Triple-negative breast cancer intracranial metastases

see also Breast cancer intracranial metastases.

- Breast Cancer Brain Metastases: A Neurosurgical Point of View From a Single-Center Experience
- Nivolumab and stereotactic radiosurgery for patients with breast cancer brain metastases: long-term results and biomarker analysis from a non-randomized, open-label, phase Ib study
- A Rare Cause of Nuchal Rigidity: Metastatic Triple-Negative Breast Cancer Involving the Skull and Upper Cervical Spine
- Emerging Therapies for Brain Metastases in NSCLC, Breast Cancer, and Melanoma: A Critical Review
- Efficacy and safety of anlotinib for triple-negative breast cancer with brain metastases
- Intracranial outcomes following neurosurgical resection in patients with brain metastases secondary to HER2-positive breast cancer versus other subtypes
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- Activity of capecitabine for central nervous system metastases from breast cancer

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Almost half of TNBC patients will develop distant metastasis during the disease course, and the median survival time is only 13.3 months after metastasis [1)]

The brain is one of the most common sites of BC metastasis and the first site in 12% of metastatic patients [2) 3)]

Treatment

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SRS is a safe and efficacious treatment for well-selected patients with triple-negative breast cancer, especially for those with favorable performance status and small- to moderate-volume metastatic

lesions [4].

Prognosis

Triple-negative breast cancer intracranial metastases (BM) face dismal prognosis due to the limited therapeutic efficacy of the currently available treatment options.

Carney et al. demonstrated that paclitaxel-loaded PLGA-PEG nanoparticles (NPs) directed to the Fn14 receptor, termed “DARTs”, are more efficacious than Abraxane–an FDA-approved paclitaxel nanoformulation–following intravenous delivery in a mouse model of TNBC BM. However, the precise basis for this difference was not investigated. Here, we further examine the utility of the DART drug delivery platform in complementary xenograft and syngeneic TNBC BM models. First, we demonstrated that, in comparison to nontargeted NPs, DART NPs exhibit preferential association with Fn14-positive human and murine TNBC cell lines cultured in vitro. We next identified tumor cells as the predominant source of Fn14 expression in the TNBC BM-immune microenvironment with minimal expression by microglia, infiltrating macrophages, monocytes, or lymphocytes. We then show that despite similar accumulation in brains harboring TNBC tumors, Fn14-targeted DARTs exhibit significant and specific associations with Fn14-positive TNBC cells compared to nontargeted NPs or Abraxane. Together, these results indicate that Fn14 expression primarily by tumor cells in TNBC BMs enables selective DART NP delivery to these cells, likely driving the significantly improved therapeutic efficacy observed in our prior work [5].

Lau et al. previously identified a complex between receptor tyrosine kinase c-Met and β1 integrin in metastases. Using novel cell culture and in vivo assays, they found that c-Met/β1 complex induction promotes intravasation and vessel wall adhesion in triple-negative breast cancer cells, but does not increase extravasation. These effects may be driven by the ability of the c-Met/β1 complex to increase mesenchymal and stem cell characteristics. Multiplex transcriptomic analysis revealed upregulated Wnt and hedgehog pathways after c-Met/β1 complex induction. A β1 integrin point mutation that prevented binding to c-Met reduced intravasation. OS2966, a therapeutic antibody disrupting c-Met/β1 binding, decreased breast cancer cell invasion and mesenchymal gene expression. Bone-seeking breast cancer cells exhibited higher c-Met/β1 complex levels than parental controls and preferentially adhered to the tissue-specific matrix. Patient bone metastases demonstrated a higher c-Met/β1 complex than brain metastases. Thus, the c-Met/β1 complex drives intravasation of triple-negative breast cancer cells and preferential affinity for bone-specific matrix. Pharmacological targeting of the complex may prevent metastases, particularly osseous metastases [6].

Das et al. employed derivatives of BT-549 and MDA-MB-468 TNBC cell lines that were adapted to grow in the presence of either 5-Fluorouracil, Doxorubicin or Docetaxel in an aim to identify molecular pathways involved in the adaptation to drug-induced cell killing. All six drug-adapted BT-549 and MDA-MB-468 cell lines displayed cross-resistance to chemotherapy and decreased apoptosis sensitivity. Expression of the anti-apoptotic co-chaperone BAG3 was notably enhanced in two-thirds (4/6) of the six resistant lines simultaneously with higher expression of HSP70 in comparison to parental controls. Doxorubicin-resistant BT-549 (BT-549rDOX20) and 5-Fluorouracil-resistant MDA-

MB-468 (MDA-MB-468r5-FU2000) cells were chosen for further analysis with the autophagy inhibitor Bafilomycin A1 and lentiviral depletion of ATG5, indicating that enhanced cytoprotective autophagy partially contributes to increased drug resistance and cell survival. Stable lentiviral BAG3 depletion was associated with a robust down-regulation of Mcl-1, Bcl-2 and Bcl-xL, restoration of drug-induced apoptosis and reduced cell adhesion in these cells, and these death-sensitizing effects could be mimicked with the BAG3/Hsp70 interaction inhibitor YM-1 and by KRIBB11, a selective transcriptional inhibitor of HSF-1. Furthermore, BAG3 depletion was able to revert the EMT-like transcriptional changes observed in BT-549rDOX20 and MDA-MB-468r5-FU2000 cells.

In summary, genetic and pharmacological interference with BAG3 is capable to resensitize TNBC cells to treatment, underscoring its relevance for cell death resistance and as a target to overcome therapy resistance of breast cancer [7].

References

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