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EDITORIAL

Expanding the role of systemic therapy for patients with active, HER2-positive breast cancer brain metastases

Approximately half of all patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer will be diagnosed with brain metastases over the course of their disease.[1] Traditionally, due to a belief that the blood—brain barrier (BBB) precludes the activity of most systemic therapies in the central nervous system (CNS), and a lack of high-level evidence for systemic therapy in the treatment of patients with active brain metastases, radiotherapy [e.g. whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS)] has been the default therapeutic modality offered to patients. However, advances in systemic therapy challenge the long-held assumption that permeability across an intact BBB is required for therapeutic activity in the CNS.[2] Furthermore, as systemic therapies demonstrate higher and clinically relevant levels of intracranial activity and longer survival, an increasingly common therapeutic dilemma is how to weigh the options of radiotherapy versus systemic therapy (and deferral of radiation) in patients with active (new or progressive) brain metastases,[3] and how to sequence available systemic therapies.

Trastuzumab deruxtecan (T-DXd) is an antibody—drug conjugate (ADC) made up of a HER2-targeted monoclonal antibody and topoisomerase-1 inhibitor payload. Based on results of the DESTINY-Breast03 clinical trial, T-DXd is now firmly established as a second-line option in patients with HER2-positive, metastatic breast cancer.[4,5] The benefit of T-DXd over ado-trastuzumab emtansine (T-DM1) was maintained in the subset of patients with stable treated brain metastases at baseline [hazard ratio (HR) for progression-free survival 0.25, 95% confidence interval (CI) 0.13-0.45]. Among patients with stable brain metastases enrolled onto DESTINY-Breast01 and DESTINY-Breast03, the intracranial objective response rate (CNS-ORR) has been reported as 50% (7/14 patients) and 64% (23/36 patients), respectively.[6,7] However, patients had to have stable, previously treated brain metastases to enter the trials; patients with active brain metastases were excluded from participation. It is thus impossible to fully glean from these trials how much of the intracranial response was contributed by prior local therapy to brain metastases and how much was contributed by T-DXd, although the difference in CNS-ORR favoring T-DXd over T-DM1 in DESTINY-Breast03 strongly suggests that T-DXd had a role in the observed intracranial responses.

Results of the TUXEDO-1 clinical trial (NCT04752059), recently published by Bartsch and colleagues,[8] partially fill in the evidence gap left by DESTINY-Breast01 and DESTINY-Breast03. Investigators enrolled a total of 15 patients with HER2-positive breast cancer who had newly diagnosed, untreated brain metastases or brain metastases progressing after previous local therapy to receive T-DXd at the standard starting dose and schedule of 5.4 mg/kg intravenously every 3 weeks. Importantly, median time from last CNS-directed local therapy was 13 months (range, 5-65 months), and patients with prior radiation treatment had to progress after radiation to enter the trial; hence, any CNS responses observed were likely due to T-DXd. At a median follow-up of 12 months, the CNS-ORR was 73.3% (95% CI 48.1%-89.1%), with two complete responses and nine partial responses. In the per-protocol population, the clinical benefit rate was an astonishing 92.9% (95% CI 66.1%-99.8%). Median progression-free survival was 11.4 months and did not differ by receipt of prior local therapy, T-DM1 exposure, hormone receptor status, or even performance status. Among six patients with newly diagnosed, previously untreated brain metastases, the response rate was 100%. Reassuringly, no new safety signals were observed in this patient population.

Several other groups have also recently reported their experiences with T-DXd in patients with active brain metastases. In the DEBBRAH trial, Pérez-García and colleagues[9] observed a CNS-ORR in two of four patients with asymptomatic, untreated brain metastases, and a CNS-ORR of 44% (95% CI 13.7-78.8) in nine patients with progressive brain metastases after prior local therapy. In a multi-institution case series, the CNS-ORR in 10 patients with active brain metastases at initiation of T-DXd was 70%.[10] Taken together, the evidence, though based on a relatively small number of patients, strongly supports intracranial activity of T-DXd in patients with both stable and active, HER2-positive, breast cancer brain metastases.

How is it that an ADC such as T-DXd can exert intracranial activity given its large molecular size? The answer likely lies in the more permeable nature of the blood—tumor—barrier, compared with the intact BBB.[11] It has been known for more than a decade that monoclonal antibodies such as trastuzumab can cross into brain metastases *in vivo*.[12] In preclinical models, both increasing doses of trastuzumab and the use of the ADC (T-DM1) are associated with intracranial tumor responses and prolonged mouse survival.[13] These preclinical observations have subsequently been confirmed in prospective clinical trials. Specifically, the phase II PATRICIA trial demonstrated intracranial responses

and clinical benefit simply by increasing exposure to intravenous trastuzumab.[14] The phase IIIb KAMILLA study reported a CNS-ORR of 43% in patients with measurable brain metastases at baseline, and CNS-ORR of 49% in patients with newly diagnosed, previously untreated brain metastases.[15] With T-DXd, intracranial activity has been reported in preclinical models of both HER2-positive and HER2-low breast cancer,[10] and could have predicted the clinical activity observed to date. Finally, these observations are not limited to HER2-directed ADCs. Indeed, sacituzumab govitecan also induces intracranial responses in preclinical models.[16] Furthermore, therapeutic levels of the SN-38 payload have been measured in patients with breast cancer exposed to sacituzumab govitecan prior to resection of a brain metastasis, and subsequent responses of unresected CNS lesions have been observed,[17] albeit in a very small study. There are several important lessons to take away from these experiences: (i) the inability of a compound to cross an intact BBB does not preclude CNS activity, (ii) preclinical activity in brain metastasis models does appear in many cases to be predictive of clinical intracranial activity, and (iii) ADCs as a class may exert intracranial activity. At the least, results of the TUXEDO-1 trial should spur heightened interest in evaluating the role of T-DXd in patients with HER2-low breast cancer brain metastases and those with brain metastases from other solid tumors, as well as for ADCs as a class in patients with brain metastases across solid tumors.

An important question raised, but not answered, by the TUXEDO-1 study is the optimal sequence of T-DXd relative to tucatinib—capecitabine—trastuzumab in patients with HER2-positive breast cancer brain metastases. In contrast to the small numbers of patients with stable or active brain metastases treated on published T-DXd trials to date, HER2CLIMB enrolled 291 patients with brain metastases. Notably, 174 patients had active brain metastases at study entry.[18] The addition of tucatinib to trastuzumab—capecitabine resulted in a >9-month absolute gain in median overall survival (HR 0.60; $P = 0.007$; median 12.5 versus 21.6 months),[19] and this difference was also seen in the subset of patients with active brain metastases. Given the dramatic survival gain reported and the much larger sample size of patients with brain metastases included in HER2CLIMB, compared with TUXEDO-1, DEBBRAH, DESTINY-Breast01, or DESTINY-Breast-03, for now, tucatinib—capecitabine—trastuzumab is the more evidence-based choice for patients with brain metastases, unless there is significant concurrent extracranial disease progression, in which case T-DXd may be preferred. However, a number of ongoing clinical trials further exploring the intracranial activity of T-DXd, including DESTINY-Breast12 (NCT04739761), HER2CLIMB-04 (T-DXd + tucatinib; NCT04539938), and other combinations (T-DXd + ZN-1041; NCT04487236) should add to the evidence base regarding the use of T-DXd in patients with brain metastases, and provide more data upon which to base sequencing decisions in the future.

Finally, if confirmed, a CNS response rate >70%, clinical benefit rate >90%, and durable disease control both intracranially and extracranially raise an important philosophical and very practical question: what is the threshold needed to make systemic therapies (as opposed to local therapy) the default modality for patients with active brain metastases? Although we generally think of local therapies as highly effective, when CNS response rates are rigorously evaluated in prospective trials, they are perhaps lower than assumed. In a randomized phase II trial limited to patients with HER2-positive breast cancer, a CNS-ORR of 42% at 4 weeks[20] was observed in the WBRT alone control arm. In a retrospective study limited to patients with HER2-positive breast cancer brain metastases, CNS-ORR after SRS alone was 57%.[21] In the future, we may come to a point where we routinely treat brain metastases as we treat liver or bone metastases, that is, systemic therapy is the default, with local therapies reserved for situations in which rapid palliation is required or systemic therapies are felt unlikely to be effective. In the CNS this is increasingly important as patients survive longer, given neurocognitive toxicity with WBRT and the potential for radiation necrosis with SRS, particularly on retreatment.

In summary, the TUXEDO-1 trial adds to the evidence base supporting intracranial activity of T-DXd in patients with HER2-positive breast cancer metastases. Although the sample size was limited, it represents the largest prospective clinical trial experience published to date inclusive of patients with active brain metastases, and a significant advance for a population of patients with unmet medical need.

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REFERENCES

1. Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). *Lancet Oncol*. 2013;14(3):244-248.
2. Lin NU. Reevaluating the role of antibody—drug conjugates in the treatment of patients with brain metastases. *Ann Oncol*. 2020;31(10):1279-1281.
3. Ramakrishna N, Anders CK, Lin NU, et al. Management of advanced human epidermal growth factor receptor 2—positive breast cancer and brain metastases: ASCO guideline update. *J Clin Oncol*. 2022;40(23):2636-2655.

4. Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. 2022;386(12):1143-1154.
5. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32(12):1475-1495.
6. Jerusalem GHM, Park YH, Yamashita T, et al. Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: a subgroup analysis of the DESTINY-Breast01 trial. *J Clin Oncol*. 2021;39(suppl 15):526.
7. Hurvitz S, Kim S-B, Chung W-P, et al. Abstract GS3-01: Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03. *Cancer Res*. 2022;82(suppl 4):GS3-01-GS3-01.
8. Bartsch R, Berghoff AS, Furtner J, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. *Nat Med*. 2022;28(9):1840-1847.
9. Pérez-García JM, Vaz Batista M, Cortez P, et al. Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: the DEBBRAH trial. *Neuro Oncol*. 2022. https://doi.org/10.1093/neuonc/noac144. In press.
10. Kabraji S, Ni J, Sammons S, et al. Preclinical and clinical efficacy of trastuzumab deruxtecan in breast cancer brain metastases. *Clin Cancer Res*. 2022. In press.
11. Lockman PR, Mittapalli RK, Taskar KS, et al. Heterogeneous blood—tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. *Clin Cancer Res*. 2010;16(23):5664-5678.
12. Dijkers EC, Oude Munnink TH, Kosterink JG, et al. Biodistribution of 89Zr-trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. *Clin Pharmacol Ther*. 2010;87(5):586-592.
13. Lewis Phillips GD, Nishimura MC, Lacap JA, et al. Trastuzumab uptake and its relation to efficacy in an animal model of HER2-positive breast cancer brain metastasis. *Breast Cancer Res Treat*. 2017;164(3):581-591.
14. Lin NU, Pegram M, Sahebjam S, et al. Pertuzumab plus high-dose trastuzumab in patients with progressive brain metastases and HER2-positive metastatic breast cancer: primary analysis of a phase II study. *J Clin Oncol*. 2021;39(24):2667-2675.
15. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial. *Ann Oncol*. 2020;31(10):1350-1358.
16. Brenner AJ, Pandey R, Chiou J, et al. 373MO Delivery and activity of SN-38 by sacituzumab govitecan in CNS tumours. *Ann Oncol*. 2020;31:S401.
17. Brenner AJ, Pandey R, Chiou J, et al. Abstract PD13-05: Delivery and activity of SN-38 by sacituzumab govitecan in breast cancer brain metastases. *Cancer Res*. 2021;81(suppl 4):PD13-05-PD13-05.
18. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610-2619.
19. Lin NU, Murthy RK, Abramson V, et al. Abstract PD4-04: Updated results of tucatinib vs placebo added to trastuzumab and capecitabine for patients with previously treated HER2-positive metastatic breast cancer with brain metastases (HER2CLIMB). *Cancer Res*. 2022;82(suppl 4):PD4-04-PD4-04.
20. Ah Kim I, Winter K, Sperduto P, et al. CTNI-05. NRG Oncology/ RTOG 1119: Phase II randomized study of whole brain radiotherapy/stereotactic radiosurgery with concurrent lapatinib in patients with brain metastases from Her2-positive breast cancer. *Neuro Oncol*. 2020;22(suppl 2):ii42.
21. Kim JM, Miller JA, Kotecha R, et al. Stereotactic radiosurgery with concurrent HER2-directed therapy is associated with improved objective response for breast cancer brain metastasis. *Neuro Oncol*. 2019;21(5):659-668.