T-DXd Side Effects in Breast Cancer Warrant Continued Attention

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Trastuzumab deruxtecan (T-DXd) has demonstrated efficacy in HER2-positive and HER2-low metastatic breast cancer. However, its use necessitates careful monitoring for specific adverse events, with interstitial lung disease (ILD) being a primary concern. Clinicians should continue to pay close attention to patient symptoms and implement established management protocols to mitigate these risks.

KEY TAKEAWAYS

- The Pivot: T-DXd offers significant clinical benefits but carries a distinct safety profile requiring proactive management.
- The Data: Interstitial lung disease (ILD) has been observed in clinical trials, requiring prompt identification and intervention.
- The Action: Prescribing clinicians should educate patients on ILD symptoms, monitor for respiratory changes, and adhere to dose modification guidelines.

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) comprising a humanized anti-HER2 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload via a cleavable tetrapeptide-based linker. It is approved for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen, and for adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. The mechanism of action involves binding to HER2-expressing cells, internalization, and subsequent release of the topoisomerase I inhibitor, leading to DNA damage and apoptosis.1

Breast cancer remains a significant global health challenge, with HER2-positive and HER2-low subtypes representing substantial patient populations. HER2-positive breast cancer, characterized by overexpression of the human epidermal growth factor receptor 2, historically carried a poor prognosis but has seen significant therapeutic advancements with HER2-targeted agents. More recently, the concept of HER2-low breast cancer has emerged, identifying a subgroup of patients with low levels of HER2 expression who can also benefit from HER2-targeted ADCs like T-DXd. This expansion of treatable populations underscores the importance of understanding the full safety profile of T-DXd.1

While T-DXd has shown superior efficacy compared to standard chemotherapy in various clinical settings, its safety profile requires specific attention. The most clinically significant adverse event associated with T-DXd is interstitial lung disease (ILD), including pneumonitis, which can be severe and, in rare cases, fatal.1 Other common adverse events include nausea, fatigue, alopecia, vomiting, constipation, decreased appetite, and myelosuppression (neutropenia, anaemia, leukopenia).1

Adverse Event Profile and Management

The incidence of drug-related ILD/pneumonitis with T-DXd has been reported across multiple clinical trials. In studies such as DESTINY-Breast03, which compared T-DXd to trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane, the incidence of any-grade ILD was 10.9%, with grade 3 or 4 events occurring in 0.8% of patients. Fatal ILD events were reported in 0.2% of patients.2 The median time to onset of ILD has varied but typically falls within the first year of treatment.2

Risk factors for T-DXd-related ILD are not fully elucidated, but pre-existing lung conditions, older age, and prior radiation therapy to the chest may increase susceptibility.1 Early detection and management are critical for improving outcomes. Patients should be counselled on the symptoms of ILD, which include dyspnoea, cough, fever, and new or worsening respiratory symptoms.1

Management guidelines recommend prompt interruption of T-DXd therapy upon suspicion of ILD. Grade 1 ILD typically requires dose interruption and close monitoring. For grade 2 or higher ILD, permanent discontinuation of T-DXd is generally recommended, along with corticosteroid treatment. For grade 2 ILD, corticosteroids (e.g., prednisone 0.5-1 mg/kg/day) should be initiated and tapered over at least 4 weeks. For grade 3 or 4 ILD, higher doses of corticosteroids (e.g., prednisone 1 mg/kg/day or methylprednisolone 1 mg/kg/day intravenously) are indicated, followed by a prolonged taper.1

Regular monitoring of pulmonary function tests and chest imaging (e.g., CT scans) may be considered, particularly for patients with pre-existing respiratory conditions or those who develop new respiratory symptoms. However, routine screening with CT scans in asymptomatic patients is not currently recommended. Instead, a high index of suspicion based on clinical symptoms is paramount.1

Other adverse events, such as nausea and vomiting, can often be managed with antiemetic prophylaxis. Myelosuppression requires regular complete blood count monitoring and dose modifications or growth factor support as appropriate. Cardiac toxicity, while less common than with other HER2-targeted therapies, should also be considered, particularly in patients with pre-existing cardiac conditions.1

The continued clinical utility of T-DXd in breast cancer is undeniable, given its demonstrated efficacy. However, this efficacy must be balanced with a thorough understanding and proactive management of its unique safety profile, particularly concerning ILD. Adherence to established monitoring and management protocols is essential for optimising patient outcomes and ensuring the safe use of this important therapeutic agent.1

CLINICAL IMPLICATIONS

The clinical benefits of trastuzumab deruxtecan in HER2-positive and HER2-low breast cancer are substantial, yet the persistent signal for interstitial lung disease (ILD) demands unwavering attention from the oncology community. It is not enough to simply acknowledge this risk; clinicians must integrate robust patient education and vigilant monitoring into their routine practice. The onus is on the prescribing physician to ensure patients understand the subtle, often insidious, onset of respiratory symptoms that could indicate ILD, and to act decisively when such symptoms arise. Delay in intervention can have severe consequences, underscoring the need for a low threshold for suspicion and prompt diagnostic workup.

From an industry perspective, the development of ADCs like T-DXd represents a significant advance, but the associated toxicities highlight the ongoing challenge of therapeutic precision. While the 'bystander effect' of T-DXd is beneficial for efficacy, it also contributes to off-target toxicities such as ILD. Future drug development in this class must continue to refine linker technology and payload delivery to improve the therapeutic index. Regulatory bodies and pharmaceutical companies must also ensure that comprehensive risk management plans are not merely theoretical documents but are actively supported by educational resources and real-world data collection to inform best practices.

For patients, the promise of extended progression-free survival and improved outcomes with T-DXd is tempered by the potential for serious adverse events. This necessitates a transparent dialogue between patient and clinician, ensuring informed consent extends beyond the initial treatment decision to include ongoing vigilance for side effects. Patients must feel empowered to report any new or worsening symptoms without hesitation, understanding that early reporting is key to effective management. The balance between efficacy and safety remains a delicate one, and in the case of T-DXd, proactive management of ILD is not merely a recommendation, but a clinical imperative.

REFERENCES

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