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# Accelerated MVAC chemotherapy in patients with advanced bladder cancer previously treated with a platinum–gemcitabine regimen

Julien Edeline [a,b], Yohann Loriot [a], Stephane Culine [c], Christophe Massard [a], Laurence Albiges [a], Aurore Blesius [a], Bernard Escudier [a], Karim Fizazi [a,*]

[a] Institut Gustave Roussy, Department of Cancer Medicine, University of Paris Sud, Villejuif, France
[b] Centre Eugène Marquis, Department of Medical Oncology, Rennes, France
[c] Centre Hospitalo-Universitaire Henri Mondor, Créteil, France

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**Abstract** ***Background:*** Gemcitabine plus cisplatinum was shown to exert comparable activity and a different toxicity profile when compared to the methotrexate, vinblastine, doxorubicin, cisplatinum (MVAC) regimen in patients with advanced bladder cancer. Accelerated MVAC (aMVAC, the four drugs being administered every 2 weeks with granulocyte colony-stimulating factor (G-CSF)) is better tolerated than conventional MVAC, with a trend for improved activity. There is no standard of care after failure of gemcitabine–platinum (GP) chemotherapy. Our aim was to assess the activity and toxicity of accelerated MVAC as second-line treatment.
***Methods:*** We reviewed data from patients previously treated with GP who had received aMVAC at two institutions at the time of disease progression.
***Results:*** Forty-five patients received aMVAC after GP: 18 (40%) and 27 (60%) had received GP in the adjuvant and the metastatic settings, respectively. The median time to progression (TTP) after first-line GP was 9.3 months. The response rate for aMVAC was 61%, including 4/38 (10%) complete responses. Median time to progression and median overall survival (OS) were 5.8 and 14.2 months, respectively. Median TTP and OS were 9.6 and 16.5 months when GP was used in the adjuvant setting and 4.4 and 5.7 months when GP was used in the metastatic setting. Grade 3–4 toxicities were observed in 31 patients (69%), including four sepsis-related deaths.
***Conclusion:*** aMVAC exerts clinical activity after previous treatment with GP, especially when GP was used in the adjuvant setting. aMVAC should however be administered with caution due to toxicity.


## 1. Introduction

Transitional-Cell Carcinoma of the Urothelium (TCCU) is a chemo-sensitive neoplasm[1] and platinum-containing regimens have been the standard of

* *Corresponding author:* Address: Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, 39 rue Camille Desmoulins, 94800 Villejuif, France. Tel.: +33 1 42 11 43 17; fax: +33 2 99 25 31 08.
*E-mail address:* fizazi@igr.fr (K. Fizazi).

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care to treat patients with metastases from TCCU since the 1980s.[2] The classic the methotrexate, vinblastine, doxorubicin and cisplatinum (MVAC) regimen (methotrexate administered on day 1, day 15 and day 22, vinblastine on day 2, day 15 and day 22, doxorubicin on day 2 and cisplatinum on day 2, one cycle every 28-day) has been considered the standard therapy after it had demonstrated superiority to the CISCA regimen (cisplatin, cyclophosphamide and doxorubicine) in the early 1990s.[3] MVAC was then challenged as standard therapy in a phase III trial comparing the classic MVAC regimen with the cisplatinum and gemcitabine (CG) combination.[4] This trial, which was initially designed to demonstrate a 50% increase in overall survival (OS) in the CG arm, yielded similar response rates (RR), progression-free survival (PFS) and OS in both arms, with a more favourable toxicity profile in the CG arm. Given these results, CG has been mostly used in the first-line metastatic setting since.

There is no standard of care after failure of gemcitabine–platinum (GP) combination treatment. A recent phase III trial showed clinical activity of vinflunine, when used after progression despite platinum-based chemotherapy, but this compound is not considered as an unequivocal second-line standard of therapy because the benefit in OS over best supportive care only is marginal.[5,6]

Accelerated MVAC (aMVAC) consists of the four drugs used in the classic MVAC regimen, given every 2 weeks with granulocyte colony-stimulating factor (G-CSF) support, thus resulting in an increased dose-intensity of chemotherapy. aMVAC was compared with classic MVAC in a phase III trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC), and demonstrated an improvement in the response rate and PFS associated with a significant decrease in toxicity.[7,8] Although no overall survival was seen, a higher proportion of long-term progression-free survivors was reported with aMVAC.

We conducted a retrospective analysis of patients treated with aMVAC for metastatic TCCU after failure of a GP regimen.

## 2. Patients and methods

### 2.1. Eligibility

We reviewed data from patients treated at the Institut Gustave Roussy, Villejuif, France and at the Centre Hospitalo-Universitaire Henri Mondor, Créteil, France, presenting with histologically-confirmed TCCU, a documented progressive metastatic disease after previous treatment with a GP regimen (either used in the adjuvant, neo-adjuvant or metastatic settings). Patients received at least one cycle of aMVAC.

### 2.2. Treatment

aMVAC was given as follows: methotrexate 30 mg/m$^2$ on day 1 or day 2, vinblastine 3 mg/m$^2$ on day 2, doxorubicin 30 mg/m$^2$ on day 2 and cisplatinum 70 mg/m$^2$ on day 2. G-CSF was given from day 4 to day 10. Cycles were repeated every 2 weeks until disease progression or intolerable toxicity.

### 2.3. Evaluation

Response was evaluated using response evaluation criteria in solid tumors (RECIST) criteria. Overall survival was defined from day 1 of the first aMVAC cycle to the date of death, patient being censored at the time of the last follow-up. Time to progression (TTP) was defined from the date of the beginning of the first aMVAC cycle to the date of documented radiological progression. Progression-free survival (PFS) was defined from the date of the beginning of the first aMVAC cycle to the date of documented radiological progression or death.

### 2.4. Statistical analysis

Differences in response rates were analysed using a $\chi^2$-test. Survival analyses were performed using the Kaplan–Meier method with a log-rank test. A $p$ value of less than 0.05 was considered statistically significant. All data were analysed with the Statistical Package for Social Sciences release 17.0 programme (SPSS, Chicago, IL).

## 3. Results

### 3.1. Patients

We identified 45 patients (34 from Institut Gustave Roussy and 11 from Henri Mondor Hospital) treated between 2002 and 2009 with aMVAC after failure of the GP regimen. A summary of patients' characteristics is presented in Table 1. Previous treatment with GP and pattern of response are summarised in Table 2.

### 3.2. Response to aMVAC

Seven patients could not be evaluated, all due to severe toxicity (6 after cycle 1, 1 after cycle 2). Best response after the administration of aMVAC for the 38 evaluable patients is reported in Table 3. The overall response rate was 60.5% (95% confidence interval (CI): 44–77%).

There was a statistically significant difference in the RR to aMVAC between patients who had been treated

Table 1
Patient characteristics.

| | |
|---|---|
| Sex | Patients (%) |
| Female | 9 (20.0%) |
| Male | 36 (80.0%) |
| Age, median (year, range) | 58 (36–79) |
| ECOG performance status (PS) | |
| PS 0 | 11 (24.4%) |
| PS 1 | 29 (64.4%) |
| PS 2 | 5 (11.1%) |
| Primary tumour site | |
| Bladder | 38 (84.4%) |
| Ureter or renal pelvic | 7 (15.6%) |
| Metastatic sites at the time of aMVAC administration | |
| Lymph nodes | 29 (64.4%) |
| Liver | 10 (22.2%) |
| Lung | 9 (20.0%) |
| Bone | 8 (17.8%) |
| Other | 7 (15.6%) |
| Presence of visceral metastasis | |
| Yes | 26 (57.8%) |
| No | 19 (42.2%) |

aMVAC = accelerated methotrexate, vinblastine, doxorubicin, cisplatinum; ECOG = eastern cooperative oncology group.

with GP in the adjuvant setting and patients who had been treated with GP in the metastatic setting (81.3% and 45.5%, respectively, $p = 0.026$). No difference was found in the RR according to the interval between the last cycle of GP and the beginning of aMVAC, 6 months or less versus more than 6 months (64.7% and 57.1%, respectively, $p = 0.64$).

In the 21 patients who where evaluable for both first-line GP and second-line aMVAC treatments, the responses to the two regimens are reported in Table 4. In these patients, there was no statistically significant association between response previously observed to prior first-line regimen and that observed with aMVAC ($\chi^2$-test, $p = 0.59$). There was no detectable difference in the RR according to the platinum compound used in the GP regimen, with a response rate of 57.1%, 54.5% and 83.3% for cisplatinum, carboplatinum or oxaliplatinum, respectively ($\chi^2$-test, $p = 0.46$).

### 3.3. Survival after aMVAC administration

After a median follow-up of 9.0 months, 31 patients (68.9%) exhibited progression, and 35 patients (77.8%) died. The Kaplan–Meier estimates of TTP and OS after the administration of aMVAC are reported in Fig. 1. Median TTP was 5.8 months (95% CI: 1.9–9.8), median PFS was 4.5 months (95% CI: 3.5–5.8) and median OS was 14.2 months (95% CI: 8.1–20.4). Median TTP was 9.6 months (95% CI: 7.3–11.8) and 4.4 months (95% CI: 3.8–5.0) when GP was used in the adjuvant and in the metastatic setting, respectively (log-rank test, $p = 0.015$). Median PFS was 8.4 months (95% CI: 5.1–11.8) and 4.0 months (95% CI: 2.9–5.20) when GP was used in the adjuvant and in the metastatic setting, respectively (log-rank test, $p = 0.003$). Median OS was 16.5 months (95% CI: 11.7–21.2) and 5.7 months (95% CI: 2.8–8.7) when GP was used in the adjuvant and in the metastatic setting, respectively, but the difference was not statistically significant (log-rank test, $p = 0.12$). There was no significant difference in TTP or OS according to the interval between GP and aMVAC (6 months or less: median TTP of 4.6 months, median OS of 8.7 months; more than 6 months: median TTP of 9.2 months, median OS of 14.4 months; log-rank test, $p = 0.23$ for TTP, $p = 0.21$ for OS).

### 3.4. Toxicity of aMVAC

The median number of aMVAC cycles administered was five (range: 1–10). Six patients (13.3%) received only

Table 2
Administration of the GP regimen.

| | |
|---|---|
| Setting of use of GP | |
| Adjuvant setting | 18 (40.0%) |
| Metastatic setting | 27 (60.0%) |
| Type of Platinum compound used: | |
| Cisplatinum | 26 (57.8%) |
| Carboplatinum | 11 (24.4%) |
| Oxaliplatinum | 8 (17.8%) |
| Number of cycles, median (range) | 6 (2–14) |
| Interval between the last cycle of GP and the first cycle of aMVAC, median (range) | 7.4 months (0.7–28.3) |
| Best response in evaluable patients ($n = 26$) | |
| Objective response | 17 (65.4%) |
| Stable disease | 6 (23.1%) |
| Progressive disease | 3 (11.5%) |
| Progression-free survival, median (95% CI) | 9.3 months (0.7–27.6) |
| Toxicity grade 3–4 | 8 (17.8%) |

GP = gemcitabine–platinum; aMVAC = accelerated methotrexate, vinblastine, doxorubicin, cisplatinum; CI = confidence interval.

Table 3
Response to aMVAC.

| | Complete response | Partial response | Stable disease | Progressive disease |
|---|---|---|---|---|
| Overall, $n = 38$ | 4 (10.5%) | 19 (50.0%) | 8 (21.1%) | 7 (18.4%) |
| When GP was used in the adjuvant setting, $n = 16$ | 3 (18.8%) | 10 (62.5%) | 2 (12.5%) | 1 (6.3%) |
| When GP was used in the metastatic setting, $n = 22$ | 1 (4.5%) | 9 (40.9%) | 6 (27.3%) | 6 (27.3%) |
| Interval between GP and aMVAC 6 months or less, $n = 17$ | 1 (5.9%) | 10 (58.8%) | 2 (11.8%) | 4 (23.5%) |
| Interval between GP and aMVAC more than 6 months, $n = 21$ | 3 (14.3%) | 9 (42.9%) | 6 (28.6%) | 3 (14.3%) |

GP = gemcitabine–platinum; aMVAC = accelerated methotrexate, vinblastine, doxorubicin, cisplatinum.

Table 4
Response to aMVAC according to response to GP ($n = 21$).

| Response to GP | Objective response | Stable disease | Progressive disease |
|---|---|---|---|
| Response to aMVAC | | | |
| Objective response | 5 (23.8%) | 3 (14.3%) | 2 (9.5%) |
| Stable disease | 5 (23.8%) | 1 (4.8%) | 0 (0%) |
| Progressive disease | 2 (9.5%) | 2 (9.5%) | 1 (4.8%) |

GP = gemcitabine–platinum; aMVAC = accelerated methotrexate, vinblastine, doxorubicin, cisplatinum.

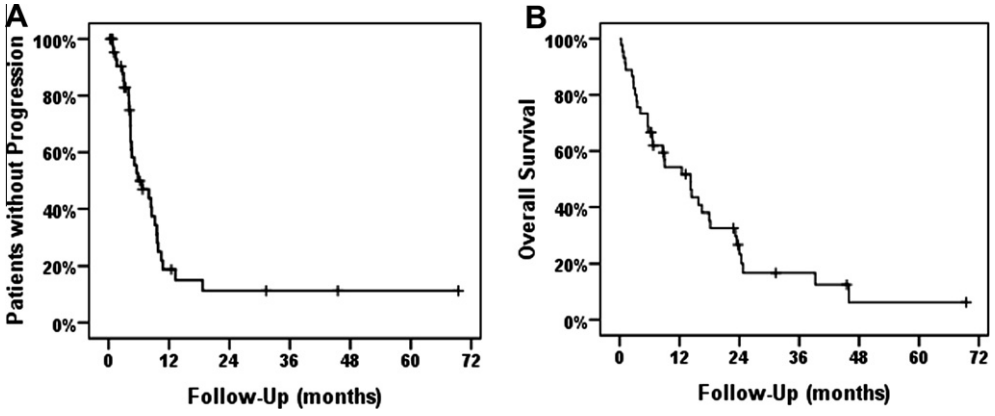


Fig. 1. Kaplan–Meier curves of time to progression (TTP) (A) and overall survival (OS) (B) for the whole cohort.

one cycle due to toxicity (four patients with severe infection, one patient with major asthenia, and one patient with sudden death from unknown cause). Thirty-one patients (68.9%) experienced grade 3 or higher toxicity, including four toxic deaths (8.8%) due to infection (three febrile neutropenia and one septic shock due to central venous catheter infection 3 weeks after the administration of aMVAC). Grade 3 or higher toxicities included mainly haematological toxicity (24 patients), dehydration requiring hospitalisation (three patients). Dose reductions were required in 21 patients (46.7%), and a drug switch in the protocol (cisplatinum to carboplatinum) or discontinuation of a drug was necessary in six patients (13.4%).

## 4. Discussion

Despite the chemosensitivity of TCCU, there is no standard of care after failure of GP treatment.[1,9] Vinflunine demonstrated modest activity after progression on a platinum-based regimen compared with best supportive care (BSC) in a randomised phase 3 study.[5,6] In this setting, vinflunine yielded only an 8.6% response rate, and improved median PFS from 1.5 months with the BSC alone up to 3 months. OS was also improved from 4.6 months up to 6.9 months, although the difference was non-significant in the intent-to-treat population, while reaching significance in the eligible population. Vinflunine was also associated with significant toxicity, including grade 3–4 neutropenia in 50% of patients, grade 3–4 anaemia in 19%, and grade 3–4 constipation in 16%. Several other drugs have been tested only in phase II trials. Pemetrexed yielded a 27.7% response rate, a median time to progression of 2.9 months and a median OS of 9.6 months.[10] Docetaxel yielded a 13.3% response rate and a median OS of 9 months.[11] Gemcitabine, paclitaxel and lapatinib were also investigated in the second-line setting, either as monotherapy or in combination, and yielded similar or inferior results.[6,12–23] The combination of vandetanib to docetaxel did not increase RR, PFS or OS in a phase 2 study (PFS and OS of 2.6 and 5.6 months respectively for the combina-

tion versus 1.6 and 6.0 months for docetaxel alone).[24] An albumin-bound paclitaxel was found to have an interesting 33% RR in this setting.[25]

Results reported in this study with the aMVAC protocol compare favourably with the results of second-line studies assessing a single agent: the 60.5% response rate and the median OS of 14.2 months both appear to be much higher, and the median PFS of 4.5 months is somewhat higher. However, direct comparison between this retrospective study and prospective phase 2 studies lead to several biases. In the aforementioned studies, the inclusion criteria were heterogeneous: first-line chemotherapy used was either in the adjuvant setting or in the metastatic setting, while gemcitabine was not necessarily administered. Agents tested in those studies therefore cannot be considered 'true' second-line therapy. Strictly second-line treatment could lead to less favourable results. Our study supports this hypothesis, with higher response rates and a longer PFS for patients treated with GP in the adjuvant setting, and a trend toward longer OS. However, even in the strict second-line population of patients treated with GP in the metastatic setting, a PFS of 4.0 months was achieved, still comparing favourably with the results reported in single agents experiences,[6,10–23] thought direct comparison should be made cautiously, given the retrospective design of the present study. However, the median overall survival of 5.7 months with aMVAC in this strict second-line setting is somewhat lower than the 6.9 months achieved with vinflunine in the phase 3 trial, and illustrates the negative prognosis of these patients. Nevertheless, it should be emphasised that the use of aMVAC is associated with long-term progression-free survivors (three patients surviving more than 2 years without progression in our series).

aMVAC is a combination of four drugs, including cisplatinum, which per se, may be explained as part of the activity of the regimen. The increased dose-density of the regimen achieved by its fortnightly schedule may also have contributed to its high response rate, specifically in patients who had progressed within 6 months after a cisplatinum-based regimen (GP), with a 76.5% response rate observed in this group. aMVAC may be able to circumvent cisplatinum resistance, as evidence by the observed objective response in two patients in whom best response to previous GP was progressive disease. Of the nine patients with stable disease or progressive disease as best response to GP, 5 (55.6%) had objective response to aMVAC. However, the GP regimen could have been tried with some efficacy in some of our patients, i.e. those progressive beyond 6 months who had initial response to GP.

In our series, the first-line platinum compound used in the GP regimen was not always cisplatinum. Oxaliplatinum was developed in combination with gemcitabine by our groups,[26,27] and carboplatinum was also routinely used instead of cisplatinum in patients with renal failures. Cisplatinum is notoriously regarded as more active than carboplatinum in TCCU,[28–30] and our results may have been influenced by the type of platinum compound used as first-line treatment. However, the high 57.1% response rate observed in patients pre-treated with cisplatinum is consistent with the result of the overall cohort, indicating that aMVAC still appears to be active when cisplatinum is used during first-line therapy.

The use of aMVAC as second line after previous GP was associated with significant toxicity, including four toxicity-related deaths due to sepsis. Grade 3–4 haematological toxicities occurred in 53.3%. Severe nausea and vomiting requiring hospitalisation for rehydration were also reported. A higher haematological toxicity was observed with aMVAC used in the second-line setting, as compared with previous experiences reported in the first-line setting,[7,8] probably due to the decreased bone marrow capacities from the previous treatment. A question remains whether this toxicity could be lowered by a different schedule (e.g. the administration of pelfigrastim on day 3 is used in a neoadjuvant trial). An important proportion of patients in this study required dose reductions of the aMVAC regimen. The use of aMVAC in pre-treated patients in a routine setting seems to be associated with frequent severe toxicity, which should be balanced with the benefit expected from its use.

In conclusion, the aMVAC regimen exerts clinical activity after previous treatment with a GP regimen. This activity does not appear to be influenced by the interval between the two regimens, but seems particularly significant when GP was used in the adjuvant setting. However, it should be administered with caution due to its toxicity, and should be proposed exclusively to selected patients with a good performance status, and adequate renal and haematological function.

## Conflict of interest statement

None declared.

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