Methotrexate, vinblastine, doxorubicin and cisplatin combination regimen as salvage chemotherapy for patients with advanced or metastatic transitional cell carcinoma after failure of gemcitabine and cisplatin chemotherapy

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We investigated the safety and efficacy of a methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) combination regimen as second-line chemotherapy for patients with advanced or metastatic transitional cell carcinoma who failed first-line gemcitabine and cisplatin (GC) chemotherapy. Thirty patients who had progressed or relapsed after GC chemotherapy as first-line treatment were enrolled in this study. The major toxicities were neutropaenia and thrombocytopaenia. A grade 3 or 4 neutropaenia occurred in 19 (63.3%) and a grade 3 or 4 thrombocytopaenia developed in nine patients (30.0%). There were no life-threatening complications during the study. The overall response was 30%. A complete response was achieved in two patients (6.7%) and a partial response in seven (23.3%). The overall disease control rate was 50%. Seven out of 16 patients who had responded previously to GC responded to M-VAC, while 2 out of 14 who had not responded to GC responded to M-VAC. The median response duration was 3.9 months and the median progression-free survival was 5.3 months. The median overall survival was 10.9 months. M-VAC showed encouraging efficacy and reversible toxicities in patients who had progressed after GC chemotherapy and, especially, M-VAC appears to be a reasonable option as a sequential treatment regimen in patients who responded previously to GC chemotherapy.

Patient AND METHODS

Patient eligibility

Patients with histologically confirmed advanced or metastatic transitional cell carcinoma were eligible to participate in this study. All patients had evidence of disease progression or relapse after GC chemotherapy as first-line treatment. For GC chemotherapy,
gemcitabine was given at a dose of 1000 mg m\(^{-2}\) on days 1, 8 and 15, and cisplatin was given at a dose of 70 mg m\(^{-2}\) on day 2. Adequate organ function was required and an Eastern Cooperative Oncology Group performance status of 0–2, an absolute granulocyte count \(\geq 1500\) mm\(^{-3}\), platelet count \(\geq 100,000\) mm\(^{-3}\), serum creatinine \(\leq 1.5\) mg dl\(^{-1}\), creatinine clearance \(\geq 50\) ml min\(^{-1}\) and a serum bilirubin \(\leq 2\) mg dl\(^{-1}\) were required for the treatment. The exclusion criteria included the presence of brain metastases or persistent toxicity from previous GC chemotherapy. Informed consent was obtained before entry into the study. The study was conducted in accordance with the Declaration of Helsinki Principle and Good Clinical Practice and was approved by an independent ethics committee.

### Treatment schedule

The patients received methotrexate 30 mg m\(^{-2}\) on days 1, 15 and 22; vinblastine 3 mg m\(^{-2}\) on days 2, 15 and 22; doxorubicin 30 mg m\(^{-2}\) on day 2; and cisplatin 70 mg m\(^{-2}\) on day 2. The cycles were repeated every 28 days. The patient response was evaluated every three cycles. An additional three cycles with same regimen were provided to patients with no progression at the response evaluation. A third-line chemotherapy regimen was initiated in patients who had progressed if the patients had a good performance status and adequate organ function.

### Response and toxicity assessment

All patients were evaluated for their response to treatment after completing three cycles except for those cases with symptomatic progression. Early evaluations were performed in patients with clinical evidence of progressive disease (PD). Patient response was evaluated according to the Response Evaluation Criteria in Solid Tumors (Therasse et al, 2000). A complete response (CR) was defined as the disappearance of all clinical and radiological signs of target lesions. A partial response (PR) was a \(\geq 30\%\) decrease in the overall sum of the diameter of the target lesions; a PD was a \(\geq 20\%\) increase in the overall sum of the diameter of the target lesions; and stable disease was neither a sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. In cases with a PR or CR, a second assessment 4 weeks later was required for confirmation of the response. The toxicity was graded according to the National Cancer Institute’s common toxicity criteria version 2.0. Patients who received at least one dose of M-VAC were assessed for toxicity.

### Statistical considerations

The duration of response was defined as the time from the first objective status assessment of response to the initial date of a documented progression. The progression-free survival was defined as the time from study entry to the initial date of evidence of progression, death or loss to follow-up. The progression-free survival of patients alive without progression was recorded at the time of the last follow-up evaluation. The overall survival was defined as the interval between the date of study entry to death or the last follow-up evaluation. The progression-free survival and the overall survival were estimated using the Kaplan–Meier method. The analyses were performed using 5% as the level of significance.

### RESULTS

#### Patient characteristics

Between May 2002 and December 2006, 30 patients were enrolled in this study. The baseline characteristics of the patients are shown in Table 1. The median age was 64 years (range, 38–79). There were 24 men and 6 women. Fourteen patients had primary tumours. Nineteen patients had visceral metastases and 11 patients had regional lymph-node metastases only.

For first-line GC chemotherapy, the median number of cycles was five (range, 2–9) and the response rate was 53.3%. There were no interrupted schedules or dose adjustments due to persistent toxicities. All patients received at least three cycles of GC except for one patient. In one patient, GC chemotherapy was discontinued during a second cycle because acute renal failure developed due to progression of pelvic lymph node metastases.

After disease progression or relapse was confirmed, the patients received the M-VAC regimen. The median treatment-free interval between GC and M-VAC was 2.5 months (range, 0.5–20.4) and the median number of cycles for the M-VAC regimen was three (range, 1–12).

#### Toxicity

All enrolled patients were evaluated for toxicity (Table 2). The treatment was generally well-tolerated. The major haematological toxicities were neutropaenia and thrombocytopenia. A grade 3 or 4 neutropaenia occurred in 19 patients (63.3%); they received granulocyte colony-stimulating factor until their neutrophil counts were restored. A grade 3 or 4 thrombocytopenia developed in nine patients (30.0%); there was no haemorrhagic event due to the thrombocytopenia. Grade 3 or 4 anaemia developed less frequently and was identified in five patients (16.7%). The major nonhaematologic toxicities were alopecia and mucositis. Grade 2 alopecia developed in 14 patients (46.7%) and grade 3 or 4 mucositis in four (13.3%); most nonhaematologic toxicities were confined to grade 1 or 2 (Table 2). All toxicities were reversible and no life-threatening complications were observed during the study.

Omission of methotrexate and vinblastine on day 15 and/or 22 or delay of a subsequent cycle occurred in cases with persistent severe haematological toxicities despite appropriate management. Methotrexate and vinblastine on day 15 or 22 were omitted in 23 patients. The median for an omitted scheduled cycle was one per patient (range, 0–16). The schedules on day 15 or 22 were delayed in 11 patients. The median number of delayed schedules was zero.

| Table 1 Characteristics of the study population |
|-----------------|-----------|
| Characteristics | No. of patients |
| Total enrolled patients | 30 |
| Age |
| Median (years) | 64 |
| Range (years) | 38–79 |
| Gender |
| Males | 24 |
| Females | 6 |
| ECOG performance status |
| 0 | 16 |
| 1 | 11 |
| 2 | 3 |
| Disease extents |
| Visceral metastases | 19 |
| Regional lymph-node metastases only | 11 |
| Sites of diseases |
| Primary | 14 |
| Local recurrence | 3 |
| Lymph nodes | 22 |
| Lung | 7 |
| Liver | 4 |
| Bone | 5 |
| Others | 2 |
Response rates and survival

The response to treatment was assessed in all registered patients. The overall response rate was 30%. A CR was achieved in two patients (6.7%) and a PR in seven (23.3%). Stable disease was observed in six patients (20.0%). The overall disease control rate was 50%. The characteristics of the responders are listed in Table 3. Seven out of 16 patients who had responded previously to GC responded to M-VAC, while 2 out of 14 who had not responded to GC responded to M-VAC. A response was observed in 4 out of 11 (36.4%) patients with only lymph node metastases and in 5 out of 19 (26.3%) patients with visceral metastases.

The median response duration was 3.9 months (95% CI: 3.7–4.1) and the median progression-free survival was 5.3 months (95% CI: 3.1–7.5). A majority of patients finally had disease progression; only three patients remained with no disease (95% CI: 3.1–7.5). A majority of patients finally had disease progression; only three patients remained with no disease (95% CI: 3.1–7.5). The overall response rate was 30%. A CR was achieved in two (6.7%) and a PR in seven (23.3%). Stable disease was observed in six patients (20.0%). The overall disease control rate was 50%. The characteristics of the responders are listed in Table 3. Seven out of 16 patients who had responded previously to GC responded to M-VAC, while 2 out of 14 who had not responded to GC responded to M-VAC. A response was observed in 4 out of 11 (36.4%) patients with only lymph node metastases and in 5 out of 19 (26.3%) patients with visceral metastases.

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### Table 2 Toxocities

| Grade | No. | %  | No. | %  | No. | %  | No. | %  |
|-------|-----|----|-----|----|-----|----|-----|----|
| Neutropenia | 1 | 3.3 | 2 | 6.7 | 6 | 20.0 | 13 | 43.3 |
| Thrombocytopenia | 5 | 16.7 | 1 | 3.3 | 3 | 10.0 | 6 | 20.0 |
| Anaemia | 9 | 30.0 | 3 | 10.0 | 4 | 13.3 | 1 | 3.3 |
| Mucositis | 1 | 3.3 | 3 | 10.0 | 4 | 13.3 | — | — |
| Alopecia | 14 | 46.7 | 14 | 46.7 | — | — | — | — |
| Nausea/vomiting | 14 | 46.7 | 8 | 26.7 | — | — | — | — |
| Anaemia | 10 | 33.3 | 5 | 16.7 | 1 | 3.3 | — | — |
| Diarrhoea | 2 | 6.7 | 1 | 3.3 | — | — | — | — |
| Constipation | 3 | 10.0 | 1 | 3.3 | — | — | — | — |
| Fatigue | 5 | 16.7 | 1 | 3.3 | — | — | — | — |
| Asthenia | 5 | 16.7 | 2 | 6.7 | — | — | — | — |
| Fever | 3 | 10.0 | 1 | 3.3 | — | — | — | — |
| Myalgia | 5 | 16.7 | 1 | 3.3 | — | — | — | — |
| Infection | — | — | — | — | 1 | 3.3 | — | — |
| Allergic reactions | 1 | 3.3 | 1 | 3.3 | — | — | — | — |
| Dizziness | 1 | 3.3 | — | — | — | — | — | — |

### Table 3 Characteristics of responders to second-line M-VAC regimen

| No. | Age | Site of disease        | Response to GC | Treatment-free interval (month) | Response to M-VAC | RD (month) | PFS (month) | Current status | Survival (month) |
|-----|-----|------------------------|----------------|---------------------------------|-------------------|------------|-------------|---------------|-----------------|
| 1   | 46  | Bone                   | PR             | 3.2                             | PR                | 6.6        | 8.6         | Death         | 11.7            |
| 2   | 54  | Supraventricular LN    | PR             | 4.5                             | PR                | 3.3        | 6.4         | Death         | 9.2             |
| 3   | 66  | Bladder                | PR             | 5.7                             | PR                | 3.7        | 7.2         | Alive         | 9.2+            |
| 4   | 72  | Lung                   | PR             | 3                               | PR                | 3.9        | 7.6         | Death         | 10.9            |
| 5   | 69  | Retropertoneal LN      | PR             | 2                               | PR                | 3.8        | 7.1         | Death         | 10.6            |
| 6   | 69  | Retropertoneal LN      | PD             | 7                               | CR                | 1.5        | 4.4+        | Alive         | 5.8+            |
| 7   | 64  | Retropertoneal LN      | CR             | 1                               | PR                | 1.5        | 2.5+        | Alive         | 5.3+            |
| 8   | 79  | Bladder                | CR             | 10.4                            | CR                | 7.2        | 10.6+       | Alive         | 11.6+           |
| 9   | 52  | Scrotum                | PD             | 2.5                             | PR                | 3.9        | 6.7         | Death         | 15.8            |

Abbreviations: CR = complete response; LN = lymph node; PD = progressive disease; PFS = progression-free survival; PR = partial response; RD = response duration.
whether the response to first-line GC treatment can be a significant predictor of the response to second-line M-VAC. Most patients enrolled in this study had good renal function and performance status. Our favourable results might have been affected by these factors. It is reported (de Wit, 2003) that an estimated one-third of patients with advanced urothelial carcinoma are medically unfit for cisplatin-based chemotherapy, and in accordance with this, in clinical practice, there is frequently a significant deterioration of the performance status or renal function in patients with advanced urothelial carcinoma; this is most frequently observed in patients with first-line treatment failure and disease progression. This makes enrolment of patients into clinical studies or the administration of systemic chemotherapy outside of the context of a clinical trial difficult (Bamias et al., 2006; Garcia and Dreicer, 2006; Pectasides et al., 2007). Substitution of new agents for cisplatin in two-drug or three-drug combinations is required in these patients. Carboplatin can be a good alternative to cisplatin because it is less nephrotoxic (de Wit, 2003). Phase II trials of carboplatin, as a substitution for cisplatin in first-line chemotherapy regimens, demonstrated that carboplatin-based therapy was less effective than cisplatin-based therapy. However, there is few data on carboplatin as a substitution for cisplatin-based therapy in second-line chemotherapy (Petrioli et al., 1996; Bellmunt et al., 1997). Randomised trials with carboplatin-based regimens in patients who failed first-line platinum-based chemotherapy and development of new combinations consisting of safer and more effective agents is needed for the treatment of patients with depleted marrow reserves and impaired renal function after the failure of first-line chemotherapy.

Over the past 20 years, a relatively large number of agents have been evaluated for second-line chemotherapy. The agents studied included ifosfamide, taxanes, gemcitabine, oxaliplatin, vinflunine and pemetrexed. However, a review of the recent literature, on phase II trials in this population, confirms that there are very limited options for patients who have been previously treated with GC, M-VAC or CMV combinations (Culine et al., 2006). Taxanes are widely used as a second-line regimen in patients with cisplatin-refractory urothelial carcinoma. The taxanes (paclitaxel and docetaxel) have provided objective response rates of 10–13% with response durations of 3.0–7.4 months (McCaffrey et al., 1997; Vaughn et al., 2002). Combinations with other agents have shown better results. Paclitaxel combined with gemcitabine, ifosfamide, methotrexate or cisplatin showed a 15–60% response rate and taxanes combined with ifosfamide a 15–25% response rate (Tu et al., 1995; McCaffrey et al., 1997; Witte et al., 1999; Kreege et al., 2001; Meluch et al., 2001; Sternberg et al., 2001; Bellmunt et al., 2002; Vaughn et al., 2002). Ifosfamide showed a 20% response rate in an ECOG study but an unacceptable frequency of grade 3–4 CNS and renal toxicities were noted (Witte et al., 1997). Toxicity remains the major limiting aspect of these regimes (Roth et al., 1994; Dreicer et al., 1996; Witte et al., 1997).

Vinflunine and pemetrexed as new single agents have been studied in phase II trials (Culine et al., 2006; Sweeney et al., 2006). Vinflunine showed an 18% response rate and a 67% disease control rate and pemetrexed, a new-generation antifolate, showed a favourable therapeutic index (an overall response rate of 27.7%). Incorporation of these new agents as second-line treatment combination regimens is expected in future studies.

Several regimes studied as second-line chemotherapy for urothelial carcinoma have variable response rates. This is likely due to the variability in drug activity as well as the different patient populations evaluated in different studies (Sweeney et al., 2006). In most studies, the regimes used for first-line chemotherapy were heterogeneous in a given study population (Tu et al., 1995). Most studies on second-line chemotherapy include patients who received M-VAC-, CMV-, GC- or taxane-based regimes, as initial chemotherapy, or patients who did not receive any chemotherapy (Tu et al., 1995; McCaffrey et al., 1997; Witte et al., 1997; Sweeney et al., 1999; Kreege et al., 2001; Meluch et al., 2001; Bellmunt et al., 2002; Vaughn et al., 2002; Culine et al., 2006). These confounding factors make it difficult to interpret the true efficacy of a second-line chemotherapy regimen. In our study, all patients received the same regimen as first-line chemotherapy.

In conclusion, this is the first report on the efficacy and toxicity of M-VAC as second-line chemotherapy in patients who failed first-line GC. The main limitation of this study was the small number of cases evaluated. M-VAC showed encouraging efficacy and reversible toxicities in patients who had disease progression after GC chemotherapy. Therefore, M-VAC appears to be a reasonable option for patients who initially responded to first-line GC chemotherapy. There are few randomised trials on second-line chemotherapy for urothelial carcinoma; therefore, large randomised controlled studies are required to confirm the findings reported here.

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