TABLE 1. Outcomes of Blood Pressure Treatment in the < 150 mm Hg and < 180 mm Hg Target Groups

	<150 mm Hg Target (n = 37)	<180 mm Hg Target (n = 36)	*P* Value
Relative perfusion measures (mean ± SD)			
Perihematoma rCBF	0.86 ± 0.12	0.89 ± 0.09	0.18
Ipsilateral hemispheric rCBF	0.95 ± 0.05	0.99 ± 0.05	0.001
Perihematoma rCBV	0.90 ± 0.14	0.91 ± 0.15	0.73
Ipsilateral hemispheric rCBV	0.98 ± 0.05	0.99 ± 0.06	0.59
Absolute perfusion measures (mean ± SD)			
Perihematoma absolute CBF, mL/100 g per min	38.88 ± 12.98	38.56 ± 10.81	0.91
Ipsilateral hemispheric absolute CBF, mL/100 g per min	42.42 ± 12.05	41.79 ± 8.68	0.80
Contralateral hemispheric absolute CBF, mL/100 g per min	44.49 ± 12.22	42.18 ± 8.40	0.35
Perihematoma absolute CBV, mL/100 g	3.81 ± 0.65	3.48 ± 0.72	0.05
Ipsilateral hemispheric absolute CBV, mL/100 g	3.99 ± 0.58	3.67 ± 0.65	0.03
Contralateral hemispheric absolute CBV, mL/100 g	4.07 ± 0.58	3.71 ± 0.65	0.02
ICH volume change (2 h post randomization)	(n = 39)	(n = 36)	
Absolute growth (median, IQR)	0.67 (–0.08 to –3.75)	0.71 (–0.04 to –2.91)	0.53
Growth >6 mL	8 (21%)	8 (22%)	0.86
Growth >1/3	9 (24%)	4 (11%)	0.17
Clinical outcomes (median, IQR)			
GCS Score (2 h)	15 (11–15)	15 (13–15)	0.50
NIHSS Score (2 h)	11 (6–17)	13 (5–17)	0.75
GCS Score (24 h)	15 (10.75–15)	14 (13–15)	0.64
NIHSS Score (24 h)	10 (5–19)	12 (6–20)	0.85
30-day mortality	7 (17.9%)	4 (11.1%)	0.40
90-day Barthel Index	95 (70–100)	95 (40–100)	0.51
90-day mRS	2.5 (1–5.75)	4 (2–5)	0.65

CBF, cerebral blood flow; CBV, cerebral blood volume; GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, national institutes of health stroke scale; rCBF, relative CBF; rCBV, relative CBV.

and morbidity rates among target groups. The 30-day mortality was noted to be 17.9% in the < 150 mm Hg target group compared to 11.1% in the < 180 mm Hg group ($P = .40$) (Table 1). The morbidity rate as noted by the NIHSS score, 2 hours and 24 hours after randomization, was not significantly different among target groups (Table 1). Similar results were noted on the 90-day BI scores ($P = .51$) and 90-day mRS scores ($P = .65$). Of note, the median mRS scores in the < 150 mm Hg and < 180 mm Hg target groups were 2.5 and 4, respectively (Table 1).

This clinical trial showed that early reduction of blood pressure in patients presenting with spontaneous ICH does not significantly affect perihematoma CBF. Moreover, despite its notable effect on relative CBF in ipsilateral cerebral hemispheres, blood pressure reduction in the management of spontaneous ICH was shown not to significantly impact mortality and morbidity. This observation lends further support to the 2010 guidelines for the management of spontaneous ICH which stated that "in patients presenting with a systolic blood pressure of 150 to 220 mm Hg, acute lowering of systolic blood pressure to 140 mm Hg is probably safe".[1]

Tarek Y. El Ahmadieh
Najib E. El Tecle
Rishi R. Lall
Anne E. Park
Bernard R. Bendok

REFERENCES

1. Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41(9):2108-2129.
2. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*. 2005;365(9457):387-397.
3. Qureshi AI, Palesch YY, Martin R, et al. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study. *Arch Neurol.* 2010;67(5):570-576.
4. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S. Effects of blood pressure levels on case fatality after acute stroke. *J Hypertens.* 2005;23(6):1217-1223.
5. Naidech AM, Bernstein RA, Bassin SL, et al. How patients die after intracerebral hemorrhage. *Neurocrit Care.* 2009;11(1):45-49.
6. Olivot JM, Mlynash M, Kleinman JT, et al. MRI profile of the perihematomal region in acute intracerebral hemorrhage. *Stroke*. 2010;41(11):2681-2683.
7. Pascual AM, Lopez-Mut JV, Benlloch V, Chamarro R, Soler J, Lainez MJ. Perfusion-weighted magnetic resonance imaging in acute intracerebral hemorrhage at baseline and during the 1st and 2nd week: a longitudinal study. *Cerebrovasc Dis.* 2007;23(1):6-13.
8. Butcher KS, Jeerakathil T, Hill M, et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial. *Stroke*. 2013;44(3):620-626.
9. Butcher K, Jeerakathil T, Emery D, et al. The Intracerebral Haemorrhage Acutely Decreasing Arterial Pressure Trial: ICH ADAPT. *Int J Stroke.* 2010;5(3):227-233.

The Intersection Between Genetic Engineering and Immunotherapy: Taking a BiTE out of Glioblastoma

Conventional methods for the treatment of glioblastoma multiforme (GBM) are nonspecific and are limited by the consequent damage to normal brain tissue. Such methods including, chemotherapy radiation therapy, and gross total resection, may prolong median survival time to 15 months but can be deleterious to the patient's quality of life. New treatment modalities arising from novel genetic recombination techniques and cell-mediated immunotherapy may provide a promising treatment strategy to treating patients with GBM.

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited.

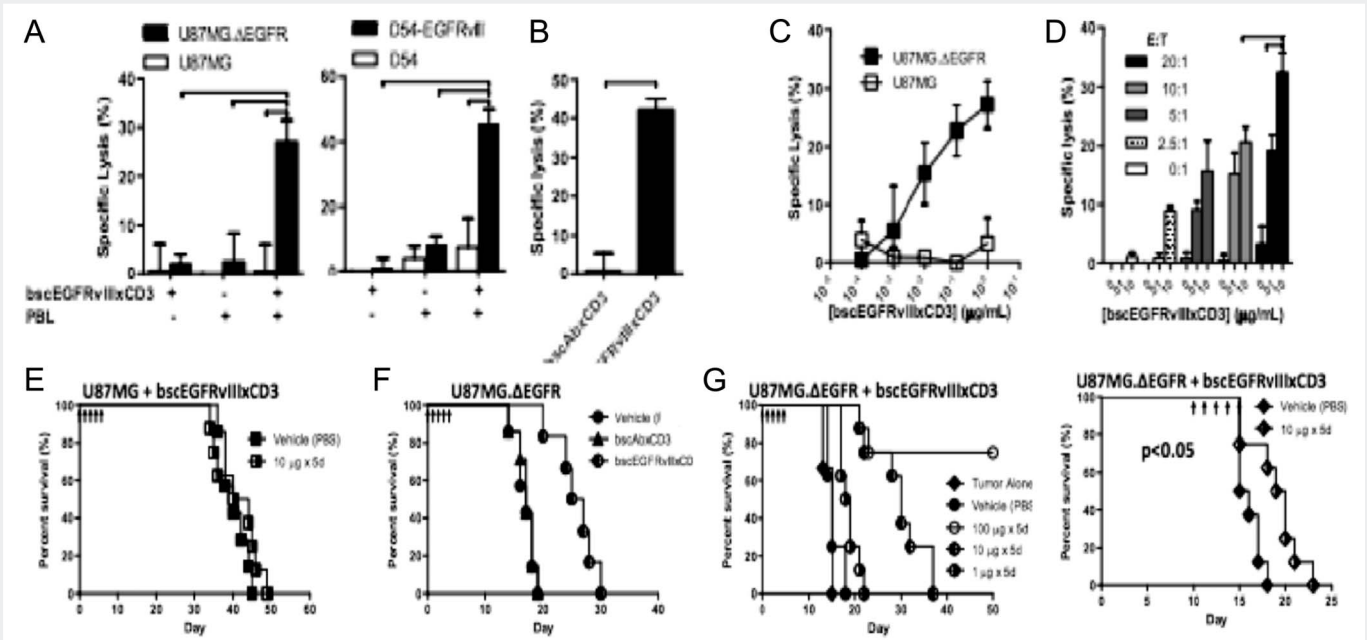

Figure. Specific targeting of genetically engineered BiTE monoclonal antibody in GBM. **A**, *Cr-release demonstrates specific lyses of U87MGΔEGFR over U87MG (left) and D54-EGFRvIII over D54 (right) in the presence of BscEGFRvIIIxCD3.* **B**, *specific lysis is not observed in the presence of negative control bscABxCD3.* **C**, *specific lysis varies proportionally with dosage.* **D**, *dose response is maintained over varying effecter : target ratios. Antitumor response produced by mice implanted with (***E***) U87MG or (***F***) U87MG.ΔEGFR and treated with bscEGFRvIIIxCD3.* **G**, *(right) dose response curve showing bscEGFRvIIIxCD3 administration to mice and (left) delayed treatment of bscEGFRvIIIxCD3 in mice expressing U87MG.ΔEGFR.*

T cell mediated antitumor immune responses have received notable recent attention. The ability to mount an immune response that discriminately targets a specific antigen provides an eloquent method of targeting cancer cells without the disastrous side effects that accompanies inflammation. Work published by Choi et al (***PNAS*, November 2012**) demonstrates the potential of bispecific antibodies as a tool to elicit cytotoxicity from circulating T cells only in the vicinity of the enticing antigen. These so-called bispecific T-cell engagers (BiTE), have dual functionality whereby their single variable antibody fragment (scFv) can simultaneously target specific tumors cells and the T-cell activation ligand (CD3). The dual nature of these BiTE antibodies provides the capability of inducing an immunologic response without the need for costimulatory signals.

The authors show the therapeutic capabilities of BiTES, via specific targeting against the mutant EGF receptor (EGFRvIII), and its ability to penetrate the CNS. EGFRvIII is a constitutively active tyrosine kinase not found in normal tissue but over expressed in GBM. Their work demonstrates that EGFRvIII-targeted BiTE (bscEGFRvIIIxCD3) molecules are antigen specific, highly cytotoxic, and can activate T cells leading to the exclusive secretion of Th1-type cytokines.

The authors genetically engineered both svFc regions by joining both domains to a flexible linker region to ultimately generate a fusion protein capable of redirecting T cells against cancer cells *in vitro*. The authors showed localized cytotoxicity and cancer-specific cell lysis which was dependent on the ability of the BiTE antibody to recognize both the target antigen and the effecter T cell.

In vitro data was further supported by data collected *in vivo*; U87MG glioma cell-line mice with either the mutated EGFRvIII or the wild type EGFR were inoculated with human peripheral blood monocytes and injected with the BiTE antibody. Under these parameters, mice over expressing wild type EGFR did not show significant survival benefit as compared to those expressing the EGFRvIII mutant. Furthermore, localized treatment and antitumor effects were seen in a dose-dependent manner. Taken together, the data points to a promising treatment for GBM—ie, the potential of genetically engineered bispecific monoclonal antibodies.

Since the biology of GBM is so complex, current research is focusing on the theory of the cancer stem cell, the microenvironmental niche, and various unregulated signaling pathways. Genetic therapy, immunotherapy, or perhaps the combination of the two may provide an eloquent, minimally invasive, and highly specific modality of targeting and eradicating cancer cells. Further studies are needed to delineate the plausibility of such treatments in human subjects with GBM.

Innocent Njoku, Jr
John A. Boockvar

Magnetic Resonance Imaging Utility in Following Sciatica and Disc Herniation After Treatment

Sciatica is an almost universal condition that is fortunately self-limited in most episodes, but can often become a vexing problem leading to a variety of treatments,

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited.