Comparison between a Cisplatin-Containing Regimen and a Carboplatin-Containing Regimen for Recurrent or Metastatic Bladder Cancer Patients

A Randomized Phase II Study

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BACKGROUND. The aim of this randomized Phase II study was to compare the efficacy and toxicity of a cisplatin-containing regimen with a carboplatin-containing regimen for patients with recurrent or metastatic bladder cancer.

METHODS. Fifty-seven patients with recurrent or metastatic bladder cancer were randomized to receive M-VEC treatment (methotrexate, vinblastine, epirubicin, and cisplatin) (n = 29) or M-VECa treatment (methotrexate, vinblastine, epirubicin, and carboplatin) (n = 28). The chemotherapy was scheduled at 28-day intervals. Recombinant granulocyte-colony stimulating factors were administered daily when the absolute neutrophil count fell below 1000/mm^3. The development of ototoxicity was evaluated by measuring auditory brain stem response.

RESULTS. Of the 57 entered patients, 55 were evaluable for response and toxicity. The overall clinical response rate was 71% (with 25% complete responses) in the M-VEC group and 41% (with 11% complete responses) in the M-VECa group (P = 0.04). M-VEC chemotherapy was associated with more pronounced side effects. There was a statistically significant difference between M-VEC and M-VECa in terms of gastrointestinal toxicity (P = 0.04), nephrotoxicity (P = 0.03), and neurotoxicity (P = 0.02) during Cycle 3 of chemotherapy. Leukopenia and neutropenia were worse in the M-VECa arm, but not significantly so (P = 0.4). Ototoxicity was only detected in one of seven examined M-VEC patients after two cycles of chemotherapy.

CONCLUSIONS. M-VECa has a low level of gastrointestinal, renal, neurologic, and otologic toxicity, but is apparently less effective than M-VEC in the treatment of recurrent or metastatic bladder cancer. However, a larger, randomized Phase III trial is needed to confirm these results. ***Cancer* 1996; 77:344-51.**

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Many chemotherapeutic drugs are reported to be effective in metastatic bladder cancer, and cisplatin is known to be one of the most effective single agents.[1,2] For many years, combination chemotherapy using methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) has been considered the standard treatment for advanced transitional cell tumors.[3-6] This regimen often achieves response rates (complete or partial) of up to 70%, with a high number of complete remissions; however, moderate to severe nausea and vomiting, myelosuppression, renal insufficiency, electrolytic imbalance, peripheral neuropathy, and auditory im-

pairment can cause problems in the administration of full dosages and the planned schedule.[3-6]

The recent use of hematopoietic growth factors (granulocyte-colony stimulating factors [G-CSF], granulocyte-macrophage colony stimulating factors [GM-CSF]) and new antiemetic drugs (5-HT3 receptor antagonists) has led to control of neutropenia and gastrointestinal toxicity in the majority of patients.[7-9] However, despite adequate supportive care and hyperhydration, the chemotherapy-induced toxic effects cannot be abrogated and some patients may still develop persistent nausea and vomiting or moderate to severe nephrotoxicity and neurotoxicity.[3-7] In conventional M-VAC, epirubicin, an anthracycline with less cardiac and haematologic toxicity, has been substituted for doxorubicin to form M-VEC.[10,11]

Cisplatin is the most active drug in the M-VAC or M-VEC regimen, but it is also characterized by gastrointestinal, renal, neurologic, and otologic toxicity and requires the intravenous administration of large amounts of fluid (necessary to control renal damage), which can cause a fluid overload that is particularly detrimental in elderly patients. Because of these side effects, cisplatin might be replaced by carboplatin, which has a better toxicity profile.[1,2,12,13] The general tolerability of carboplatin makes this drug very attractive in the treatment of elderly patients with advanced bladder cancer. Nevertheless, although carboplatin may safely be substituted for cisplatin in the treatment of many tumors, comparative trials between multidrug regimens containing cisplatin or carboplatin are still required before carboplatin can be recommended for widespread clinical use.

The aim of this randomized Phase II study was to compare the efficacy and toxicity of M-VEC (methotrexate, vinblastine, epirubicin, and cisplatin) and M-VECa (methotrexate, vinblastine, epirubicin, and carboplatin) in the treatment of recurrent or metastatic bladder cancer.

MATERIALS AND METHODS

In accordance with Simon's recommendation, the original design required the enrollment of at least 35 patients per arm to ensure adequate power if the better treatment were to have a 15% higher response rate than the other treatment, with a significance level of 0.05 and a power of 90%.[14]

The eligibility criteria included a histologically proven diagnosis of recurrent or metastatic bladder cancer, an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or less; an age of 75 years or younger; at least one bidimensionally measurable lesion; an absolute neutrophil count (ANC) of 1500/mm^3 or more; a normal platelet count ($\geq$ 100,000/mm^3); a serum creatinine level of 1.5 mg/dL or less; a serum bilirubin level of 1.5 mg/dL or less; haemoglobin of 11.0 g/dL or more; a normal left ventricular ejection fraction ($\geq$ 50%); no previous systemic therapy for recurrent or metastatic disease; and at least a 4-week interval since prior radiotherapy. Patients who had previously received adjuvant chemotherapy that had been discontinued at least one year before entering the study were also eligible. Written informed consent was obtained from all of the participating patients.

The eligible patients were stratified for disease extent (local vs. metastatic), and were then randomized to receive either M-VEC (methotrexate, vinblastine, epirubicin, and cisplatin) or M-VECa treatment (methotrexate, vinblastine, epirubicin, and carboplatin).

Laboratory tests, such as serum electrolytes (including calcium and magnesium), serum alkaline phosphatase, serum bilirubin, serum creatinine, and creatinine clearance, and imaging examinations (chest X-ray, pelvic and abdominal computerized tomography, bone scan, skeletal survey, and liver ultrasound) were performed before the start of the study; the laboratory tests were then repeated at every cycle and the imaging studies were repeated every three cycles (bone scan every six cycles). In all patients with local recurrence, the disease was also staged by means of urinary cytology and cystoscopy examination with cystoscopic resection biopsy. A complete blood cell count with differential was repeated weekly and on every day of chemotherapy. Cardiac performance was examined by means of electrocardiography and echocardiography every three cycles. A physical examination was performed, and performance status and weight were evaluated at every cycle.

The development of ototoxicity was evaluated by measuring auditory brain stem response (ABR).[15] All patients with preexisting diseases of the acoustic system identified by means of pure-tone audiometry and impedance were excluded from the ABR studies. The eligibility criteria for the subsequent evaluations were normal hearing thresholds of 25 decibels or less, normal ABR, a normal tympanogram, and a normal stapedius reflex threshold (both ipsilateral and contralateral). The ABR examinations were recorded in a sound-treated room, using 2000 clicks of alternating polarity presented to the patients at a rate of 21 clicks per second. The baseline stimulus intensity was 100 decibels. Electrodes were placed on the vertex and the ipsilateral and contralateral mastoid processes (the last acting as the ground electrode). Vertex-positive ABR waves were numbered from I to V; the latency waves I, III, V, and the interpeak latency interval I–III, III–V, and I–V were considered for the analysis. The tests were performed using an Amplaid MK15 with a preamplifier; at least two tests were performed at each session in order to ascertain the reproducibility of the ABR. The ABR evaluations were repeated after two cycles of chemotherapy (one week after the last cisplatin or car-

boplatin administration), and then every two cycles or when the patient was withdrawn from the study. Normal mean latency values and standard deviations were Wave I, 1.8 ± 0.5 milliseconds (msec); Wave III, 3.9 ± 0.7 msec; and Wave V, 5.7 ± 0.8 msec. A change in latency of 0.4 msec in an individual patient was considered significant on the basis of our laboratory norms.

Clinical Response Criteria

All patients were evaluated for response after every three cycles of treatment. Osteolytic bone metastases were considered evaluable disease; patients with osteoblastic bone metastases were excluded from the study. The imaging examinations used to define the clinical response were always reviewed by the same group of three radiologists from our university. Standard response criteria were used.[16]

Chemotherapy Schedule and Dose Modification

The combination chemotherapy consisted of cisplatin (70 mg/m^2 intravenous [i.v.] by 1-hour infusion on Day 2) in the M-VEC arm and carboplatin (250 mg/m^2 i.v. by 1-hour infusion on Day 1) in the M-VECa arm, plus methotrexate (30 mg/m^2 slow i.v. push on Days 1, 15, and 22), vinblastine (3 mg/m^2 slow i.v. push on Days 2, 15, and 22), and epirubicin (50 mg/m^2 slow i.v. push on Day 2) in both treatment arms. The chemotherapy cycles were scheduled at 28-day intervals. All patients received antiemetics consisting of ondansetron, 8 mg, plus methylprednisolone, 125 mg, in 50 mL of 0.9% normal saline solution by intravenous infusion 30 minutes before each cisplatin or carboplatin administration; oral antiemetics (ondansetron, 4 mg twice daily) were also given to patients developing persistent emesis. All M-VEC patients received at least 1 liter of 0.9% normal saline solution and mannitol diuresis during cisplatin administration in order to protect against cisplatin-induced nephrotoxicity. Furosemide was not administered. Toxicity was evaluated according to the World Health Organization criteria for reporting the results of cancer treatment.[17] Chemotherapy was not administered as scheduled if any hematologic toxicity occurred. Cisplatin, carboplatin, doxorubicin, and vinblastine were reduced by 50% if the ANC was less than 1500/mm^3, if the leukocyte count was less than 2500/mm^3, or if the platelet count was less than 75,000/mm^3; methotrexate was decreased by 50% when patients showed Grade 3 mucositis. Cisplatin and carboplatin were also reduced by 50% if the glomerular filtration rate was less than 60 mL/min. Chemotherapy was delayed for 1 or 2 weeks in patients with an ANC of less than 1000/mm^3, or if there was a drop of more than 20% from baseline in LVEF, and was discontinued if there was any evidence of congestive heart failure or other severe toxicities. The patients with local recurrence who achieved a clinical response or clinically stable disease were assessed by means of surgical restaging (laparotomy with cystectomy) after three to six cycles of chemotherapy. Chemotherapy was administered until evidence of disease progression or for a maximum of nine cycles.

Recombinant G-CSFs (filgrastim, 300 μg subcutaneously) were administered daily when the ANC was less than 1000/mm^3, and continued until hematologic recovery (ANC > 3000/mm^3). The incidence of neutropenia (ANC < 1000/mm^3), its mean duration, and the incidence of febrile neutropenia were recorded. All patients in both treatment groups who also presented with osteolytic bone metastases received dichloromethylene bisphosphonates (C12MDP), 300 mg in 250 mL of 0.9% saline solution by intravenous infusion for 7 days, in association with their chemotherapy.

Statistical Methods

The chi-square test was used for the response analysis and for the comparison of Grade 2–4 toxicities. Fisher's exact test was used if fewer than five patients were expected in one of the categories. The Kaplan–Meier method was used to estimate survival distributions and median response durations, and the log rank procedure was used for further comparisons.[18,19] The statistical analysis of ototoxicity between posttreatment and baseline ABR recordings was performed using the *t* test for paired data.

RESULTS

From January 1989 to June 1994, 57 patients entered the study; 29 were randomly allocated to the M-VEC and 28 to the M-VECa arm (patient accrual was prematurely terminated due to loss of funding). The characteristics of the patients are listed in Table 1; there was a good balance between the two groups. Of the 57 entered patients, 2 were not evaluable because the treatment was never begun (1 case with abdominal metastases in the M-VEC group) or the patient refused to continue treatment before the completion of the first cycle (1 case with local recurrence in the M-VECa group). The M-VEC patients received a total of 178 cycles, with a median of 4.5 (range 1–12); the M-VECa patients received a total of 189 cycles, with a median of 5 (range 2–12). A maximum of 9 cycles had been originally planned, but we decided to prolong treatment to 12 cycles in 4 patients who showed a partial remission after 9 cycles (1 in the M-VEC group and 3 in the M-VECa group) and tolerated their treatment well. Three patients (one from the M-VEC group and two from the M-VECa group) received only one or two cycles because of the occurrence of rapid progressive disease, but they were included in the analysis of response and toxicity; all of the other cases received at least three cycles. Dosage modifications or treatment delays were needed

TABLE 1
Characteristics of 57 Eligible Patients with Recurrent or Metastatic Bladder Cancer Treated with M-VEC or M-VECa

Patient characteristics	M-VEC	M-VECa
Eligible patients	29	28
Evaluable patients	28	27
Sex		
Male	21	23
Female	8	5
Age (median), years	66	64
Range, years	52–75	47–72
Performance status (ECOG)		
≤1	15	11
≤2	11	13
≤3	3	4
Radical cystectomy	19	15
Transurethral resection	5	8
Partial cystectomy	4	5
No surgery	1	—
Adjuvant chemotherapy (3 cycles of M-VEC)	5	3
Previous radiotherapy	0	0
Tumor sites		
Local recurrence	7	9
Bladder and bone	3	4
Liver and bone	2	2
Lung and bone	2	4
Abdominal and subcutaneous	—	1
Lung and liver	1	—
Lymph nodes	4	2
Lung	3	2
Liver	2	1
Abdominal/pelvic	5	3

M-VEC: methotrexate, vinblastine, epirubicin, and cisplatin; M-VECa: methotrexate, vinblastine, epirubicin, and carboplatin; ECOG: Eastern Cooperative Oncology Group.

TABLE 2
Clinical Response in 55 Evaluable Patients with Recurrent or Metastatic Bladder Cancer Treated with M-VEC or M-VECa

	M-VEC (28)		M-VECa (27)	
Stage	Recurrent	Metastatic	Recurrent	Metastatic
No. of patients	7	21	8	19
CR	3	4	2	1
PR	3	10	3	5
SD	1	5	3	7
PD	0	2	0	6
Overall RR	71%		41%	

M-VEC: methotrexate, vinblastine, epirubicin, and cisplatin; M-VECa: methotrexate, vinblastine, epirubicin, and carboplatin, CR:complete response; PR: partial response; SD: stable disease; PD: progressive disease; RR: response rate (complete response + partial response.

in 48% of the 138 administered M-VEC cycles and in 36% of the 159 administered M-VECa cycles.

For the 28 M-VEC and 27 M-VECa evaluable patients, the overall clinical response rate (complete response [CR] + partial response [PR]) was 71% (95% confidence interval [CI], .54 to .88) in the M-VEC group and 41% (95% CI, .22 to .59) in the M-VECa group (P = .04) (Table 2).

In the M-VEC group, 7 patients achieved complete remission (25%) (95% CI, .09 to .41), (3 with local recurrence, 2 with retroperitoneal lymph node metastases, 1 with abdominal metastases, and 1 with lung metastases), and 13 achieved partial remission (46%); 6 patients had stable disease (21%) and 2 progressive disease (8%).

In the M-VECa group, 3 patients achieved complete remission (11%) (95% CI, 0 to .22), 2 with local recurrence and 1 with lung metastases, and 8 achieved partial remission (30%); 10 patients had stable disease (37%), and 6 progressive disease (22%). There was no significant difference in the proportions of CRs between M-VEC and M-VECa treated patients (P = .2) (Fisher's exact test). In 17 patients who also had osteolytic bone metastases, partial recalcification was achieved in 4 of the 7 patients in the M-VEC group and in 3 of the 10 patients in the M-VECa group. In all patients with painful bone lesions, there was a progressive analgesic effect with an overall improvement in performance status: from 2.3 mean ± 0.7 standard deviation to 1.4 mean ± 0.5 standard deviation in the M-VEC group (P = .02) and from 2.4 mean ± 0.7 standard deviation to 1.7 mean ± 0.6 standard deviation in the M-VECa group (P = .03). Seven of the 16 patients with local recurrence had surgical restaging after chemotherapy (three CR and one PR from the M-VEC group and 1 CR and 2 PR from the M-VECa group), with the following pathologic (p) response: 2 pCR, 1 pPR, and 1 pSD (stable disease) in the M-VEC group and 1 pCR and 2 pSD in the M-VECa group. These seven patients received an additional two to three cycles of chemotherapy.

In the patients with metastatic disease, the median response duration was 8 months in the M-VEC group and 4.5 months in the M-VECa group, and the median survival was 13+ months (range, 4–31+) in the M-VEC group and 9.5+ months (range, 3–27+) in the M-VECa group. Nine patients with metastatic disease (7 in the M-VEC group and 2 in the M-VECa group) are still living with a median follow-up of 21 months (range, 12–31); 2 M-VEC patients with stable disease and 1 M-VECa patient with progressive disease were lost to follow-up after 4, 6, and 4 cycles of chemotherapy, respectively. The 7 surgically restaged patients with local recurrence had a 1-year survival rate of 85%, and the 3 patients achieving a complete pathologic response are still disease free after 23 and 41 months (M-VEC patients) and 32 months (M-VECa patient). Log rank tests did not show any statistically significant difference between the M-VEC and the M-VECa group in the comparison of response duration (P = .08) or survival (P = .3).

TABLE 3
Percentage of Patients Experiencing Grade 2–4 WHO Toxicity

	M-VEC			M-VECa		
Type of toxicity	Cycle 1	Cycle 3	Cycle 6	Cycle 1	Cycle 3	Cycle 6
Evaluated patients	28	27	24	27	25	19
Nausea/vomiting	43	52	54	18	20	31
Diarrhea	4	15	17	7	8	10
Mucositis	7	11	17	4	8	16
Leukopenia	18	33	37	22	44	58
Thrombocytopenia	7	11	21	11	20	26
Anemia	7	15	25	4	8	10
Nephrotoxicity	11	37	54	4	8	16
Neurotoxicity	4	33	58	0	4	10
Alopecia	25	67	75	22	72	79

WHO: World Health Organization; M-VEC: methotrexate, vinblastine, epirubicin, and cisplatin; M-VECa: methotrexate, vinblastine, epirubicin, and carboplatin.

Toxicity

M-VEC chemotherapy was associated with more pronounced side effects (Table 3). Leukopenia was worse in the M-VECa group, but not significantly so on the third cycle ($P = .4$) and on the sixth cycle ($P = .3$). The incidence of neutropenia (ANC $< 1000/mm^3$) was 7% in the M-VEC group and 11% in the M-VECa group during the first cycle of chemotherapy; after G-CSF treatment, prompt haematologic recovery was observed in the neutropenic patients of both treatment groups. Febrile events with an ANC of less than $500/mm^3$ occurred in 3 patients (1 in the M-VEC group and 2 in the M-VECa group) during the 5th, 6th, and 8th cycles, respectively. These three patients required antibiotic treatment and some hospitalization; one patient in the M-VEC group died because of severe sepsis and two other patients continued treatment after a delay of two weeks. Thrombocytopenia was mild, short lived, and reversible and mainly occurred on the 22nd day of chemotherapy. Nausea and vomiting were generally mild but more pronounced in the M-VEC group on the third cycle ($P = .04$). There was a statistically significant difference in nephrotoxicity between the M-VEC and the M-VECa patients on the third cycle ($P = .03$) and on the sixth cycle ($P = .02$). However, many hypothesis tests on the toxicity data were undertaken and some false-positives might have arisen by chance alone. Two responding patients discontinued treatment after the fourth and sixth cycles due to persistent creatinine levels of more than 3 mg/dL; none of the M-VECa patients had to discontinue treatment for severe nephrotoxicity. There was a statistically significant difference in neurotoxicity between the M-VEC and the M-VECa patients on the third cycle ($P = .02$); the difference was more striking on the sixth cycle ($P = .002$).

No significant drop of more than 20% from baseline in LVEF was observed in either group and no patient developed congestive heart failure. The use of G-CSF caused slight and transient medullary bone pain in 24% of patients. Only 19 of the 57 entered patients (7 in the M-VEC group and 12 in the M-VECa group) were included in the ototoxicity study (34 did not meet our preestablished criteria, and 4 of the 23 patients with initially normal hearing and ABR were excluded because they received only 1 cycle of chemotherapy). Of these 19 patients, 1 in the M-VEC group and 3 in the M-VECa group had not received full dose cisplatin or carboplatin during the second cycle because of toxicity. Only 1 of the 7 examined M-VEC patients (6 males and 1 female, aged 47–70 years, range, 3–7 delivered cycles) developed evidence of ototoxicity after 2 cycles of chemotherapy; the latency of Wave V at ABR increased significantly from 5.874 to 6.336 msec and the differences in I–V IPLI with respect to baseline was 0.502 msec. No further deterioration in ABR or at pure-tone audiogram after another two cycles of chemotherapy was noted in this patient. None of the 12 examined M-VECa patients (10 males and 2 females, aged 51–71 years) developed ABR-measured ototoxicity or abnormal audiograms during treatment (range, 3–9 delivered cycles). The ABR changes in mean wave latency and IPLI are listed in Table 4: the comparison between post-treatment and baseline ABR recordings did not show any statistically significant difference between the M-VEC and the M-VECa patients.

DISCUSSION

With the combination chemotherapies we used, a statistically significant difference between the overall clinical response rate in the M-VEC group (71% with 25% CR) and that in the M-VECa group (41% with 11% CR) was observed ($P = .04$). However, the difference in overall response (CR + PR) was of borderline significance, the overlapping of the two confidence intervals indicating

TABLE 4
Mean ± Standard Deviation of Latencies Milliseconds of ABR Waves and Interpeak Latency Interval in 19 Recurrent or Metastatic Bladder Cancer Patients before and after 2 Cycles of M-VEC or M-VECa

	M-VEC (7 patients)			M-VECa (12 patients)		
	Baseline	2 cycles	*P* value	Baseline	2 cycles	*P* value
Wave I	1.78 ± 0.07	1.81 ± 0.07	ns	1.75 ± 0.10	1.76 ± 0.11	ns
Wave III	3.77 ± 0.14	3.83 ± 0.13	ns	3.86 ± 0.17	3.88 ± 0.11	ns
Wave V	5.81 ± 0.11	5.89 ± 0.24	ns	5.78 ± 0.13	5.80 ± 0.15	ns
I–III (IPLI)	1.99 ± 0.09	1.99 ± 0.16	ns	2.11 ± 0.18	2.12 ± 0.19	ns
III–V (IPLI)	2.04 ± 0.14	2.08 ± 0.15	ns	1.91 ± 0.16	1.91 ± 0.13	ns
I–V (IPLI)	4.03 ± 0.09	4.07 ± 0.21	ns	4.03 ± 0.15	4.04 ± 0.17	ns

M-VEC: methotrexate, vinblastine, epirubicin, and cisplatin; M-VECa: methotrexate, vinblastine, epirubicin, and carboplatin; IPLI: interpeak latency interval; ns: not significant.

that the results are not striking. In line with the results of other trials, high response rates were obtained mainly in patients with local recurrence in both treatment arms; long term disease free survivals were observed in patients with local recurrence who achieved a pathologically complete response after surgical restaging.[3,7,20,21] With regard to bone metastases, the high recalcification rate of the osteolytic lesions in the M-VEC patients (4 of 7 patients), as well as the decrease in bone pain, may indicate an important role for the coadministration of effective chemotherapy with drugs inhibiting osteoclastic reabsorption (such as bisphosphonates) to bladder cancer patients with bone metastases.[22] The overall clinical response rate observed in the M-VEC group (71%) was high, whereas the proportion of complete responses (25%) was lower than that reported in other trials.[3–5] The 41% response rate, particularly the 11% complete remission rate in the M-VECa group, appears to be much lower than those usually reported when conventional M-VAC or M-VEC regimens are used in the treatment of urothelial tumors (an overall remission rate of 43–72%, with complete remissions of 13–35%).[3–7,20,21] Nevertheless, many prognostic factors (such as old age, performance status > 1, metastatic vs. locally advanced disease, or the presence of liver and bone metastases) can affect response rates.[3–7]

It is also possible that a higher initial dose of carboplatin than that used by us (250 mg/m^2) may increase overall response (particularly complete response), given that some authors have reported higher response rates than those observed in our M-VECa patients with the use of carboplatin, 300 mg/m^2, combined with methotrexate and vinblastine[23,24]; however, although hematopoietic growth factors are now available, one must take into account the increase in leukopenia and thrombocytopenia when carboplatin is combined with other drugs.[12,13,25]

In this study, with allowance for concomitant marrow-suppressive drugs, the carboplatin dose was established at 250 mg/m^2 per body surface area, and administered according to serum creatinine and creatinine clearance. Calvert et al have recently published a formula for calculating the optimal carboplatin dose, which involves the glomerular filtration rate and the area under the carboplatin plasma disappearance curve (AUC).[26] The retrospectively calculated median carboplatin AUC for our patients was 3.76 mg/mL/minute, which is lower than an ideal level of approximately 4.5–5 mg/mL minute for patients receiving carboplatin as part of a combination regimen.[26–28] However, the substitution of carboplatin for cisplatin does not always guarantee a similar response rate and, in the case of urothelial cancer, the response to carboplatin alone is usually less than that to cisplatin alone (11–19% vs. 26–55%).[12,13,23,28–31] Although the number of patients in this study was too small to establish whether carboplatin is the ideal substitute for cisplatin in the first-line treatment of recurrent or metastatic bladder cancer, the drug's clear toxicological advantages, as well as the fact that it is much easier to handle, make it particularly useful in elderly patients. Indeed, the level of treatment-related toxicity was lower in the M-VECa group than in the M-VEC group, and fewer delays or dosage modifications were required with M-VECa (36% of administered cycles) than with M-VEC (48% of administered cycles). Leukopenia was worse in the patients receiving the carboplatin-containing regimen, although the therapeutic use of G-CSF led to prompt hematologic recovery and the administration of the subsequent chemotherapeutic cycle. Moreover, two myelosuppressive drugs, such as carboplatin and epirubicin, could be coadministered in the same multidrug regimen without the development of severe leukopenia. Although the use of G-CSF was useful in avoiding severe leukopenia, it did not guarantee the full dose administration of all of the planned cycles, and dosage reductions because of an ANC of less than 1500/mm^3 were often required in both treatment groups.

As expected, the other toxicities usually reported with M-VAC or M-VEC chemotherapy (nausea and vomiting,

nephrotoxicity, and neurotoxicity) were more pronounced in our M-VEC patients. A low incidence of severe thrombocytopenia (usually reported with carboplatin) was observed; this may be explained by the close hematologic monitoring during every cycle, or even to the use of suboptimal carboplatin doses. The use of epirubicin (50 mg/m^2), repeated for as many as 12 cycles in some responding patients, did not cause any significant cardiotoxicity in either group; this is in line with the view that the risk of developing clinical cardiomyopathy is associated with the administration of cumulative doses of 900 mg/m^2.[32] Ototoxicity measured by means of ABR changes was observed in only one of the seven M-VEC patients examined after two cycles of chemotherapy. This patient had not received any other ototoxic drugs, such as aminoglycosides or loop diuretics, and the presence of brain metastases was excluded by computerized tomography; thus, the prolongation of Wave V latency and I–V interpeak latency interval in this case could indicate early and clinically occult ototoxicity due to cisplatin administration although, in accordance with other studies, these findings seem to indicate that a moderate cisplatin dose of 70 mg/m^2 may cause only a low level of ototoxicity.[33–35] The absence of any significant ABR changes in the 12 M-VECa patients examined may confirm the apparent lack of ototoxicity associated with moderate carboplatin doses.[12,36]

Nevertheless, because we found very little ototoxicity in our patients, we cannot advocate the use of ABR for monitoring ototoxicity, although it is an objective procedure that seems to be more accurate than pure-tone audiometry in detecting early hearing deterioration.[15,35] Further ABR studies, especially with the use of cisplatin at doses of more than 100 mg/m^2, are needed.

In conclusion, the M-VECa regimen guarantees a low level of gastrointestinal, renal, neurologic, and otologic toxicity, but is apparently less effective than M-VEC in the treatment of recurrent or metastatic bladder cancer. However, because of our small sample size, a larger randomized Phase III trial is needed to confirm these results.

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