Safety and efficacy of trastuzumab deruxtecan and concomitant radiation therapy in breast cancer patients: an international retrospective cohort study

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Highlights

- **The possibility to combine antibody drug conjugates (ADCs) with RT is highly debated**
- **No information come from trials, even if limited palliative RT was allowed in DESTINY-Breast03 and ASCENT**
- **Minimal requirements of reporting RT parameters and RT quality assurance data are lacking and should be included in future clinical trials**
- **Combining T-DM1 with brain SRT significantly increases the risk of symptomatic radionecrosis**
- **The same warning has been remarked by two recently published retrospective studies that showed an increased risk of symptomatic radionecrosis with ADCs and concurrent SRT**

Introduction

Trastuzumab deruxtecan (T-DXd) has emerged as the standard treatment for patients with metastatic HER2-positive (HER2+) breast cancer (BC) following disease progression on first-line therapy containing taxanes and trastuzumab.
Results from DESTINY-Breast04 have extended the approval of T-DXd to include HER2-low patients. Radiation therapy (RT) is an integral component of multimodal treatment in the metastatic setting.
This retrospective study aims to evaluate the safety of the concurrent use of T-DXd and RT in a consecutive, multicentre international cohort.

Features	n (%)
Sites of RT treated metastases	
Central nervous system	39 (54.9)
Bone	21 (29.6)
Lymph nodes	3 (4.2)
Liver	1 (1.4)
Other	7 (9.9)
Number of treated metastases	
1-5	55 (77.5)
>5	13 (18.3)
NA	3 (4.2)
RT intent (67 patients)	
Ablative	36 (53.7)
Palliative	31 (46.3)
RT technique	
3D-CRT	7 (9.9)
IMRT-VMAT	37 (52.1)
CyberKnife	7 (9.9)
Gamma Knife	4 (5.6)
NA	16 (22.5)
EQD2	
<50Gy	56 (78.9)
≥50Gy	12 (16.9)
NA	3 (4.2)
BED	
<50Gy	44 (62)
≥50Gy	24 (33.8)
NA	3 (4.2)

Table 1. Treatment details of RT courses.

Methods and Materials

We conducted a retrospective analysis of patients diagnosed with metastatic HER2+ or HER2-low BC, who were treated at six leading European institutions across four different countries.
Patients started treatment with T-DXd between May 2021 and March 2024, with some receiving concomitant RT with palliative or ablative intent and others not.
We defined ablative RT based on biological dose with threshold of minimum 50Gy EQD2(10) delivered in a maximum of 12 fractions, according to the EORTC and European Society for Radiotherapy (ESTRO) OligoCare (EORTC-1822-RP) study.
The primary objective of the study was to assess the association between RT administration and adverse events (AEs) exceeding grade (G) 2. In all cases RT was administered immediately before Cycle 1 of therapy with T-DXd or during systemic treatment without any drug interruption.

	No RT cohort n=80		RT cohort n=67		Whole series n=147	
Adverse event *	Any grade	Grade ≥3	Any grade	Grade ≥3	Any Grade	Grade ≥3
Hematologic, n (%)						
Neutropenia	15 (18.8)	4 (5.0)	3 (4.5)	0 (0)	18 (12.2)	4 (2.7)
Thrombocytopenia	10 (12.5)	1 (1.3)	1 (1.5)	0 (0)	11 (7.5)	1 (0.7)
Anaemia	21 (26.3)	4 (5.0)	6 (9.0)	1 (1.5)	27 (18.4)	5 (3.4)
Non hematologic, n (%)						
Nausea	39 (48.8)	2 (2.5)	27 (40.3)	0 (0)	66 (44.9)	2 (1.4)
Diarrhoea	10 (12.5)	1 (1.3)	6 (9.0)	1 (1.5)	16 (10.9)	2 (1.4)
ILD/pneumonitis	7 (8.8)	2 (2.5)	7 (10.4)	4 (6.0)	14 (9.5)	6 (4.1)
Fatigue	47 (58.8)	6 (7.5)	29 (43.3)	5 (7.5)	76 (51.7)	11 (7.5)
Radionecrosis	0 (0)	0 (0)	1 (1.5)	0 (0)	1 (0.7)	0 (0)
Radiation dermatitis	0 (0)	0 (0)	3 (2.0)	0 (0)	3 (2.0)	0 (0)
Total events	68 (85.0)	16 (20)	44 (65.7)	8 (11.9)	112 (76.2)	24 (16.3)

Table 2. Incidence of haematologic and non-haematologic adverse events in patients treated with T-DXd with or without concurrent RT.

Results

A total of 147 consecutive patients treated with T-DXd, with or without concomitant RT, were retrospectively evaluated. Sixty-seven patients received RT immediately before or during T-DXd administration, accounting for 71 courses of concomitant RT, while 80 patients did not receive RT.
The median age was 53 years (range, 28–88), and the median follow-up from T-DXd initiation was 15 months (range, 1–46) for the entire cohort. Visceral metastases were present in 132/147 patients (89.8%), with similar distribution across the RT and no RT groups. Brain metastases (BM) were reported in 60 patients, with a higher incidence in the RT cohort (42/67, 62.7%) compared to the no RT group (18/80, 22.5%).
Most patients received T-DXd as forth or further line of systemic therapy (52.4%, N=77/147). Following our definition, all the patients treated with RT in the metastatic setting received concomitant RT with T-DXd. The median RT dose was 44Gy (range 8–48), delivered over a median of four fractions (range 1–20). The median EQD2 was 82Gy (range 12–104) and the median BED was 98Gy (range 14–125).
The most frequent treatment site was the CNS (54.9%, n=39/71), followed by the bone (29.6%, n=21/71). Thirty-six patients (53.7%) received ablative RT and 31 (46.3%) received palliative RT. More than half of RT courses were delivered with IMRT/VMAT techniques **(Table 1)**.
Permanent discontinuation of T-DXd due to toxicity occurred in 19 patients: 8 (11.9%) in the RT group and 11 (13.8%) in the no-RT group. Overall, 24/147 patients (16.3%) experienced ≥G3 AEs, with no significant difference between the no RT (16/80, 20.0%) and RT (8/67, 11.9%) cohorts (p = 0.30). When analysing acute AEs separately, ≥G3 toxicity occurred in 13/80 patients (16.2%) in the no RT group and 7/67 (10.4%) in the RT group (p = 0.31). Late ≥G3 AEs were observed in 8/80 (10.0%) and 5/67 (7.5%) patients, respectively (p = 0.59) **(Table 2)**. **No significant association was found between concomitant RT and overall (p = 0.30), acute (p = 0.31), or late (p = 0.59) severe AEs.**
EQD2 (<50Gy vs ≥50Gy) and BED (<50Gy vs ≥50Gy) were not associated with acute or late toxicity of any grade. **Age ≥50 years was the only factor significantly associated with an increased risk of acute toxicity (p = 0.035).** ILD of ≥G2 occurred in 7/67 patients (10.4%) in the RT cohort and 7/80 (8.8%) in the no RT cohort. Among patients with BM in the RT cohort, 32/42 (76.2%) received intracranial irradiation (39 lesions). Intracranial RT was not associated with ≥G3 acute (p = 0.69), ≥G3 late (p = 1.00), any-grade acute (p = 0.32), or late AEs (p = 0.27). One case of symptomatic radionecrosis (SRN) was reported after fractionated stereotactic RT (fSRT; 25 Gy in 5 fractions to >5 lesions), at a median follow-up of 11 months. CNS techniques included whole-brain RT (WBRT, n=12/39; 30.7%), fSRT, (n=20/39; 51.3%), and stereotactic radiosurgery (SRS, n=7/39; 18.0%). All patients were treated for intact BM; none underwent surgery followed by RT to the surgical cavity.

Discussion

To our knowledge, we reported the largest retrospective series evaluating the safety and efficacy of T-DXd in combination with RT comparing to a control group of patients who did not receive RT. Nevertheless, we acknowledge the major limitations inherent to a real-world, retrospective analysis.

Conclusions

Concomitant administration of T-DXd and RT appears feasible and well tolerated, without an apparent increase in severe acute or late AEs. Prospective studies are warranted to optimise sequencing and assess long-term outcomes.

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