Neuroepidemiology 2010;34:130

DOI: 10.1159/000274805

Reply to: Age as a Predictive Factor in Glioblastomas: Population-Based Study

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Kita et al. [1] demonstrated that age-dependent survival of patients with glioblastoma (GBM) is only apparent amongst patients who have received radiation treatment as opposed to surgery alone or best supportive care. The authors point out the important implication that age-dependent differences in GBM malignancy/survival may be manifest only upon application of therapy. Of note, the age dependency of objective responses to radiation has been reported previously for GBM [2]. As acknowledged by the authors and the author of the accompanying comment [3], the lack of controls for the Karnofsky performance status and the extent of resection may have confounded their analysis of survival. However, we would like to bring to attention a previous publication that mirrors their findings. Rosenblum et al. [4] mined previously unreported Brain Tumor Study Group data and found no differences in survival between groups of GBM patients less than or equal to 50 years of age ($n = 14$) versus those older than 50 years ($n = 35$) who had surgery only. While their sample size was small compared with that of Kita et al. [1], prognostic factors of the Karnofsky performance status and the extent of resection were equally distributed amongst their two groups. They also concluded that differential age-dependent treatment responses contribute to age-related survival for GBM patients and of importance, demonstrated that GBM stem cell sensitivity to the alkylating agent BCNU in clonogenic assays had a highly correlated inverse relationship to the age of the GBM patients from which the cells were isolated [4].

Therefore, the findings of Kita et al. [1] corroborate those of Rosenblum et al. [4] published 26 years previously, and provide further support that patient age impacts GBM survival due in part to decreased treatment response. While no ready mechanistic explanation exists for age-dependent GBM survival, the authors' extensive population-based work in molecular epidemiology has

established a benchmark for understanding human gliomas. Of note, they have shown a lack of significant age-dependent differences in EGFR amplification, TP53 or PTEN mutation, p16 deletion of LOH at 10q for GBM patients older than 34 years [5] and conclude that these common molecular genetic alterations are not likely to contribute to age-dependent GBM treatment responses. Therefore, in the 26-year interval between these two studies, little progress has been made in understanding the mechanisms which contribute to age-dependent treatment responses in GBM patients. To address this deficiency, we have studied age-dependent features of normal and transformed neural stem and progenitor cells and in a syngeneic mouse glioma model recently demonstrated that transformed neural stem and progenitor cells exhibit age-dependent malignancy in vivo [6]. Continued progress in molecular epidemiology and animal models are complementary approaches that will enhance efforts to uncover age-dependent mechanisms of gliomagenesis and treatment resistance that can be leveraged to improve patient outcomes.

References

- 1 Kita D, Ciernik IF, Vaccarella S, Franceschi S, Kleihues P, Lutolf UM, Ohgaki H: Age as a predictive factor in glioblastomas: population-based study. *Neuroepidemiology* 2009;33:17–22.
- 2 Barker FG 2nd, Chang SM, Larson DA, Sneed PK, Wara WM, Wilson CB, Prados MD: Age and radiation response in glioblastoma multiforme. *Neurosurgery* 2001;49:1288–1297.
- 3 Hutterer M: Elderly patients with glioblastoma multiforme – An underestimated subpopulation? *Neuroepidemiology* 2009;33:23–24.
- 4 Rosenblum ML, Gerosa M, Dougherty DV, Reese C, Barger GR, Davis RL, Levin VA, Wilson CB: Age-related chemosensitivity of stem cells from human malignant brain tumours. *Lancet* 1982;i:885–887.
- 5 Ohgaki H, Kleihues P: Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol* 2005;64:479–489.
- 6 Mikheev AM, Stoll EA, Mikheeva SA, Maxwell JP, Jankowski PP, Ray S, Uo T, Morrison RS, Horner PJ, Rostomily RC: A syngeneic glioma model to assess the impact of neural progenitor target cell age on tumor malignancy. *Aging Cell* 2009;8:499–501.

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