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The blood-brain barrier limits the therapeutic efficacy of antibody-drug conjugates in glioblastoma

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Therapeutic targeting of oncogenic pathways that aims at inhibiting pathway "activity" in glioblastoma (GBM) faces several hurdles including the existence of redundant pathways and the development of compensatory mechanisms that lead to resistance. An alternative approach consists of the use of antibody-drug conjugates (ADC) that combine the targeting of highly expressed surface molecules with toxins that kill the tumor cell. A promising and clinically advanced ADC is Depatuxizumab mafodotin (Depatux-M). It consists of an Epidermal Growth Factor Receptor (EGFR)-targeting antibody that is conjugated to monomethyl auristatin F (MMAF). Internalization of the ADC leads to the release of cysteine-mc-MMAF, which inhibits microtubule polymerization. Because EGFR is amplified and/or mutated in a large subset of GBM, Depatux-M was viewed as a promising drug for the therapy of these deadly tumors and tested in clinical trials.

Two large recent studies failed to support clinical benefit of Depatux-M in GBM. INTELLANCE-2 was a randomized phase II trial in recurrent GBM with EGFR amplification; it compared Depatux-M alone or combined with temozolomide vs a control arm of temozolomide or lomustine.[1] Monotherapy was no better than the control arm, while combination therapy showed a trend towards improved overall survival. INTELLANCE-1 randomized newly diagnosed GBM patients with EGFR amplification to standard chemoradiation +/– Depatux-M and failed to show a survival benefit (AB Lassman, SNO Annual Meeting 2019). A recent study by Marin et al published in this journal sought to determine the reasons for the clinical failure of Depatux-M and uncovered evidence that heterogeneous distribution of the ADC across the blood-brain barrier (BBB) is a major factor in limiting its clinical efficacy in GBM.[2]

To uncover the mechanism(s) underlying the clinical failure of Depatux-M in GBM, Marin et al conducted a study that used PDX models with varying EGFR characteristics. In vitro testing of the PDXs' sensitivity to Depatux-M showed that PDXs that have EGFR amplification leading to high expression of the receptor were significantly more sensitive to the ADC than those with no EGFR amplification and lower receptor expression. A similar finding was also observed in vivo in heterotypic (flank) xenografts derived from the same PDXs. Specifically, most animals with EGFR amplified heterotypic xenografts exhibited a significant prolongation of animal survival, while animals with no EGFR amplified xenografts were unresponsive to Depatux-M systemic administration. However, some of the initially responsive xenografts recurred, suggesting acquired or inherent resistance to Depatux-M. Using a combination of screening and molecular approaches, the authors investigated the mechanisms of resistance to Depatux-M and identified EGFR expression downregulation and the development of a short EGFR variant lacking the antibody epitope as the main causes of ADC resistance. The efficacy of Depatux-M was subsequently evaluated using orthotopic (intracranial) xenografts derived from the same PDXs. In contrast to near-uniform activity of Depatux-M in flank tumors, only two of the orthotopic PDXs were responsive to systemic delivery of Depatux-M. Measurement of Depatux-M in the xenografts and additional experimental evidence indicated that poor drug delivery across the BBB was responsible for the limited drug efficacy. This was confirmed by the demonstration that BBB disruption with VEGFA or direct convection-enhanced delivery of Depatux-M restored tumor sensitivity to Depatux-M. Altogether, the above data show that heterogeneous delivery across the BBB limits the efficacy of an EGFR-targeting ADC in GBM and that resistance to the ADC can develop via EGFR expression downregulation or mutations leading to loss of the antibody epitope.

The findings of the above-described study indicate that limited drug delivery of the Depatux-M ADC into brain tumors may have been a key contributor to lack of efficacy in the recently failed clinical trials. This could partly explain the greater success of ADCs in some extracranial malignancies[3] and suggests that approaches to open the BBB or local delivery of ADCs would improve the efficacy of these promising drugs. Despite its scientific and practical usefulness, one limitation of the findings is that they are derived from an animal model, albeit one that uses representative human xenografts. Whether the findings reflect what occurred in the GBM

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clinical trials remains to be determined. This would have required the analysis of tumor tissues from the clinical trials, which are not easily accessible for such studies. Besides knowledge about the role of the BBB in limiting ADC therapeutic efficacy, another interesting finding of the study is the development of resistance to the ADC in originally responsive xenografts via receptor downregulation or mutation. This is likely to pose a greater challenge that will be much more difficult to overcome in the long term than overcoming BBB and tumor drug penetration. Additionally, tumor heterogeneity and the likely absence of EGFR expression in many individual tumor cells in any given tumor, even those with amplified EGFR, further diminishes the promise of ADC use for GBM therapy.

Several lines of evidence, as reviewed by Marin and elsewhere[4] suggest antibodies do not achieve good penetration of an intact BBB. The importance of "window of opportunity" studies to assess whether agents reach not only areas of GBM with permeable BBB as reflected in gadolinium contrast enhancement but also non-enhancing surrounding tissue with infiltrating tumor cells has long been known.[5] Nonetheless, such studies with therapeutic antibodies in neuro-oncology are rare, with none published through December 2019,[6] perhaps reflecting an underlying assumption of discouraging results. Against this backdrop, the paucity of such data in the development of Depatux-M runs counter to accepted neuro-oncological principles. We identified a single case of the ^{111}indium-labeled antibody manifesting uptake into a high-grade astrocytoma, with neither quantification of degree of uptake or correlation with gadolinium contrast enhancement.[7] Careful preclinical studies like that of Marin, or window of opportunity studies, likely would have obviated the need to expose hundreds of patients with GBM to an ineffective agent.

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