Managing Trastuzumab Deruxtecan: Dosing and Adverse Event Insights

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Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate used in various cancers. While effective, understanding its safety profile, particularly across different doses, is crucial for optimizing patient care. This pooled analysis offers a comprehensive look at treatment-emergent adverse events to guide clinicians in real-world practice.

KEY TAKEAWAYS

- The Pivot: This analysis provides a detailed, pooled safety profile of trastuzumab deruxtecan (T-DXd) across two doses (5.4 mg/kg and 6.4 mg/kg), offering a clearer picture of adverse event frequency and severity than individual trials.
- The Data: Common adverse events included nausea (74.6% at 5.4 mg/kg; 65.5% at 6.4 mg/kg), fatigue (56.5% at 5.4 mg/kg; 52.8% at 6.4 mg/kg), and neutropenia (34.6% at 5.4 mg/kg; 49.3% at 6.4 mg/kg). Adjudicated drug-related interstitial lung disease (ILD) occurred in 12.0% (5.4 mg/kg) and 10.9% (6.4 mg/kg) of patients.
- The Action: Proactive management of gastrointestinal and hematologic adverse events is essential, with particular attention to older patients and those with renal impairment. Monitoring for ILD/pneumonitis is also critical, despite severe cases being infrequent.

Understanding Trastuzumab Deruxtecan's Safety Profile

Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2 (HER2)-directed antibody-drug conjugate approved for various HER2-expressing or HER2-mutated cancers. While its efficacy is well-established, a thorough understanding of its safety profile, including dose-related adverse events, is vital for its safe and effective use in clinical practice. This pooled analysis aimed to characterize treatment-emergent adverse events (TEAEs) across two commonly used doses of T-DXd to support real-world application 1.

Study Design and Methodology

This analysis aggregated data from nine phase I-III clinical trials (DS8201-A-J101; DESTINY-Breast01/02/03/04; DESTINY-Lung01/02; DESTINY-Gastric01/02). The study population comprised 1678 patients with metastatic breast, gastric, or lung cancer, exhibiting varying HER2 expression or HER2 mutation status. Patients received T-DXd at either 5.4 mg/kg or 6.4 mg/kg every three weeks. The researchers evaluated the time to onset and dose-related outcomes for key TEAEs, including nausea, vomiting, neutropenia, fatigue, and interstitial lung disease (ILD). An analysis of antiemetic use was also conducted, though it was limited to data collected before a 2020 protocol amendment that recommended prophylactic antiemetics 1.

Key Findings: Common Adverse Events

The analysis identified several common TEAEs, defined as occurring in 20% or more of patients. These included fatigue, nausea, vomiting, neutropenia, anemia, and thrombocytopenia. The majority of these events were classified as grade 1 or 2 in severity. Specifically, nausea was reported in 74.6% of patients receiving 5.4 mg/kg and 65.5% of those receiving 6.4 mg/kg. Fatigue occurred in 56.5% (5.4 mg/kg) and 52.8% (6.4 mg/kg) of patients. Neutropenia was observed in 34.6% of patients at the 5.4 mg/kg dose and 49.3% at the 6.4 mg/kg dose 1.

Treatment modifications due to TEAEs were also common. Dose reductions were necessary in 22.6% of patients on 5.4 mg/kg and 29.7% on 6.4 mg/kg. Drug interruptions occurred in 42.8% (5.4 mg/kg) and 47.6% (6.4 mg/kg) of patients. Discontinuation of T-DXd due to TEAEs was reported in 17.7% of patients receiving 5.4 mg/kg and 16.6% of those receiving 6.4 mg/kg 1.

Interstitial Lung Disease Incidence

Interstitial lung disease (ILD) or pneumonitis is a known, serious adverse event associated with T-DXd. This pooled analysis found that adjudicated drug-related ILD occurred in approximately 11-12% of patients, specifically 12.0% in the 5.4 mg/kg group and 10.9% in the 6.4 mg/kg group. While the incidence was notable, the study indicated that severe cases of ILD/pneumonitis were infrequent 1.

Clinical Implications and Proactive Management

The findings from this pooled analysis underscore the importance of proactive management strategies for patients receiving trastuzumab deruxtecan. The high incidence of gastrointestinal TEAEs like nausea and vomiting, along with hematologic events such as neutropenia, necessitates vigilant monitoring and timely intervention. The study highlights that most TEAEs were low grade, but the rates of dose reduction and interruption suggest that these events can significantly impact treatment continuity if not managed effectively 1.

Why this matters for clinical practice today: This comprehensive safety profile reinforces the need for clinicians to integrate robust supportive care measures into their treatment plans for patients on T-DXd. Given the prevalence of nausea, particularly, prophylactic antiemetic regimens should be considered standard practice, especially in light of the protocol change recommending it. For neutropenia, regular blood count monitoring and consideration of growth factor support may be warranted. The consistent incidence of ILD across both doses, even if severe cases are less common, emphasizes the ongoing need for patient education on pulmonary symptoms and prompt investigation of any new or worsening respiratory complaints. Special attention should be paid to older patients and those with renal impairment, as these subgroups may be at higher risk for certain adverse events, requiring individualized dose adjustments or closer monitoring.

Limitations and Future Directions

While this pooled analysis provides valuable insights, it is important to acknowledge its limitations. The antiemetic analysis was restricted to data collected before a standardized prophylactic antiemetic recommendation, which may not fully reflect current management practices. Future research could focus on identifying specific patient characteristics that predict a higher risk for severe ILD or other significant TEAEs, allowing for more personalized risk stratification and preventative strategies. Further studies could also explore optimal management algorithms for specific TEAEs to minimize treatment interruptions and improve patient quality of life 1.

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REFERENCES

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