes, gemcitabine and ifosfamide. Our group has reported results with the combination regimen of ifosfamide, paclitaxel and cisplatin (ITP) recycled every 3–4 weeks. ITP was reported to be effective and tolerable in previously untreated patients with advanced TCC [5,6]. 30 of 44 assessable patients (68%; 95% confidence interval (CI) 52–81%) demonstrated a major response. 10 patients (23%) had a complete response (CR) and 20 (45%) had a partial response (PR), with response durations ranging from 4 to 36 months. At a median follow-up of 28 months, median survival was 20 months (95% CI 12–27 months). 11 (25%) patients are disease free. The median survival of phase II trials is affected by a number of prognostic factors including extent of metastatic disease and the per cent of patients with locoregional disease. However, the median survival of 20 months (95% CI, 12–27 months) in this trial is the best reported result for unresectable or metastatic TCC patients receiving chemotherapy, and is greater than our previously observed institutional experience with M-VAC (median survival 12–13 months) [7].

Despite the activity of the ITP regimen, the majority of patients succumb to their disease, necessitating new approaches to treatment. Building on this regimen by simply adding agents to the combination may not be useful, given the expected degree of overlapping myelosuppression anticipated when adding a fourth agent to the combination. One new approach in chemotherapy exploits the Norton–Simon hypothesis, a mathematical

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prediction of chemotherapy sensitivity based on gompertzian growth rates displayed by malignant tumours. This concept predicts that efficacy is increased with sequenced 'dose-dense' therapy with either single agents or combination regimens compared with either alternating chemotherapy regimens or combination chemotherapy in which maximal doses of each agent are limited by overlapping toxicities [8,9]. When multiple drug regimens rather than single agents are sequenced, the dose of the individual drugs cannot be compromised. This approach exploits the probability that a cell resistant to one drug is sensitive to others. To achieve success, each drug in the combination must be used at a sufficiently high dose level and not compromised by overlapping toxicity, such as myelosuppression, a frequent dose-limiting toxicity in chemotherapy treatment. Sequence of the agents or combinations is critical in this hypothesis. If using therapies A and B in which each letter depicts a single drug or combination, the temporal arrangement of sequenced therapy (A-A-A-B-B-B) would be predicted to be superior to an alternating sequence (A-B-A-B-A-B).

Attempting to improve further our favourable experience with the ITP combination, we are seeking to test the Norton–Simon hypothesis that sequential chemotherapy might result in improved response and survival in patients with metastatic TCC. Therefore, we sought to study the sequenced therapy of doxorubicin and gemcitabine (AG) followed by ITP. The rationale for the selection of agents was that phase II studies demonstrated that single-agent gemcitabine was an active agent in TCC, and retrospective data for doxorubicin in TCC suggest a strong relationship between increasing dose and overall response. Since insufficient data existed for the combination of doxorubicin plus gemcitabine, a phase I study was necessary to determine the maximum tolerated dose of this doublet and to assess whether this doublet followed immediately by the ITP triplet was tolerable in patients with advanced TCC.

2. Methodology

Eligibility criteria were: unresectable or metastatic transitional cell carcinoma of the urothelial tract; Karnofsky performance status (KPS) of 60; adequate haematological parameters (neutrophil count $\geqslant 1500/10^6$/l; platelet count $\geqslant 150\ 10^9$/l); serum creatinine $\leqslant 133$ μmol/l or creatinine clearance $\geqslant 1$ ml/s/1.73 m^2; bilirubin $\leqslant 1.5$ times normal; and serum glutamic oxaloacetic transaminase (SGOT) < 2 times normal; normal cardiac function; written, informed consent.

Patients initially received six cycles of doxorubicin plus gemcitabine (AG) with cycles repeated every 2 weeks. The plan of phase I investigation was to first maximise the gemcitabine dose to 2000 mg/m^2, then maximise the doxorubicin dose to 50 mg/m^2 if possible. On day 1 of each 2-week cycle, patients received doxorubicin intravenous (i.v.) push plus gemcitabine i.v. infusion at 10 mg/m^2/min at one of five planned dose levels (Table 1). Patients self-administered recombinant human granulocyte colony-stimulating factor (rhG-CSF) at 5 μg/kg/day subcutaneously (s.c.) on days 3–11 of each cycle.

Starting 2 weeks after completing AG, ITP was given for four cycles every 21 days, either as an inpatient or outpatient regimen. Paclitaxel 200 mg/m^2 by 3-h infusion, followed by cisplatin 70 mg/m^2, and then ifosfamide 1500 mg/m^2 were given intravenously on day 1; ifosfamide was repeated on days 2 and 3. Mesna prophylaxis at 300 mg/m^2 i.v. was given 30 min prior to and 4 and 8 h after ifosfamide. Substitution of oral mesna at 600 mg/m^2 was allowed for the 4- and 8-h i.v. doses. Patients received premedication with oral dexamethasone 20 mg at -14 hours and -7 h, plus diphenhydramine hydrochloride 50 mg and cimetidine 300 mg both i.v. at -1 h. Hydration with 5% dextrose/$\frac{1}{2}$ normal saline with 20 mEq potassium chloride per litre was infused at 150–250 ml/h (minimum 2 l per day) and continued until the patient completed chemotherapy and was able to take adequate liquids orally. Patients self-administered rhG-CSF 5 μg/kg/day s.c. from day 6 to 17 of each cycle.

Complete response (CR) was defined as disappearance of all clinical evidence of tumour by physical examination, radiographic studies or both for a minimum of 4 weeks. Partial response (PR) was defined as $\geqslant 50\%$ decrease of the summed products of the perpendicular diameters of all measurable lesions for at least 4 weeks, without the simultaneous increase in the size of any lesion, or the appearance of any new lesion. All other patients were considered non-responders. Bone lesions were not considered to be measurable lesions.

3. Patient characteristics and drug delivery

15 patients were enrolled in this trial. Patients had a median KPS of 90 (range: 70–90). Two-thirds of patients (10/15) had evidence of visceral metastases. Metastatic disease sites included lung in 7 patients, liver in 2 patients and bone in 4 patients. Based on our published model of prognostic factors, 5 (33%) patients had zero risk factors 9 (60%) had one risk factor and 1 (7%) had two risk factors [10].

3 patients were treated at each of the five dose levels outlined in Table 1. 9 patients received six cycles of AG and four cycles of ITP chemotherapy at full doses and on schedule. 2 patients received six cycles of AG, but required modifications of ITP. Of these 2 patients, 1

Table 1
Dose levels and grade 3 or 4 toxicity observed with AG–ITP

Dose level	Doxorubicin dose (mg/m^2)	Gemcitabine dose (mg/m^2)	Grade 3, 4 Toxicities	
			Doxorubicin and gemcitabine	Ifosfamide, paclitaxel and cisplatin
I	30	1000	Nausea pulmonary	Anaemia, neutropenia
II	30	1500	None	Anaemia, neurocortical, neutropenia
III	30	2000	Fatigue, anaemia	Anaemia, nausea, thrombocytopenia, neutropenia, nadir fever[a]
IV	40	2000	None	Anaemia, leucopenia, thrombocytopenia, fatigue, nausea, neutropenia
V	50	2000	Anaemia	Thrombocytopenia, leucopenia

[a] Episodes of neutropenic fever: 1 (7%) patient and 1/117 (1%) cycles.

patient had ifosfamide omitted from the final three cycles of therapy because of grade 3 neurocortical toxicity during the first ITP cycle, and 1 patient with grade 3 emesis after three cycles of ITP received only paclitaxel for the final treatment cycle. 4 patients did not complete planned therapy. 1 patient at dose level III withdrew consent after two AG cycles and was lost to follow-up. One patient at dose level I developed grade 4 pulmonary toxicity after the third cycle of AG. This patient received two further cycles of doxorubicin alone before crossover to ITP. After one cycle of ITP, his condition deteriorated and he received no further therapy. 2 patients, including 1 each at dose levels II and III, developed progressive disease after four and three cycles of AG, respectively, and were unable to continue therapy.

4. Patient tolerance

Grade 3 and 4 toxicity is outlined in Table 1. One patient at dose level I developed progressive pulmonary interstitial changes after the third cycle of AG. It was not possible to distinguish clinically between interstitial lung disease from TCC and gemcitabine-induced pulmonary toxicity. Therefore, this patient was graded as having possible grade 4 pulmonary toxicity since gemcitabine has been associated with rare, idiosyncratic pulmonary toxicity [11]. Gemcitabine was discontinued after recovery, and the patient received two further cycles of therapy consisting of doxorubicin. Other grade 3 or 4 toxicity included nausea, fatigue and anaemia. Haematological toxicity was otherwise limited, with one incidence each of grade 2 leucopenia and grade 2 thrombocytopenia. Most patients experienced grade 1 fatigue. The toxicity associated with the ITP triplet was predominantly haematological, including neutropenia, thrombocytopenia and anaemia. There was one episode of uncomplicated neutropenic fever. Non-haematological toxicity included emesis, 1 patient with grade 3 neurocortical toxicity attributed to ifosfamide and 1 patient with grade 3 fatigue.

5. Response

Response assessment was available for 14 patients. Response was first assessed after the AG doublet and again after completion of all therapy. Antitumour activity of the doxorubicin–gemcitabine doublet included 1 patient with complete regression (CR) of tumour (treated at dose level IV) and 7 patients with $\geqslant 50\%$ regression (PRs). 3 patients developed progressive disease whilst receiving the doxorubicin–gemcitabine doublet, including one each at dose levels I–III. For the 6 patients treated at levels IV and V, 1 complete regression and 5 partial regressions (PR) were observed after AG but prior to ITP. Nine major responses were observed after completing all therapy, including 3 CR and 6 PR. Among 6 patients treated at the two highest AG–ITP dose levels, there were 3 CR and 3 PR.

6. Discussion

It is concluded from this study that doxorubicin 50 mg/m^2 and gemcitabine 2000 mg/m^2 (AG) every 2 weeks for six cycles followed by four cycles of ifosfamide 1500 mg/m^2 days 1–3, paclitaxel 200 mg/m^2 and cisplatin 70 mg/m^2 on day 1 every 3 weeks (ITP) is achievable in patients with advanced TCC. The AG doublet was well tolerated; no grade 3 or 4 neutropenia or thrombocytopenia was observed. This lack of observed myelosuppression may be due to the manner in which the doublet was studied. The trial was designed to rapidly recycle the AG doublet and not to observe the nadir blood counts. Therefore, blood counts were drawn only at the time of the 2-week recycling intervals; growth factor support resulted in rapid resolution of blood counts allowing rapid recycling of therapy. Grade 3–4 non-haematological toxicity was limited to fatigue and one episode of a possible grade 4 pulmonary toxicity. The haematological toxicity observed with ITP in sequential therapy was similar to our previous experiences [5,6]. Although neutropenia was common, only one episode of neutropenic fever was observed. It is

likely that the intensity of the sequential AG–ITP regimen contributed to the development of grade 3 anaemia in 6 patients. Based on this observation, we are now administering prophylactic erythropoietin to all patients in the phase II trial whose haemoglobin falls below 100 g/l.

Non-haematological toxicity from ITP was tolerable, but emesis appeared to be more prevalent in this trial than in our previous experience with ITP. This observation may be the consequence of previous chemotherapy. Neurotoxicity was infrequent, perhaps because only four cycles of ITP were administered. In our previous experience, most patients who developed grade 3–4 neurotoxicity had received more than four cycles of ITP [5].

The goal of this study was to achieve the highest predetermined level of gemcitabine (2000 mg/m^2) and doxorubicin (50 mg/m^2); it is possible that higher doses are achievable because an actual maximum tolerated dose was not reached. However, based on the dose–response phenomenon of doxorubicin in TCC, it is unlikely that further increments in the doxorubicin dose will result in greater clinical activity [12]. Furthermore, the maximal gemcitabine dose of 2000 mg/m^2 every other week was felt to be a practical goal of the trial, particularly given the 200-min infusion time for this dose [13].

The encouraging activity observed in this trial may be the consequence of several factors such as: the Norton–Simon model predicting greater activity of sequenced therapy; a possible dose–response phenomenon for doxorubicin in TCC; or, the prolonged infusion rate of gemcitabine [13] of 10 mg/m^2/min. The antitumour activity, particularly at the highest dose levels of AG–ITP, is encouraging and warrants further study. Therefore, our centre is investigating this sequence in a phase II study to determine in preliminary fashion the survival of patients treated with this novel sequence of chemotherapy.

References

1. Sternberg C, Yagoda A, Scher HI, *et al*. Methotrexate, vinblastine, doxorubicin, and cisplatinum for advanced transitional cell carcinoma of the urothelium: efficacy and patterns of response and relapse. *Cancer* 1989, **64**, 2448–2458.
2. Loehrer P, Einhorn LH, Elson PJ, *et al*. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a Cooperative Group Study. *J Clin Oncol* 1992, **10**, 1066–1073.
3. Logothetis CJ, Dexeus F, Sella A, *et al*. A prospective randomized trial comparing CISCA to M-VAC chemotherapy in advanced metastatic urothelial tumors. *J Clin Oncol* 1990, **8**, 1050–1055.
4. Saxman S, Propert K, Einhorn L, *et al*. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine and doxorubicin in patients with metastatic urothelial cancer: a Cooperative Group Study. *J Clin Oncol* 1997, **15**, 2564–2569.
5. Bajorin DF, McCaffrey JA, Hilton S, *et al*. Treatment of patients with transitional cell carcinoma of the urothelial tract with ifosfamide, paclitaxel, and cisplatin: a phase II trial. *J Clin Oncol* 1998, **16**, 2722–2727.
6. McCaffrey J, Dodd PM, Hilton S, *et al*. Ifosfamide + paclitaxel + cisplatin (ITP) chemotherapy for patients with unresectable or metastatic transitional cell carcinoma. *Proc ASCO* 1999, **18**, 329a.
7. Sternberg C, Yagoda A, Scher HI, *et al*. Methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988, **139**, 461–469.
8. Norton L, Simon R. The Norton–Simon hypothesis revisited. *Cancer Treat Rep* 1986, **70**, 163–169.
9. Norton L. Implications of kinetic heterogeneity in clinical oncology. *Semin Oncol* 1985, **12**, 231–249.
10. Bajorin DF, Dodd PM, Mazumdar M, *et al*. Long-term survival in metastatic transitional cell carcinoma and prognostic factors predicting outcome to chemotherapy. *J Clin Oncol* 1999, **17**, 3173–3181.
11. Tempero MA, Brand R. Fatal pulmonary toxicity resulting from treatment with gemcitabine. *Cancer* 1998, **82**, 1800–1801.
12. Scher HI, Geller NL, Curley T, *et al*. Effect of relative dose-intensity on survival of patients with urothelial cancer treated with M-VAC. *J Clin Oncol* 1993, **11**, 400–407.
13. Plunkett W, Huang P, Gandhi V. Preclinical characteristics of gemcitabine. *Anticancer Drugs* 1995, **6**, 7–13.