European Journal of Cancer 54 (2016) 69–74

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

# Standard or accelerated methotrexate, vinblastine, doxorubicin and cisplatin as neoadjuvant chemotherapy for locally advanced urothelial bladder cancer: Does dose intensity matter?

Damien Pouessel [a], Sylvie Chevret [b,c,d], Frédéric Rolland [e], Gwenaelle Gravis [f], Lionel Geoffrois [g], Guilhem Roubaud [h], Safae Terrisse [i], Helen Boyle [j], Christine Chevreau [k], Jérôme Dauba [l], Guillaume Moriceau [m], Ingrid Alexandre [n], Gaël Deplanque [o], Angélique Chapelle [p], Elodie Vauleon [q], Alexandre Colau [r], François Audenet [s], Thomas Grellety [t], Stéphane Culine [a,d,*]

[a] *Department of Medical Oncology, Hôpital Saint-Louis, AP-HP, Paris, France*
[b] *Department of Biostatistics and Medical Information, Hôpital Saint-Louis, AP-HP, Paris, France*
[c] *Inserm, UMR 717, Hôpital Saint-Louis, AP-HP, Paris, France*
[d] *Paris Diderot University, Paris, France*
[e] *Institut de Cancérologie de l'Ouest, Nantes, France*
[f] *Institut Paoli Calmettes, Marseille, France*
[g] *Centre Alexis Vautrin, Nancy, France*
[h] *Institut Bergonié, Bordeaux, France*
[i] *Institut Gustave Roussy, Villejuif, France*
[j] *Centre Léon Bérard, Lyon, France*
[k] *Institut Claudius Régaud, Toulouse, France*
[l] *Centre Hospitalier, Mont-de-Marsan, France*
[m] *Institut de Cancérologie de la Loire, Saint-Etienne, France*
[n] *Centre Médical de Bligny, Briis-sous-Forges, France*
[o] *Hôpital Saint-Joseph, Paris, France*
[p] *Centre OncoGard, Nîmes, France*
[q] *Centre Eugène Marquis, Rennes, France*
[r] *Hôpital des Diaconesses, France*
[s] *Hôpital Georges Pompidou, Paris, France*
[t] *Centre Hospitalier Saint-André, Bordeaux, France*

Received 21 September 2015; received in revised form 2 November 2015; accepted 16 November 2015
Available online xxx

* *Corresponding author*: Department of Medical Oncology, Hôpital Saint-Louis, 1, Avenue Claude Vellefaux, 75010 Paris, France. Tel.: +33 1 42 49 46 95; fax: +33 1 42 49 98 95.
*E-mail address:* stephane.culine@aphp.fr (S. Culine).

http://dx.doi.org/10.1016/j.ejca.2015.11.017

**KEYWORDS**
Urothelial carcinoma;
Transitional cell carcinoma;
Muscle-invasive disease;
Neoadjuvant chemotherapy;
Dose intensity

**Abstract** ***Background:*** There is continuing controversy regarding the optimal regimen for neoadjuvant chemotherapy (NAC) in bladder cancer.
***Patients and methods:*** We performed a retrospective analysis of 241 consecutive bladder cancer patients who received a combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) using a standard (52 patients) or an accelerated schedule (189 patients) as NAC before radical cystectomy in 17 centres of the French GEnito-urinary TUmour Group from March 2004–May 2013.
***Results:*** The median age was 62 years. As expected, the median number of cycles, the median total dose of cisplatin and the median cisplatin dose intensity were higher in patients treated with the accelerated regimen. Conversely, the median duration of chemotherapy was shorter. Regarding toxicity, grade III/IV neutropenia, grade III thrombocytopenia and grade III anaemia as well were more frequently observed in patients treated with the standard regimen. Among 211 (88%) patients who proceeded to cystectomy, 75 (35%) patients achieved an ypT0 pN0 status (no pathologic residual tumour cells) with no significant difference according to the MVAC schedule. Three-year overall survival rates were 66.5% (95% confidence interval [CI], 56–79) and 72% (95% CI, 59.5–88) in the standard and accelerated cohorts, respectively. In the multivariate analysis, two independent prognostic parameters were retained: the ypT0 stage and the ypN0 stage. Heterogeneity test did not show any interaction with NAC regimens.
***Conclusion:*** Similar pathological response and survival rates were observed whatever the chemotherapy regimen used. Haematological toxicity was greater in patients who received standard MVAC.


## 1. Introduction

Radical cystectomy with lymphadenectomy is considered the curative standard of care in patients with muscle-invasive transitional cell carcinoma (TCC) of the bladder. The disease-free survival at 5 years is approximately 50%, depending on the presence of extravesical extension and lymph node metastases [1]. The rationale for giving neoadjuvant chemotherapy (NAC) before cystectomy is to treat early micro-metastases present at diagnosis. Large randomised trials and meta-analyses support the concept that NAC provides a greater benefit than surgery alone, with higher pathological complete response rates in primary tumours (32–38% versus 12–15%) and a 5% absolute benefit on overall survival (OS) at 5 years (45–50%) [2–4]. However such evidence was obtained with cisplatin-based regimens that are no longer currently used, such as the 4-week standard methotrexate, vinblastine, doxorubicin and cisplatin (S-MVAC) regimen which combines methotrexate, vinblastine, doxorubicin and cisplatin, or the 3-week CMV, which includes the same drugs without doxorubicin.

Accelerated methotrexate, vinblastine, doxorubicin and cisplatin (A-MVAC) is administered on a shortened 2-week schedule with the support of granulocyte colony-stimulating factor (G-CSF), resulting in double the dose-intensity of cisplatin and doxorubicin while reducing by one third the dose-intensity of methotrexate and vinblastine. In metastatic disease, a phase III trial comparing S-MVAC to A-MVAC showed an improvement in complete response rate from 11–25% ($p = 0.006$) and a significant benefit on OS from 13.5–22% at 5 years ($p = 0.04$) [5]. These findings could result from the doubling of the cisplatin dose intensity and may suggest that an increase in pathological response rate could be achieved with the administration of the A-MVAC in the neoadjuvant setting. We are reporting a retrospective study from the French GEnito-urinary TUmour Group (GETUG) focussing on neoadjuvant S-MVAC or A-MVAC in a large cohort of patients treated during the last decade.

## 2. Materials and methods

### 2.1. Patients

We performed a retrospective analysis of patient records for 241 consecutive bladder cancer patients who received S-MVAC (52 patients) or A-MVAC (189 patients) as NAC in 17 centres of the GETUG from March 2004–May 2013. In 11 centres, patients were treated only with A-MVAC. All patients had histologically proven pure or predominant TCC of the bladder with clinical and radiological evidence of T2–4a, N0–N3, M0 disease, and a calculated glomerular filtration rate of 60 ml/min or greater. Clinical T stage was defined by transurethral biopsy samples. Radiologic assessment by computed tomography scan or magnetic resonance imaging was used to determine clinical N stage. Patients