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Patient Experiences Before and After Enfortumab Vedotin Neoadjuvant Treatment in Cisplatin-Ineligible Muscle-Invasive Bladder Cancer

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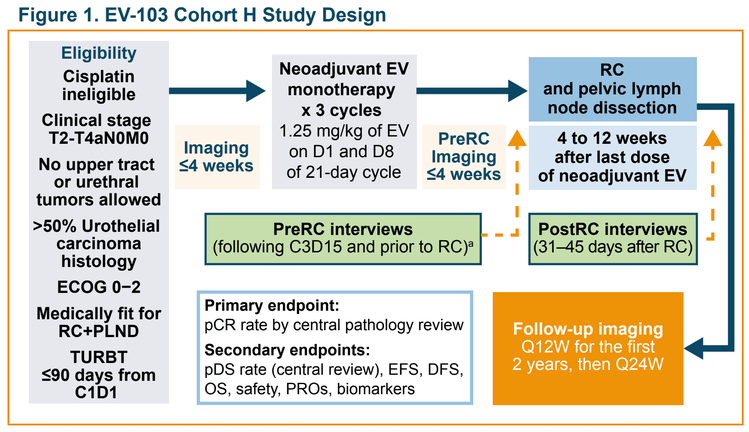
Background and Objective

- About one-quarter of bladder cancers are defined as muscle-invasive bladder cancer (MIBC) at initial diagnosis.[1]
- Painless haematuria (blood in urine) is the most commonly reported symptom associated with MIBC. Other irritative symptoms include dysuria, frequent urination, urgency to urinate, incontinence, and symptoms related to urinary tract obstruction.[2,3]
- Patients with MIBC have a high recurrence rate (>50% within 2 years of radical cystectomy [RC]) and a poor prognosis due to the presence of micro-metastases at diagnosis.[4,5]
- Current standard of care for patients with MIBC is neoadjuvant chemotherapy with cisplatin-based chemotherapy, as supported by Level 1 evidence.[6]
- Approximately 20–50% of patients with MIBC are ineligible for neoadjuvant cisplatin due to underlying comorbidities;[7] thus, there is a need for new therapies in this setting.
- Enfortumab vedotin (EV), alone or in combination, is being evaluated in the EV-103 phase 1b/2 open-label trial in patients with urothelial carcinoma (NCT03288545) and has recently demonstrated promising antitumor activity in patients with MIBC ineligible for cisplatin, with 36% of patients achieving a pathologic complete response (pCR) and 50% experiencing pathologic downstaging with no new safety signals identified.[8]
- Here, we report qualitative data from patient interviews from Cohort H of the EV-103 study which evaluated patient experiences with EV neoadjuvant treatment in patients with MIBC ineligible for cisplatin.

Methods

- Cohort H of the EV-103 trial enrolled cisplatin-ineligible patients with cT2-T4aN0M0 MIBC who were eligible for RC and had an ECOG of 0–2. Patients received 3 cycles of EV (1.25 mg/kg) on Days 1 and 8 in 3 21-day cycles prior to RC. The primary endpoint was pCR rate (ypT0N0) by central review. Key secondary endpoints included pathological downstaging rate (yp T0, Tis, Ta, T1, N0) and safety.
- Enrolled patients (aged ≥18 years) included those who provided verbal consent and were able to participate in two 45-minute telephone interviews.
- Interviewers used a semistructured interview guide, which was developed for both pre- and post-cystectomy interviews and included initial open-ended questions to encourage spontaneous responses followed by more specific questions to clarify concepts of interest.
- Pre-cystectomy interviews focused on MIBC impacts and treatment experience and were conducted post-EV treatment (Cycle 3, Day 15) and prior to cystectomy (**Figure 1**)
  - Interview questions were designed to gather patient perspectives on MIBC signs, symptoms, and the impacts on those symptoms as well as functioning and overall health-related quality of life (HRQoL) prior to EV treatment and following EV treatment.
- Post-cystectomy interviews focused on patients' HRQoL after cystectomy and their perceptions of benefits/risks of EV treatment; interviews were conducted 31–45 days post-surgery (**Figure 1**).
  - Interview questions were designed to capture patients' symptoms, functioning, and overall HRQoL following cystectomy, and their perceptions of treatment benefit and meaningfulness.
- All study documents were reviewed and approved by the Institutional Review Board prior to contact with patients.

Figure 1. EV-103 Cohort H Study Design



[a]PreRC interviews were conducted following C3D15 and prior to RC but captured patients' perspectives pre-EV treatment and perspectives post-EV treatment prior to cystectomy.
DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; EV: enfortumab vedotin; OS: overall survival; pCR: pathological complete response rate; pDS: pathological downstaging; PROs: patient-reported outcomes; RC+PLND: radical cystectomy + pelvic lymph node dissection; TURBT: transurethral resection of bladder tumor

Qualitative data analysis

- Demographic information and clinical characteristics were summarized descriptively.
- Telephone interviews were audio recorded, transcribed, and coded using ATLAS.ti version 8.0 (Atlas.ti GmbH, Berlin), a software package designed to facilitate the storage, coding, and analysis of qualitative data. A coding scheme was developed based on the interview guide and research objectives, which classified actual terms reported by patients to describe concepts of interest; patients provided responses either spontaneously (without prompting from the interviewer) or with probing (explicit prompting from the interviewer following the initial open-ended question to clarify concepts of interest).

Results

Study population

- Fourteen of 22 enrolled patients completed ≥1 interview; 13 (92.9%) and 11 (78.6%) completed the pre- and post-cystectomy interviews, respectively.
  - Three patients completed only the pre-cystectomy interview due to EV-related adverse events (AEs) (n=2) in the preoperative period and death (n=1).
  - One patient completed only the post-cystectomy interview due to AEs associated with EV treatment and the urgent scheduling of a cystectomy.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Pre-cystectomy n=13	Post-cystectomy n=11	Total n=14*
Patient demographics at baseline			
Mean age, years (SD)	72.8 (6.4)	72.5 (6.7)	72.9 (6.4)
Male, n (%)	11 (84.6%)	9 (81.8%)	12 (85.7%)
Race, White, n (%)	13 (100.0%)	11 (100.0%)	14 (100.0%)
Ethnicity, Non-Hispanic/Latino, n (%)	12 (92.3%)	10 (90.9%)	13 (92.9%)
Clinical characteristics post-cystectomy			
Type of cystectomy, n (%)			
Open		8 (72.7%)	
Robotic		2 (18.2%)	
Robotic completed by open surgery		1 (9.1%)	
Type of urinary diversion or reconstruction, n (%)			
Ileal conduit		9 (81.8%)	
Orthotopic neobladder		2 (18.2%)	

*Patients who completed either or both pre- and post-cystectomy interviews.
EV, enfortumab vedotin; SD, standard deviation.

Patient demographics

- Mean (SD) age was 72.9 (6.4) years; patients were mostly male (85.7%), and all were White (**Table 1**).
- The mean (SD) time from the first cycle of EV treatment to cystectomy was 3.4 (0.8) months.

Pre-cystectomy interviews

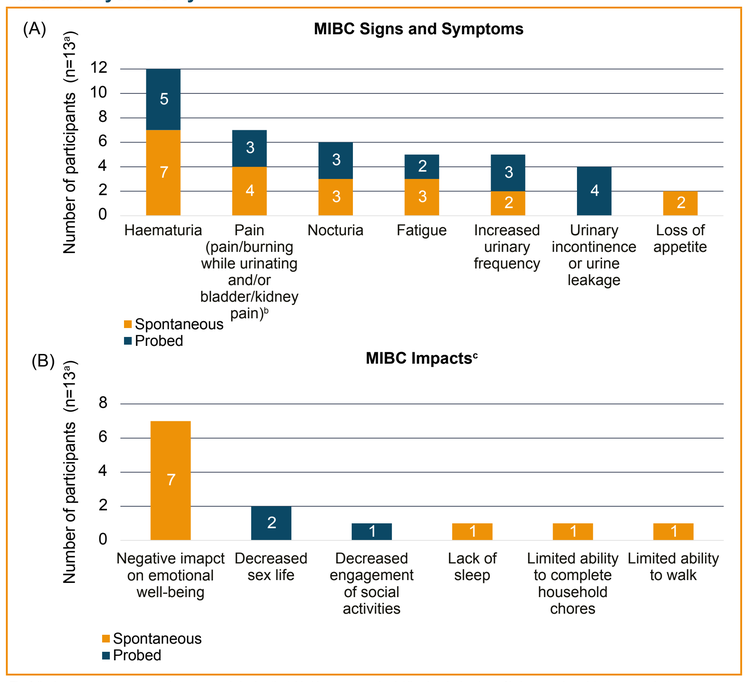
MIBC signs, symptoms, and impacts prior to study enrolment

- MIBC signs, symptoms, and impacts prior to EV treatment reported during pre-cystectomy interviews (n=13) are reported in **Figure 2**.
- The most frequently reported baseline symptoms pre-EV included haematuria (92.3%), pain (inclusive of both pain/burning while urinating and bladder/kidney pain) (53.8%), nocturia (46.2%), fatigue (38.5%), and increased urinary frequency (38.5%).
- The most frequent impacts, as perceived by patients, prior to treatment with EV, were reduced emotional well-being (53.8%) and decreased sex life (15.4%).

EV-treatment experience

- Of the patients (n=11) providing evaluable data on treatment experience, none had any concerns regarding the frequency of EV treatment. Of the 10 patients reporting on the administration of EV, most (8/10, 80%) found it to be "fine/good/pleasant." Of the 8 patients who provided evaluable data when asked to describe their opinion of EV treatment overall:
  - Three (37.5%) reported a good experience with EV treatment, and 3 (37.5%) considered EV treatment to be manageable/mild/neutral; there were no reports of a negative experience with EV treatment.
  - One patient (12.5%) described EV treatment as disappointing due to a lack of response to treatment and 1 (12.5%) reported feeling better after EV treatment.
- Patients most commonly indicated they liked the speed of EV treatment administration but disliked the length of study visits (4/13, 30.8% for both).

Figure 2. Overview of MIBC Signs, Symptoms (A) and Impacts (B) Prior to EV and Pre-Cystectomy



[a]The following concepts were reported spontaneously by 1 patient: bladder pressure, cloudy/discolored urine, loss of balance, and persistent urge to urinate.
[b]n=5 patients reported pain/burning while urinating, and n=3 reported bladder/kidney pain; however, 1 patient reported both pain/burning while urinating and bladder/kidney pain.
[c]Impacts were perceived by patients as related to MIBC but may have other underlying causes.
EV, enfortumab vedotin; MIBC, muscle-invasive bladder cancer.

Changes in MIBC signs, symptoms, and impacts post-EV and pre-cystectomy

- Post-EV and compared with baseline, 9/12 (75.0%) patients reported an improvement in haematuria, 4/5 (80.0%) reported less pain or burning while urinating, 2/3 (66.7%) reported less bladder/kidney pain, and 2/6 (33.3%) indicated an improvement in nocturia.
- Patients reported no meaningful changes in MIBC impacts, eg, emotional and sexual well-being, following EV treatment.

Tolerability of EV

- Following EV treatment, patient-reported AEs included rash (10/13, 76.9%) and fatigue and loss of taste (9/13, 69.2% reported the latter two AEs) (**Figure 3**).
  - Of 10 patients who experienced rash, most (7/10, 70.0%) sought care, while 2 (2/10, 20%) did not, and data were missing for 1 patient. Of the 7 patients who sought care, 5 (5/7, 71.4%) received topical medication, while 2 (2/7, 28.6%) did not receive another type of treatment.
- Overall, most (9/13, 69.2%) patients were willing to continue EV treatment and would recommend (11/13, 84.6%) the treatment to others.

Post-cystectomy interviews

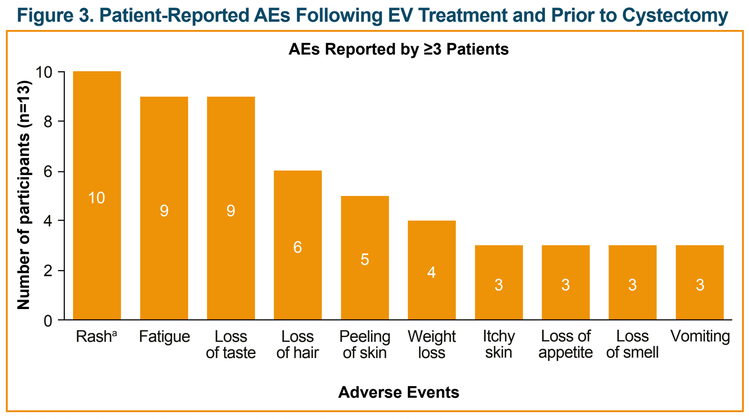
Treatment characteristics

- The mean (SD) time between cystectomy and post-cystectomy interview was 62.2 (19.9) days.
- Of the 11 patients who completed the post-cystectomy interviews, most (8/11, 72.7%) underwent an open cystectomy and received an ileal conduit bladder (9/11, 81.8%).
- Three of the 11 (27.3%) patients achieved a pCR while 5 (45.5%) did not (**Table 1**).

Overall HRQoL

- During post-cystectomy interviews (n=11), patients most commonly reported an improvement in HRQoL (5/11, 45.5%) or that they had mostly recovered and had a good HRQoL (3/11, 27.3%), while 3 (27.3%) patients reported a decreased HRQoL.
- Regarding MIBC impacts post-cystectomy, participants most often reported a detrimental impact on emotional well-being (8/11, 72.7%) and physical functioning (8/11, 72.7%) (**Table 2**).
- Patient-reported HRQoL varied depending on the timepoint when patients were interviewed following cystectomy; those who reported having a good HRQoL were interviewed at a later timepoint (59–78 days), while patients who reported a decreased HRQoL were interviewed at an earlier timepoint (43–58 days).

Figure 3. Patient-Reported AEs Following EV Treatment and Prior to Cystectomy



All AEs (including rash) were reported spontaneously by patients. Neuropathy was reported by 2 patients.
[a]Rash was the only AE for which the interview guide probed.
AEs, adverse events; EV, enfortumab vedotin.

Table 2. Summary of MIBC Impacts Post-Cystectomy

Post-Cystectomy Impacts	n=11 n (%)	
	Spontaneous[a]	Probed[b]
Affected physical functioning	8 (72.7%)	0
Affected emotional well-being	1 (9.1%)	7 (63.6%)
Affected sleep	3 (27.3%)	2 (18.2%)
Affected leisure activities	2 (18.2%)	3 (27.3%)
Affected sex life	0	5 (45.5%)
Affected participation in desired activities	4 (36.4%)	0
Affected ability to do things	1 (9.1%)	2 (18.2%)
Prevented return to work/school/daily activities	1 (9.1%)	2 (18.2%)

[a]Without prompting from the interviewer.
[b]Explicit prompting from the interviewer following the initial open-ended question to clarify concepts of interest.
MIBC, muscle-invasive bladder

Patient perceptions of benefit/risks of EV treatment

- Patients reported the following perceived benefits associated with EV treatment: limits cancer progression (5/11, 45.4%), shrinks/eradicates tumors (4/11, 36.4%), enables bladder removal (2/11, 18.2%), and facilitates surgery (2/11, 18.2%).
- Of the patients who were asked whether they believed they received benefit from receiving EV as treatment prior to cystectomy, almost all (10/11, 90%) patients indicated a perceived treatment benefit.

Patient perceptions of EV-treatment meaningfulness

- Patients were asked to define aspects of EV treatment that they found meaningful and to indicate particular scenarios in which they would be willing to undergo additional EV treatment.
- Of those who responded, most (7/11, 63.6%) indicated they would be willing to undergo additional EV treatment if recommended by their doctor.
  - Of the 4 patients who were not willing, 2 (50%) would not undergo further EV therapy due to treatment-related AEs, and 2 (50%) would prefer to wait until bladder removal (if needed).
- Of the patients who did not achieve a pCR (n=8), almost all (7/8, 87.5%) indicated they would be willing to undergo more cycles of EV treatment to achieve a pCR.
- Seven patients (7/11, 63.6%) reported they would not delay surgery for more cycles of EV without increased likelihood of a pCR; their rationale being that if bladder removal was inevitable, they would prefer to have it removed as soon as possible.

Limitations

- Patient interviews were optional, and data were not collected from all patients. As such, there may have been patients who experienced more severe signs, symptoms, and impacts that were not included in the analysis.
- Not all patients were interviewed both pre- and post-cystectomy due to the impact of treatment-related AEs and the rapid scheduling of a cystectomy for some patients.
- For some interview questions, responses were not provided by the patient due to limited time and challenges with interpreting the questions.

Conclusions

- Findings from the Cohort H qualitative patient interviews show that patients enrolled in the study initially reported haematuria, pain, nocturia, fatigue, and increased urinary frequency as the most common baseline symptoms prior to EV treatment along with common MIBC impacts, which included reduced emotional well-being and decreased sex life.
- These symptoms align with the key concepts in currently available MIBC-specific patient-reported outcomes (PRO) instruments (eg, BCI, FACT-BI, EORTC QLQ-BLM30 and FACT-BI-Cys).
- Patients reported measurable change in haematuria and pain following EV treatment; these may be considered as potential endpoints in future trials to assess improvement or stabilization.
- In pre-cystectomy interviews most patients reported treatment-related AEs, but the majority (69.2%) would be willing to continue EV treatment and would recommend (84.6%) treatment to others.
- Post-cystectomy interviews indicated a general improvement in patients' health, although detrimental impacts on emotional well-being and physical functioning were noted.
- Patients had several perceived benefits of EV treatment; most indicated they would undergo further cycles of EV therapy if it led to better outcomes.
- These insights into patient experience can inform development of future trials in MIBC, especially selection of PRO measures.

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