Exploratory Analysis of the Association Between Nausea, Vomiting, and Fatigue in Metastatic Breast Cancer Patients Treated with Trastuzumab Deruxtecan

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BACKGROUND

- The treatment landscape for HER2+ breast cancer (BC) continues to evolve, offering new hope for patients.
- In recent years, trastuzumab deruxtecan (T-DXd), a HER2-targeting antibody-drug conjugate (ADC), has emerged as a highly effective treatment option for pre-treated patients with HER2+ and HER2-low advanced or metastatic BC.
- Among the most commonly reported adverse events, nausea, vomiting (NV) and fatigue are negatively affecting patients' quality of life.[1]
- With growing interest in evaluating clusters of adverse events, addressing NV may indirectly contribute to better management of fatigue.

T-DXd-induced Nausea and Vomiting

- International antiemetic guidelines classify T-DXd as moderate-to-high risk for NV and recommend an NK_1RA-containing prophylactic regimen.[2]
- A pooled analysis of trials including mBC patients treated with T-DXd showed all-grade NV frequencies of 75% and 46%, respectively.[3]
- Patients may experience long-lasting NV beyond day 5 post-T-DXd administration; this long-delayed phase NV may pose a significant burden on patients' quality of life (QoL).[4-6]
- Enhancing patients' QoL, maintaining dose intensity and preventing treatment discontinuation are crucial, especially because patients may remain on T-DXd for an extended time period.
  - Effective control of NV is imperative from the first cycle of treatment.
  - Antiemetics with longer half-life and extended NK_1 receptor occupancy may be an appropriate option.

T-DXd-induced Fatigue

- Fatigue is a common and debilitating issue during cancer treatment, particularly in mBC, where it may stem from the cancer itself or its treatment.
- Fatigue is a frequently reported side effect associated with T-DXd, observed in both clinical trials and in real-world practice.[7]
  - In the Destiny-Breast trials and in a recent systematic review the incidence of T-DXd-induced fatigue was ~47%.[7]
- While antiemetic guidelines offer recommendations for preventing T-DXd-induced NV, managing fatigue requires a holistic, multifaceted approach due to the lack of effective treatments for cancer-related fatigue.

OBJECTIVE

- The objective of this retrospective analysis was to examine the association between fatigue recorded during the present cycle and NV assessed in the previous one in HER2+/HER2-low mBC patients.

METHODS

- This was a single-center, exploratory retrospective analysis of patients with HER2+/HER2-low mBC patients receiving T-DXd.
- Occurrence and severity of NV and fatigue were extracted and analyzed from clinical records at Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy.
- The association between occurrence of fatigue and previous NV was tested using a logistic regression with Generalized Estimating Equation, with mild adjustments to account repeated measures.

Nausea, vomiting and fatigue are among the most prevalent adverse effects associated with T-DXd. While no targeted interventions exist for T-DXd-related fatigue, this analysis investigated a potential association between these toxicities. Findings indicate a trend suggesting that NV in one treatment cycle may increase the likelihood of fatigue in subsequent cycles. Given that NV can be mitigated with antiemetic therapy (in this case NEPA), optimizing NV control may represent a strategy to reduce fatigue.

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RESULTS

Patient Demographics

- The analysis included 25 patients, followed for 5 cycles for a total of 118 cycles.
- Patient characteristics are summarized in **Table 1**.
- All but 1 patient received antiemetic prophylaxis from the first cycle, with most (n = 23, 92%) receiving NEPA, a fixed-combination of an NK_1RA (netupitant/fosnetupitant) and $5\text{-}HT_3RA$ (palonosetron) and 12 mg dexamethasone (DEX). Of the remaining two patients, one received ondansetron with 8 mg DEX while the other initially received only 12 mg DEX but switched to NEPA + DEX in subsequent cycles.

Table 1. Patient Characteristics

Characteristic	Total Patients N = 25
Age at start of T-DXd	
Median (range)	**64** (41, 78)
HER2 Status	
HER2-positive	**10** (40%)
HER2-low	**15** (60%)
Line of T-DXd	
1st	**5** (20%)
2nd	**6** (24%)
3rd or later	**14** (56%)

Association Between Nausea & Vomiting and Fatigue

- NV was well-controlled with NEPA.
- Although not statistically significant, the odds ratio indicates that patients with any grade of prior NV may have a higher likelihood of experiencing fatigue compared to those without prior NV (**Table 2**).

Table 2. Results of a Logistic Regression Analysis Testing the Association Between Occurrence of Fatigue and Prior NV

Parameter	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
Previous CINV (yes vs. no)	**3.038**	**0.497**	**18.573**	**0.2290**
Treatment Cycle 2 vs. previous cycle	1.365	0.481	3.872	0.5588
Treatment Cycle 3 vs. previous cycle	0.895	0.280	2.861	0.8510
Treatment Cycle 4 vs. previous cycle	1.988	0.526	7.505	0.3109
Treatment Cycle 5 vs. previous cycle	1.409	0.317	6.262	0.6524

- Consistently, the estimated probability of developing fatigue was higher in patients who experienced NV in the prior cycle (45.8% vs. 21.8%, **Table 3**).

Table 3. Probability of Developing Fatigue as a Function of the Presence or Absence of NV in the Prior Cycle (Estimates Obtained from the Logistic Model of Table 2)

Previous CINV	Probability to Develop Fatigue	Lower 95% CI	Upper 95% CI
YES	0.4579	0.1370	0.8181
NO	0.2176	0.1025	0.4037

CONCLUSIONS

- While no specific treatments exist for T-DXd-related fatigue, preventing NV—along with behavioral and integrative therapies — may help reduce its occurrence.
- The findings of this retrospective analysis suggest a potential link between prior NV and fatigue, indicating that controlling NV may help manage fatigue in mBC patients receiving T-DXd.
- These preliminary findings need to be confirmed in prospective studies.

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