Blood pressure drug may prevent immunotherapy-induced brain swelling in patients with glioblastoma

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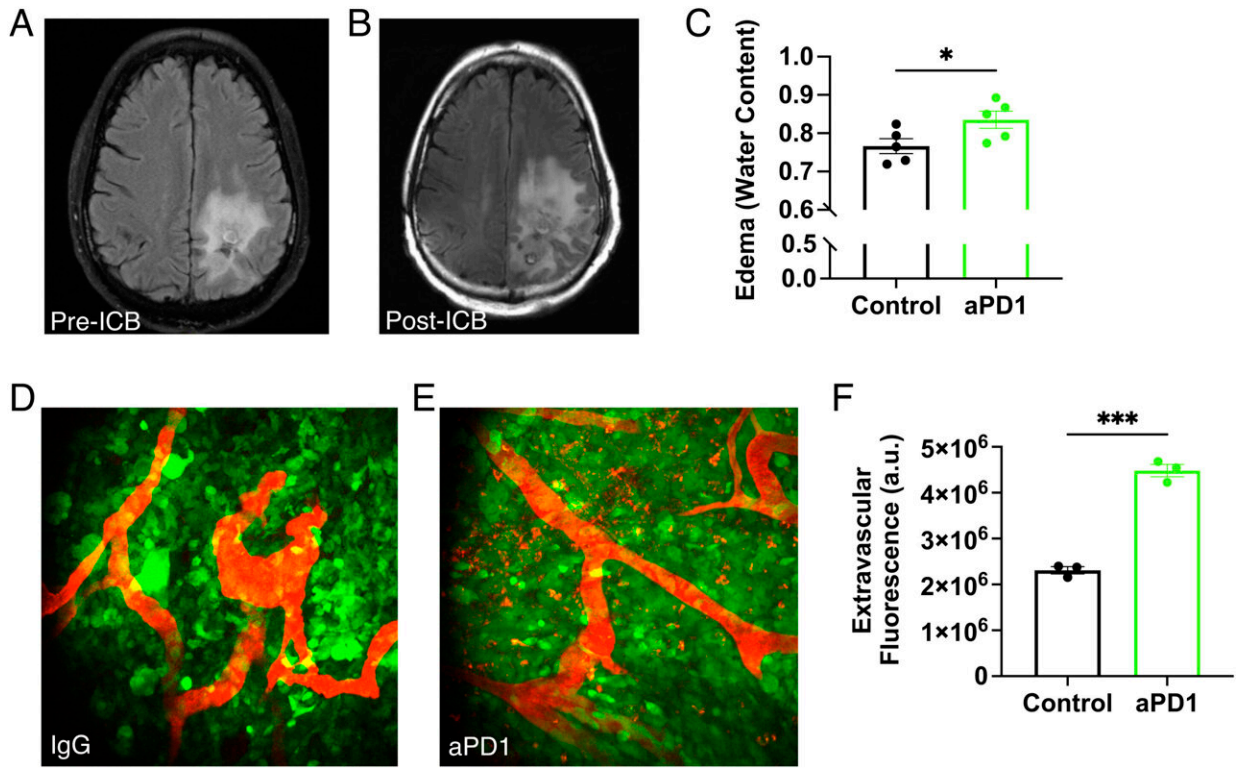

ICB increases GBM vascular leakage and induces brain edema. MR T2-weighted-Fluid-Attenuated Inversion Recovery (T2-FLAIR) images obtained from a recurrent GBM patient (A) before and (B) after 4 mo of anti-PD-L1 (MEDI4763; NCT02336165) treatment show increased edema after ICB treatment. In addition to ICB-induced inflammation, this change may be due in part to underlying tumor activity or growth. (C) In mice, anti-PD1 antibody (aPD1) treatment increases edema in GL261 tumors compared to IgG control [as measured by wet-dry weight (i.e., water content) evaluation of tumor tissue; n =

5]. Multiphoton visualization of the brain vasculature via injected tetramethylrhodamine (TAMRA) labeled albumin (red) imaged through transparent cranial windows in mice bearing GFP+ GL261 GBM (green) shows that compared to IgG controls (D) there is increased extravasation in anti-PD1-treated tumors after the third consecutive dose (E). (F) Quantification shows that more albumin in anti-PD1-treated mice has leaked outside of the tumor blood vessels (n = 3). (Bar plots: mean ± SEM; Student's unpaired t test; *P Proceedings of the National Academy of Sciences (2023). DOI: 10.1073/pnas.2219199120

Patients with glioblastoma—the deadliest type of primary brain tumor—may potentially benefit from immunotherapy medications called immune checkpoint inhibitors that stimulate an immune response against cancer cells.

However, they may also experience brain swelling, or cerebral edema, during treatment.

Cerebral edema is currently controlled by steroids that are highly immunosuppressive and thus, counter the benefit of immunotherapy. Thus, new drugs that control edema safely without causing immunosuppression are urgently needed.

New research led by investigators at Massachusetts General Hospital (MGH) reveals that the blood pressure drug losartan can prevent immunotherapy-induced edema.

The findings, which are published in *PNAS*, indicate that taking losartan may allow patients to continue receiving immune checkpoint inhibitors without developing adverse effects in the brain.

Through the use of mouse models of cancer, single-cell RNA

sequencing, immune cell blocking studies, and analyses of patient imaging scans, the scientists demonstrated that immunotherapy-induced edema results from an inflammatory response that disrupts the blood-tumor barrier, a modification of the blood-brain barrier that occurs with brain cancer.

This response involves the enzymes matrix metalloproteinases 14 and 15, which reside in cells lining tumor-associated blood vessels and induce blood vessel leakage to cause edema.

Experiments revealed that losartan can prevent immunotherapy-related edema by reducing the expression of these enzymes.

Losartan also had many other beneficial effects in the tumor environment that enhanced the body's anti-tumor immune response.

Combined with an immune checkpoint inhibitor, losartan improved survival in mouse models of glioblastoma, curing 20% of mice, which increased to 40% when combined with the standard of care involving chemoradiation followed by surgery.

"Cerebral edema is in and of itself a hallmark of primary brain tumors such as glioblastoma. In glioblastoma patients, we found that immune checkpoint blockade on average increases cerebral edema by approximately 20%. This is not only neurologically detrimental to patients; it can even be lethal," says senior author Rakesh K. Jain, Ph.D., director of the E.L. Steele Laboratories for Tumor Biology at Massachusetts General Hospital and the Andrew Werk Cook Professor of Radiation Oncology at Harvard Medical School.

"Most patients who experience edema receive steroids to reduce the brain swelling; however, these drugs are highly immunosuppressive and thus counteract the effects of immunotherapy. Therefore, we have

identified a viable pharmaceutical option for edema control that addresses the underlying mechanism of immunotherapy-induced edema, and also sensitizes the tumor microenvironment to immune checkpoint blockade therapy."

Jain notes that because losartan is safe, effective, and affordable, it can be readily prescribed along with immunotherapy to patients with glioblastoma.

Building on their previous approach published in *PNAS* in 2020 to identify biomarkers of response to immunotherapy, the team also identified factors in the tumor environment that may predict which patients are most likely to benefit from such a combination.

More information: Meenal Datta et al, Losartan controls immune checkpoint blocker-induced edema and improves survival in glioblastoma mouse models, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2219199120

Ivy X. Chen et al, A bilateral tumor model identifies transcriptional programs associated with patient response to immune checkpoint blockade, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2002806117

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