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Thèse

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par

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TITRE

Toxicité cutanée de l'Enfortumab-vedotin dans le carcinome urothélial : étude de son impact pronostique et prédictif de la réponse au traitement. Étude rétrospective multicentrique française.

Présentée et soutenue publiquement le 09/10/25 devant un jury composé de :

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Résumé de thèse :

L'enfortumab vedotin (EV), est un anticorps monoclonal drogue conjugué ciblant la nectine 4. Il a été approuvé en Europe en 2021 pour le traitement du carcinome urothélial localement avancé (laUC) et métastatique (mUC) après échec d'un sel de platine et de l'immunothérapie. Sa toxicité cutanée en est un effet indésirable fréquent et peut parfois être sévère. L'objectif de cette étude est d'évaluer l'association entre la toxicité cutanée induite par l'EV et son efficacité clinique, notamment sur la réponse au traitement.

Nous avons conduit une étude rétrospective multicentrique française incluant 69 patients atteints de la/mUC traités par EV. L'objectif principal était d'évaluer l'impact de la survenue d'une toxicité cutanée sur la survie globale (OS). Les objectifs secondaires incluaient la survie sans progression (PFS), le temps jusqu'au premier traitement ultérieur (TTFST) et la recherche de facteurs prédictifs de toxicité cutanée.

Parmi les 69 patients inclus, l'OS était de 10 mois en médiane (IC 95% = [6 ; 14]), la PFS médiane était de 5 mois (IC 95% = [3,9 ; 6,1]) la médiane de TTFST était de 6 mois (IC 95% = [3,7 ; 8,3]). La survenue d'une toxicité cutanée n'était pas associée à un allongement statistiquement significatif, que ce soit en OS (médiane à 10 mois dans les deux groupes, p = 0,30), en PFS (médiane à 5 mois en cas de toxicité versus 4 mois sinon, p = 0,41), en TTSFT (médiane à 6 mois en cas de toxicité versus 4 mois sinon, p = 0,30).
En analyses univariées comme en multivariée, les trois facteurs pronostiques de la survie globale identifiés étaient l'état général (OMS 0-1 vs 2-3), le ratio de neutrophiles sur lymphocytes > 5 (NLR) et le taux d'hémoglobine. En univarié, on observait pour l'état général : HR = 0,28, IC 95% = [0,14 ; 0,57], p < 0,001, pour le NLR : HR = 2,75, IC 95% = [1,28 ; 5,90], p = 0,009 et pour le taux d'hémoglobine HR = 0,59, IC 95% = [0,43 ; 0,82], p = 0,002. En multivarié, pour l'état général : HR = 0,27, IC 95% = [0,12 ; 0,62], p = 0,002 ; pour le NLR > 5 : HR = 3,34, IC 95% = [1,45 ; 7,79], p = 0,005 et le taux d'hémoglobine : HR = 0,59, IC 95% = [0,43 ; 0,82], p = 0,002 .

La toxicité cutanée était l'effet indésirable le plus fréquent (38%), et survenait précocement (médiane de 15 jours). Elle représentait la principale toxicité ≥ grade 3 (11,5%), incluant notamment deux cas de nécrose épidermique toxique, un syndrome de Steven-Johnson et un décès.

Les patients avec toxicité cutanée étaient significativement plus âgés, avec un envahissement tumoral moindre et un taux d'hémoglobine plus élevé.

Dans cette cohorte, la toxicité cutanée induite par EV n'était pas significativement associée à une amélioration de la survie. En revanche, l'état général et le NLR apparaissaient comme des facteurs pronostiques.

Cutaneous toxicity of Enfortumab vedotin in urothelial carcinoma: prognostic and predictive impact on treatment response. A French multicenter retrospective study

Abstract:

Background: Enfortumab vedotin (EV) is an antibody–drug conjugate targeting nectin-4. It was approved in Europe in 2021 for patients with locally advanced (laUC) or metastatic urothelial carcinoma (mUC) after progression on platinum-based chemotherapy and immunotherapy. Cutaneous toxicity is a frequent and sometimes severe adverse event. We aimed to assess the association between EV-induced cutaneous toxicity and clinical efficacy, particularly treatment response.

Methods: We conducted a French multicenter retrospective study including 69 patients with la/mUC treated with EV. The primary endpoint was the impact of cutaneous toxicity on overall survival (OS). Secondary endpoints were progression-free survival (PFS), time to first subsequent treatment (TTFST), and predictors of cutaneous toxicity.

Results: Among 69 patients, median OS was 10 months (95% CI, 6–14), median PFS was 5.0 months (95% CI, 3.9–6.1), and median TTFST was 6.0 months (95% CI, 3.7–8.3). The occurrence of cutaneous toxicity was not associated with a statistically significant improvement in OS (median 10 months in both groups; p=0.30), PFS (median 5 vs 4 months; p=0.41), or TTFST (median 6 vs 4 months; p=0.30). In univariable and multivariable analyses, prognostic factors for OS were performance status (ECOG 0–1 vs 2–3: HR 0.28; 95% CI, 0.14–0.57; p<0.001; multivariable HR 0.27; 95% CI, 0.12–0.62; p=0.002), neutrophil-to-lymphocyte ratio (NLR) >5 (HR 2.75; 95% CI, 1.28–5.90; p=0.009; multivariable HR 3.34; 95% CI, 1.45–7.79; p=0.005), and hemoglobin level (HR 0.59; 95% CI, 0.43–0.82; p=0.002; retained in multivariable analysis). Cutaneous toxicity was the most frequent adverse event (38%), occurred early (median onset 15 days), and represented the main grade ≥3 toxicity (11,5%), including two cases of toxic epidermal necrolysis, one Stevens–Johnson syndrome, and one death. Patients who developed cutaneous toxicity were significantly older, had a lower tumor burden, and higher hemoglobin levels.

Conclusions: In this cohort, EV-induced cutaneous toxicity was not associated with improved survival outcomes. In contrast, performance status and NLR emerged as key prognostic factors for overall survival.

Mots clés :

Carcinome urothélial métastatique
Enfortumab vedotin
Anticorps-drogue conjugué
Toxicité cutanée

Key words:

Metastatic urothelial carcinoma
Enfortumab vedotin
Antibody–drug conjugate
Cutaneous toxicity

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SERMENT D'HIPPOCRATE

En présence des enseignants et enseignantes
de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits aux indigents,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis(e) dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux(euse) et reconnaissant(e) envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs parents.

Que les hommes et les femmes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert(e) d'opprobre
et méprisé(e) de mes confrères et consœurs
si j'y manque.

Table des matières

Abbreviation list:

ADC – Antibody–Drug Conjugate
AGEP – Acute Generalized Exanthematous Pustulosis
BC – Bladder Cancer
BMI – Body Mass Index
CI – Confidence Interval
CNIL – Commission Nationale de l'Informatique et des Libertés
CTCAE – Common Terminology Criteria for Adverse Events
DFS – Disease-Free Survival
eGFR – Estimated Glomerular Filtration Rate
EV – Enfortumab Vedotin
HR – Hazard Ratio
Hb – Hemoglobin
ICI – Immune Checkpoint Inhibitor
ICU – Intensive Care Unit (si utilisé dans ton texte, à vérifier)
ITT – Intention-To-Treat
IQR – Interquartile Range
laUC – Locally Advanced Urothelial Carcinoma
MIBC – Muscle-Invasive Bladder Cancer
mUC – Metastatic Urothelial Carcinoma
MMAE – Monomethyl Auristatin E
NLR – Neutrophil-to-Lymphocyte Ratio
NE – Not Estimable
OS – Overall Survival
PERCIST – PET Response Criteria in Solid Tumors
PET – Positron Emission Tomography
PFS – Progression-Free Survival
PS – Performance Status
RECIST – Response Evaluation Criteria in Solid Tumors
SJS – Stevens–Johnson Syndrome
TEN – Toxic Epidermal Necrolysis
TRAE – Treatment-Related Adverse Event
TTFST – Time to First Subsequent Therapy
UC – Urothelial Carcinoma
UTUC – Upper Tract Urothelial Carcinoma

I Introduction:

Bladder cancer (BC) is the eleventh most common cancer worldwide (1). According to GLOBOCAN 2022 data, there were an estimated 614,298 new cases of bladder cancer and 220,596 associated deaths worldwide in that year. Its incidence is approximately four times higher in men than in women.
The SEER Study has demonstrated a downward trend in the mortality rate over the past two decades. Specifically, the age-adjusted death rates exhibited an average annual decline of 1.1% between 2014 and 2023 (2).
Smoking has been identified as the most significant risk factor for bladder cancer, accounting for approximately 50% of cases. In addition, occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons has been demonstrated to be a substantial contributing factor (3).
The evidences presented here underscore the fact that bladder cancer remains a significant public health problem.

Approximately 25% of bladder cancer cases present as muscle-invasive disease (MIBC) at diagnosis (3). Although neoadjuvant chemotherapy improves five-year overall survival (OS) and reduces the risk of mortality by 8% (HR 0.87; 95% CI = [0.79 - 0.96]) in localisedMIBC, more than 50% of patients will experience lethal metastatic recurrence after radical surgery (4).

The CHECKMATE-274 trial demonstrated, that the addition of adjuvant nivolumab to the treatment of high-risk patients (T3, T4, N+) results in a significant improvement in median disease-free survival (DFS), irrespective of PDL1 expression, the benefit was more pronounced in PDL1 positive tumors. In patients with PDL1 ≥ 1%, median DFS reached 52.6 months with nivolumab versus 8.4 months with placebo (HR = 0.52 ; 95% CI = [0.37–0.72]; p < 0.001), whereas in the overall in intention to treat (ITT) population (including PDL1 negative patients), median DFS was 22 versus 11 months (HR = 0.71 ; 95% CI = [0.58–0.86]; p < 0.001).
Similarly, interim OS data showed a trend favoring nivolumab, in PDL1 ≥ 1% patients, as HR = 0.56 (95% CI = [0.36–0.86]; p = 0.007, not meeting prespecified significance boundaries), while in the ITT population, median OS was 69.5 versus 50.1 months (HR = 0.76 ; 95% CI = [0.61–0.96]; p = 0.02). The analysis revealed a substantial decline in recurrence rate, with more than a two-fold increase in median DFS in the ITT population and more than a six-fold increase in patients with PDL1 ≥1%.
Nevertheless, despite the significant benefit observed with adjuvant nivolumab, disease recurrence still occurred in 55% of patients in the ITT population and in 44% of patients with PD-L1–positive tumors (5).

Historically, in the metastatic settings, the Platinum based chemotherapy was the standard for first line therapy, with a median OS of 14 months with the combination gemcitabine-cisplatin (6).
Then immune check points inhibitors (ICI) demonstrated a benefit in second line, for patients who had progressed after platinum-based chemotherapy with Pembrolizumab (OS = 10,1 months **;** 95%CI = [8,0 – 12,3]**)** (7), or in maintenance with Avelumab when patients were not progressive after first line chemotherapy (OS = 21.4 months; 95%CI = [18.9 – 26.1])(8).

Novel therapeutics are emerging in metastatic MIBC, notably with Enfortumab Vedotin (EV).
It is Antibody-Drug Conjugate (ADC), a monoclonal antibody targeting Nectin-4 that is connected by a linker to a cytotoxic payload (MMAE = monomethyl auristatin E), to deliver chemotherapy specifically to cancer cells. EV was first approved in Europe in April 2022 **(**after an early access program granted in July 2021) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who had previously received both platinum-based chemotherapy and ICI (9). More recently, it became the new standard first-line option following the EV-302 trial (2023) (10), which demonstrated that the combination EV - Pembrolizumab significantly improved OS compared to platinum-based chemotherapy, to a median of 31 months (95% CI = [25.4; NE]).

Nectin-4 is a transmembrane protein expressed in tumor cells. It is involved in a cell adhesion, usually found in human epidermal keratinocytes, as well as in the epithelium of sweat glands and hair follicles (11) (12) (13). Cutaneous toxicity is a frequent treatment-related adverse event (TRAE) associated with

EV. Safety results from EV-301 showed that 16% of patients experienced maculopapular rash, and 7.4% experienced grade ≥ 3 (13). Pruritus occurred in 32% of patients (any grade) and in 1.4% with grade ≥ 3. These reactions are polymorphic and may range from simple cutaneous rash to severe life-threatening conditions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN, also known as Lyell's syndrome).

Three retrospective studies including respectively 51, 68 and 63 patients showed a positive association between cutaneous toxicities and morphological response rate (14), as well as survival outcomes (15) (16) in patients treated with EV, in contrast with another recent retrospective cohort of 58 patients concluding on the absence of association in term of progression free survival (PFS) and OS (17).

Moreover, identifying clinical and biological predictors of EV response and toxicity is essential for managing the risk of skin toxicity and other treatment-related adverse effects more effectively. The aim of this multicenter retrospective study was to evaluate the relationship between EV-related cutaneous toxicity and improvement in OS.

II. Materials and methods:

II. 1. Study design

This is a retrospective multicenter study conducted in 4 French centers from the Centre Val de Loire Region of France (CHU of Tours, CORT 37, Cancerology Center of Sarthe, Polyclinique of Blois).
The eligibility criteria were:
- Patients over 18 years old
- Histologically confirmed urothelial carcinoma (at least a contingent of urothelial carcinoma)
- Locally advanced or metastatic disease
- Patients who received at least one EV perfusion
- Performance status ≤ 2 at EV initiation
- First EV perfusion administered between 14/09/2021 and 02/04/2025

Patients were excluded if they declined to allow the use of their medical data.

II. 2. Ethics

This study was conducted with the authorization of the French Data Protection Agency (the "Commission Nationale de l'Informatique et des Libertés" or CNIL) and was approved by an independent local ethics review board from Tours University Hospital (n° 23596737). Patients still alive received an information letter and had the possibility to decline the use of their data.

II. 3. Outcomes

The primary endpoint was to compare OS between patients who experienced cutaneous toxicity any grade, and patients who had no cutaneous toxicity during EV treatment. OS was defined as the time from the first EV administration to the date of death from any cause or was censored at the date of last follow-up.
The secondary endpoints were:

- Progression-free survival (PFS), defined as the time from the first EV administration to the date of morphological progression (according to RECIST v1.1 criteria), metabolic progression (according to PERCIST criteria), clinical progression or death from any cause. Patients with no progression were censored at their last morphological or metabolic evaluation.
- Time to First Subsequent Therapy (TTFST), defined as the time from the initiation of EV to the date of initiation of the subsequent systemic therapy or death from any cause. Patients alive who had not started subsequent therapy by the data cut-off date were censored at their last follow-up.
- Description of the frequency and characteristics of cutaneous toxicities.
- Identification of potential predictive factors for cutaneous toxicity.

II. 4. Dermatologic toxicity:

Patients were classified as having cutaneous toxicity if they experienced any grade of dermatologic adverse event, according to **CTCAE v5.0**, when they were treated with EV. This included any kind of skin reactions, notably maculopapular rash, erythema, pruritus.

II. 5. Statistical analysis

For qualitative variables, frequency and percentage were reported. Quantitative variables were described using the median, and interquartile ranges (IQR).

Depending on the distribution, comparisons between groups were performed using either Student's t-test or the Wilcoxon rank-sum test for quantitative variables. Chi-squared tests or Fisher's exact tests were performed for qualitative variables.
Prognostic factors were analyzed using a Cox proportional hazards regression model. Hazard ratios (HRs) were reported with their 95% confidence intervals (95% CI). Variables with a p-value of less than 0.10 in the univariate analyses, were included in the multivariate analysis.
The significance threshold was set at a two-sided p-value of 0.05 for all tests. All statistical analyses were conducted using IBM SPSS version 25.

III. Results:

III. 1. Patients characteristics

Table 1: Baseline characteristics and univariate analyses of factors associated with cutaneous toxicity (n = 69):

Variable	Total (N = 69)	Any cutaneous toxicity (N = 26)	No cutaneous toxicity (N = 43)	P- Value
Age at EV initiation, years				**0.03**
Median [IQR]	72 [67; 77]	74 [70; 80]	70 [65; 75]	
Sex ratio n (%)				0.95
Male	56 (81)	21 (81)	35 (81)	
Female	13 (19)	5 (19)	8 (19)	
BMI at EV initiation, kg/m^2				0.06
Median [IQR]	25 [23; 28]	26 [25; 28]	24 [21; 27]	
ECOG PS at EV initiation, n (%)				0.14
0	5 (7)	4 (15)	1 (2)	
1	38 (55)	15 (58)	23 (54)	
2	14 (20)	4 (15)	10 (23)	
3	2 (3)	-	2 (5)	
Missing data	10 (15)	3 (11)	7 (16)	
Primary tumor location, n (%)				0.46
Bladder	42 (61)	14 (54)	28 (65)	
UTUC	21 (30)	9 (35)	12 (28)	
Unknown origin	6 (9)	3 (11)	3 (7)	
Histological subtype, n (%)				0.86
Yes	14 (20)	5 (19)	9 (21)	
No	55 (80)	21 (81)	34 (79)	
Type of histological subtype, n (%)				
Squamous cell	3	2	1	
Poorly differenciated	3	2	1	
Micropapillary	3	-	3	
Sarcomatoid	3	-	3	
Adenocarcinoma	1	-	1	
Missing data	1	-	1	
Metastatic stage, n (%)				**0.02**
M0	8 (11)	6 (23)	2 (5)	
M1a	4 (6)	2 (8)	2 (5)	
M1b	57 (83)	18 (69)	39 (90)	
Number of previous systemic therapies, n (%)				0.65
1	3 (4)	1 (4)	2 (5)	
2	44 (64)	19 (73)	25 (58)	
3	19 (27)	5 (19)	14 (32)	
4	3 (4)	1 (4)	2 (5)	
Full dose initiation, n (%)				0.23
Yes	56 (81)	23 (88)	33 (77)	
No	13 (19)	3 (12)	10 (23)	
Hb, g/dl				**0.03**
Median [IQR]	11.9 [10.6; 12.7]	12.5 [10.9; 13.4]	11.1 [10.6; 12.6]	
Missing data	16	4	12	
Ratio NLR				0.53
Median [IQR]	4.9 [3.6; 7.9]	4.98 [3.9; 6.4]	4.9 [3.6; 10.9]	

Variable		Total (N = 69)	Any cutaneous toxicity (N = 26)	No cutaneous toxicity (N = 43)	P- Value
Missing data		16	4	12	
GFR, m^2	ml/min/1.73				0.59
Median [IQR]		52 [39; 69]	58 [42; 69]	49 [39 ; 70]	
Missing data		20	5	15	

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; GFR, glomerular filtration rate; Hb, hemoglobin; IQR, interquartile range; M1a, lymph node metastases only; M1b, extra nodal metastases; NLR neutrophil-to-lymphocyte ratio; UTUC, upper tract urothelial carcinoma.

Between 14/09/2021 and 02/04/2025, 69 patients had started EV. The median follow-up period was 6.4 months (IQR = [0.2; 28.1].
The patients were predominantly male (56/69, 81%) and the median age at diagnosis was 71 years. At baseline, ECOG PS was ≤ 1 in 43 patients (62%), 14 patients (20%) had a performance status of 2, and two had a score of 3 (3%).
Bladder cancer was the most common primary tumor site, accounting for 42/69 cases (61%). Histological variants were identified in a minority of patients (14/69, 17%).
Metastases were present at initiation of EV in 61 patients (89%). In those 61 patients, lymph node metastases only were observed in four patients; all others had visceral disease.
Most patients (81%) started EV at full dose.

Patients who experienced skin toxicity differed from the rest of the cohort on their tumor burden, as they were significantly older (74 vs 70 years old respectively, p = 0.03) and with a lower tumor burden (69% had extra nodal metastases vs 90% respectively, p = 0.02). on the biological parameters, they had a significantly higher hemoglobin level (12.5 vs 11.1 g/dl, p = 0.03).

III. 2. Overall survival (OS)

Median OS was 10 months (95% CI = [6; 14]) for the entire cohort. It did not differ between patients with and without cutaneous toxicity (10 months in median in both groups) (Figure 1).

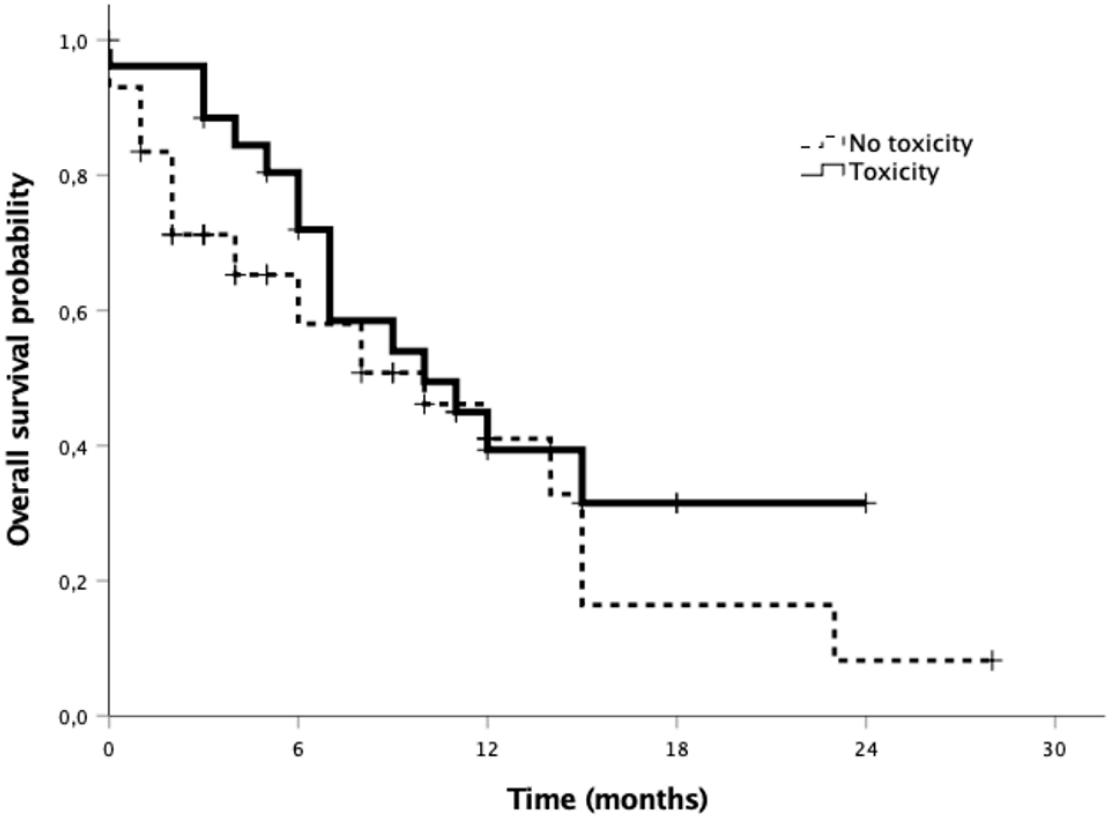

Figure 1: Kaplan–Meier survival curves according to the presence or absence of cutaneous toxicity.

Hemoglobin level and Eastern Cooperative Oncology Group performance status (ECOG PS) were the only protective factors identified (Tables 2 and 3). Patients with an ECOG PS 0–1 had a significantly lower risk of death compared to those with ECOG PS ≥ 2 (HR = 0.28; 95% CI = [0.14; 0.57]; p < 0.001), and higher hemoglobin levels were also associated with improved OS (HR = 0.64; 95% CI = [0.47; 0.86]; p = 0.003). In contrast, a neutrophil lymphocyte ratio (NLR) > 5 was associated with an increased risk of death (HR = 2.75; 95% CI = [1.28; 5.90]; p = 0.009).
In the multivariate analysis, ECOG PS 0–1 (HR = 0.27; 95% CI = [0.12; 0.62]; p = 0.002), hemoglobin level (HR = 0.59; 95% CI = [0.43; 0.82]; p = 0.002) and NLR > 5 (HR = 3.34; 95% CI = [1.45; 7.79]; p = 0.005) remained independently associated with OS.

Table 2: OS univariate analyses, from EV initiation (n = 69):

	Univariate		
Characteristic	**HR**	**95% CI**	**p-value**
Cutaneous Toxicity			
Yes	1.40	[0.73; 2.67]	0.31
Age			
≥ 72 years old	1.6	[0.85; 3.02]	0.14
Sexe			
Female	1.20	[0.54; 2.58]	0.67
Primary tumor location			
Bladder	0.69	[0.35; 1.38]	0.3
Histological subtype			
Yes	0.73	[0.35; 1.56]	0.42
BMI			
≥ 25 kg/m^2	1.41	[0.75; 2.65]	0.3
ECOG PS at EV initiation			
< 2	0.40	[0.24; 0.68]	**0.001**
Metastases			
Yes	1.29	[0.51; 3.28]	0.6
Lymph nodes metastases only			
Yes	0.82	[0.65; 11.6]	0.2
Extra nodal metastases			
Yes	0.66	[0.28; 1.56]	0.3
Previous lines of therapy			
≥3	0.91	[0.46; 1.77]	0.77
Full dose initiation			
Yes	0.96	[0.45; 2.01]	0.91
Hb	0.64	[0.47; 0.86]	**0.003**
Ratio NLR			
> 5	2.75	[1.28; 5.88]	**0.009**
GFR	1.02	[1.00; 1.04]	**0.047**

Abbreviations: BMI, body mass index; CI = confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; GFR, glomerular filtration rate; Hb, Hemoglobin; HR, hazard ratio; NLR, Neutrophile-to-lymphocyte ratio; UTUC, upper tract urothelial carcinoma.

Table 3: OS multivariate analysis, from EV initiation (n = 69):

		Multivariate	
Characteristic	**HR**	**95% CI**	**p-value**
Hb	0.59	[0.43; 0.82]	**0.002**
Ratio NLR			
> 5	3.34	[1.45; 7.79]	**0.005**
ECOG PS			
< 2	0.27	[0.11; 0.62]	**0.002**

Abbreviations: CI, Confidence Interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; HR, hazard Ratio; NLR, neutrophil-to-lymphocyte ratio.

III. 3. Progression free survival (PFS)

The median PFS for the entire cohort was 5 months (range 3.9 – 6.1). It did not differ significantly between patients with and without cutaneous toxicity (median PFS = 5 vs. 4 months, p = 0.41).
Hemoglobin level was identified as a protective factor (HR = 0.78, 95% CI = [0.62–0.98]; p = 0.032).
No other variable was significantly associated with progression free survival.

III. 4. Time to first subsequent therapy

The median TTFST was 6.0 months (range 3.7–8.3) for the entire cohort. The median TTFST was 6.1 months (range 0.6–24.3) for patients with cutaneous toxicity and 4.0 months (range 0.2–18.2) for those without (p= 0.30).

III. 5. Toxicity characteristics

In this cohort, the most common adverse event was cutaneous toxicity, reported in 26 patients (38%) followed by fatigue (n = 19, 27%), diarrhea (n = 18, 26%), weight loss (n = 16, 26%) and anemia (n = 16, 26%). Peripheral neuropathy was observed in 15 patients (22%).
Cutaneous toxicity usually occurred early, with a median onset of 15 days (IQR = [8; 113]). Half the cases of cutaneous toxicity were rashes (n = 11), the second most frequent cutaneous toxicity was xeroderma and/or pruritus (n = 8).
Among the grade ≥ 3 adverse events, cutaneous toxicity was the most frequent, occurring in 8 patients (11,5 %). Grade III events included one case of acute generalized exanthematous pustulosis (AGEP), one case of pruritus and two rashes (macular eruptions). Grade IV events consisted of two cases of toxic epidermal necrolysis (TEN) and one case of Stevens–Johnson syndrome (SJS). The single grade V event (death) was due to TEN. Neutropenia occurred in six patients (9%), including four cases of febrile neutropenia requiring hospitalization and intravenous antibiotics. Severe fatigue was observed in six patients, while significant weight loss (>20% of baseline weight) was observed in five patients (7%). Of the four cases of diabetes, three were grade ≥ 3, requiring the initiation of insulin therapy. Two of these cases occurred in patients with no prior history of diabetes.
Management of the cutaneous toxicities involved moisturizers only for three patients, topical corticosteroids for ten patients and systemic corticosteroids for two patients. Five patients required hospitalization. Dose adjustments were made due to cutaneous toxicity for three patients, two reductions of 20% and one reduction of 40%. Moreover, treatment was stopped due to skin toxicity for 10 patients (14% of the entire cohort; 38% of patients with cutaneous toxicity) : three interruptions were only temporary and seven were definitive ones (including one death).
Peripheral neuropathy occurred after a median of five cycles with a wide range (IQR: 1-14). Motor involvement was observed in only one patient. This resulted in permanent treatment discontinuation in five cases and a dose reduction in three additional patients.

IV- Discussion:

Our study showed that, regardless of grade, Enfortumab Vedotin-related cutaneous toxicity was not associated with significantly different OS, PFS or TTFST compared to patients without EV-related cutaneous toxicity.

In our cohort, rash occurred in 29% of patients, and grade ≥ 3 rashes in 10% of patients, compared with 16.2% and 7.4% respectively, in the EV-301 trial. This may be due to the differences between the populations studied. Compared with the EV-301 phase III trial, our cohort included patients with poorer baseline conditions, as reflected by the proportion with ECOG PS ≥ 2 (23% vs 0% in EV-301) (13). They were also more heavily pretreated patients, with a greater number of prior systemic therapy lines (≥ 3) (32% *vs* 13% in the phase III trial). In terms of disease burden, extra nodal metastases were rather similar (84% *vs* 77%). These baseline differences may also participate to explain that survival outcomes in our cohort were modestly worse than in the EV-301 trial. Median PFS was 5 months (95% CI = [3.9; 6.1]) and median OS was 10 months (95% CI = [5.8; 14.2]), compared with 5.5 months (95% CI = [5.3; 5.8]) for PFS and 12.9 months (95% CI = [10.6; 15.2]) for OS in EV-301.
In the study by Vlachou *et al.* (2024), 27 out of 56 patients (48%) developed EV-related cutaneous toxicity, which was significantly associated with improved OS in both univariate and multivariate analyses (HR = 0.48; 95% CI = [0.25; 0.90]; p = 0.02)(15). The median OS was found to be 9.4 months in the entire cohort, 7.4 months in patients who did not exhibit cutaneous toxicity, and 11.9 months in those who did. In a similar vein, Belkaïd *et al.* (2025) documented EV-related cutaneous toxicity in 18 of 63 patients (29%), observing a substantial correlation with enhanced OS in univariate analysis (HR = 0.38; 95% CI = [0.16; 0.92]; p = 0.02) (16). However, this association was not confirmed in the multivariate analysis (HR = 0.41; 95% CI = [0.16; 1.06]; p = 0.07). In this cohort, median OS was 15.1 months overall, 8.2 months in patients without cutaneous toxicity, and 18.6 months in those with cutaneous toxicity. One possible explanation for the absence of a significant association between EV-related cutaneous toxicity and survival outcomes in our cohort may be the greater severity of the toxicities observed in our population. In the Belkaïd *et al.* study, most cutaneous toxicities were grade 1-2 (n = 17, 27%), with only one case of grade 3 toxicity (1.6%) and no grade 4–5 (16). In the study by Vlachou *et al.*, most cutaneous adverse events were grade 1–2 (n = 35, 44%), with only seven (9%) patients experiencing a grade ≥ 3 (15). In contrast, in our cohort, 11,5 % of patients experienced a grade ≥ 3 cutaneous toxicity, including four grade 3 events, three grade 4 events and one fatal case.
The clinical implications of our findings nuance those of Vlachou and Belkaïd: EV-related skin toxicities are likely associated with better treatment efficacy, but only when they are of moderate severity (grade I–II). Severe grade III toxicities often led to treatment interruption or discontinuation, which reduces drug exposure and its efficacy. Optimizing the management of cutaneous toxicities could help reduce EV discontinuations. Recently, clinical guidelines have been published to support clinicians in managing these adverse events (18).

In our cohort, EV-related cutaneous toxicity occurred more frequently in patients with a better baseline condition, characterized by lower tumoral burden and higher hemoglobin levels. One possible explanation relates to treatment exposure: patients in poorer general condition (e.g. older age, impaired ECOG PS or visceral metastases) may have been more likely to initiate EV at a reduced or adapted dose, which could have limited the occurrence of skin toxicity. Conversely, patients with a more favorable baseline status may have started EV treatment at the full dose, which could have increased the likelihood of developing cutaneous adverse events. However, this hypothesis should be interpreted with caution, as this association was not formally demonstrated in our analyses.

A potential biological explanation for the link between early EV-related cutaneous toxicity and improved treatment efficacy lies in the shedding of nectin-4. This is a biological process whereby the extracellular portion (ectodomain) of a membrane-anchored protein is cleaved and released into the extracellular space or bloodstream. In the case of nectin-4, this cleavage is mediated by metalloproteases, generating soluble nectin-4 that can act as a decoy. This reduces the binding of drugs to tumor cells and the epidermis (19) (20). Shedding has three other implications: it reduces the density of nectin-4 on tumor cells, representing a mechanism of resistance through target downregulation.

Also, soluble nectin-4 contribute to tumor progression by promoting neoangiogenesis and proliferation *via* the Src, PI3K, Akt, and endothelial nitric oxide synthase (eNOS) signaling pathways (19) (21). Finally, soluble nectin-4 appears to be a biological and dynamic marker of disease progression (22). Thus, greater shedding could be associated with both reduced cutaneous toxicity and poorer clinical outcomes, whereas limited shedding could result in higher drug delivery to both tumor and skin, manifesting as rash and potentially better efficacy.
The relationship between cutaneous toxicity and EV efficacy may not be solely explained by shedding, as many other factors are involved. Recent findings by Klumper and al. (47 patients) have challenged the notion of ubiquitous nectin-4 expression reported in the initial EV-101 trial, demonstrating a significant decrease in nectin-4 expression during metastatic progression. Furthermore, the tumor microenvironment has been demonstrated to play a crucial role in modulating the efficacy of EV (23) (24). The endothelial barrier, elevated interstitial pressure, and complex stromal architecture within solid tumors can hinder the penetration of ADCs.

These considerations highlight the need to investigate additional predictive factors. Potential candidates include nectin-4 gene amplification (24), which has shown a strong correlation with treatment response, serum-based biomarkers such as soluble Nectin-4 correlate with progression (22).
Recently, nectin-4–targeted positron emission tomography (PET) imaging has emerged as a promising non-invasive approach to identify patients who most likely to benefit from EV, guide treatment adaptation, and serve as a complementary biomarker for real-time assessment of target engagement in EV therapy (25) (26).

We observed however that an ECOG PS ≥ 2 and an elevated NLR were significant risk factors for a shorter OS, whereas a higher hemoglobin level was consistently identified as a protective factor across endpoints. NLR has already been investigated as a prognostic indicator in various cancers (27) and even in non-oncological conditions including sepsis, traumatology and cardiovascular disease (28) (29) (30). NLR has been demonstrated to reflect systemic inflammation, with elevated values indicating pro-tumor neutrophil activity and reduced anti-tumor immunity (27)(31). In the context of platinum-refractory urothelial carcinoma, a pretreatment NLR ≥ 3 has been shown to be a prognostic indicator associated with a poorer OS (HR = 1.57; 95% CI = [1.19; 2.07], p = 0.01) (32). Conversely, a decline in the NLR during therapy with the immune checkpoint inhibitor, pembrolizumab, has been observed to be associated with enhanced survival outcomes. More recently, high NLR has also been linked to poorer OS in la/mUC patients receiving EV after ICI therapy (HR 2.50; 95% CI = [1.03; 6.08], p = 0.04) (33).

The main limitation of our study lies in its retrospective design and the amount of missing data. For example, baseline laboratory results prior to the first EV cycle could not be retrieved for one center. Cutaneous toxicity was not easy to assess retrospectively. The study also included a relatively small number of patients, thus limiting the power of our statistical analyses. Due to the multicenter nature of the study, there were differences in patient management, such as initiating EV at a reduced dose, as well as in the timing and modality (CT scan vs PET scan) for the evaluation of clinical outcomes.
One strength of our study is that we chose OS as the primary endpoint. In a population of patients treated in the third-line setting for bladder cancer, OS is the most clinically meaningful outcome to assess the impact of treatment.

V- Conclusion:

In conclusion, our analysis did not demonstrate a significant association between EV-related cutaneous toxicity and survival outcomes. These findings should be interpreted with caution, as the study was retrospective and on a limited sample size. Compared with the Vlachou and Belkaïd studies, our cohort exhibited a higher proportion of severe cutaneous toxicities, which may also have contributed to the absence of a survival benefit.

In addition, exploratory analyses suggested that the NLR could be a prognostic factor, especially when considered alongside ECOG PS. However, further research is required to confirm its role in risk stratification.

As the therapeutic landscape is shifting towards an earlier use of EV in combination strategies, as tested in the EV-303 trial, it is even more important to be able to predict EV toxicity, in order to refine patient selection and improve outcomes.

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31 pages – 3 tableaux – 1figures

Résumé :
L'enfortumab vedotin (EV), est un anticorps monoclonal drogue conjugué ciblant la nectine 4. Il a été approuvé en Europe en 2021 pour le traitement du carcinome urothélial localement avancé (laUC) et métastatique (mUC) après échec d'un sel de platine et de l'immunothérapie. Sa toxicité cutanée en est un effet indésirable fréquent et peut parfois être sévère. L'objectif de cette étude est d'évaluer l'association entre la toxicité cutanée induite par l'EV et son efficacité clinique, notamment sur la réponse au traitement.

Nous avons conduit une étude rétrospective multicentrique française incluant 69 patients atteints de la/mUC traités par EV. L'objectif principal était d'évaluer l'impact de la survenue d'une toxicité cutanée sur la survie globale (OS). Les objectifs secondaires incluaient la survie sans progression (PFS), le temps jusqu'au premier traitement ultérieur (TTFST) et la recherche de facteurs prédictifs de toxicité cutanée.

Parmi les 69 patients inclus, l'OS était de 10 mois en médiane (IC 95% = [6 ; 14]), la PFS médiane était de 5 mois (IC 95% = [3,9 ; 6,1]) la médiane de TTFST était de 6 mois (IC 95% = [3,7 ; 8,3]). La survenue d'une toxicité cutanée n'était pas associée à un allongement statistiquement significatif, que ce soit en OS (médiane à 10 mois dans les deux groupes, p = 0,30), en PFS (médiane à 5 mois en cas de toxicité versus 4 mois sinon, p = 0,41), en TTSFT (médiane à 6 mois en cas de toxicité versus 4 mois sinon, p = 0,30).
En analyses univariées comme en multivariée, les trois facteurs pronostiques de la survie globale identifiés étaient l'état général (OMS 0-1 vs 2-3), le ratio de neutrophiles sur lymphocytes > 5 (NLR) et le taux d'hémoglobine. En univarié, on observait pour l'état général : HR = 0,28, IC 95% = [0,14 ; 0,57], p < 0,001, pour le NLR : HR = 2,75, IC 95% = [1,28 ; 5,90], p = 0,009 et pour le taux d'hémoglobine HR = 0,59, IC 95% = [0,43 ; 0,82], p = 0,002. En multivarié, pour l'état général : HR = 0,27, IC 95% = [0,12 ; 0,62], p = 0,002 ; pour le NLR > 5 : HR = 3,34, IC 95% = [1,45 ; 7,79], p = 0,005 et le taux d'hémoglobine : HR = 0,59, IC 95% = [0,43 ; 0,82], p = 0,002 .

La toxicité cutanée était l'effet indésirable le plus fréquent (38%), et survenait précocement (médiane de 15 jours). Elle représentait la principale toxicité ≥ grade 3 (11,5%), incluant notamment deux cas de nécrose épidermique toxique, un syndrome de Steven-Johnson et un décès.
Les patients avec toxicité cutanée étaient significativement plus âgés, avec un envahissement tumoral moindre et un taux d'hémoglobine plus élevé.

Dans cette cohorte, la toxicité cutanée induite par EV n'était pas significativement associée à une amélioration de la survie. En revanche, l'état général et le NLR apparaissaient comme des facteurs pronostiques.

Mots clés :
Carcinome urothélial métastatique, Enfortumab vedotin Anticorps-drogue conjugué Toxicité cutané

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