Comment re: Temozolomide Preferentially Depletes Cancer Stem Cells

To the Editor:

Beier and colleagues (1), in contrast to previous studies (2–4), show that temozolomide depletes clonogenic and highly tumorigenic cells in glioblastoma cultures and reduces tumorigenicity *in vivo*. The *in vivo* studies, however, raise concerns. Tumor xenografts were measured on T2-weighted magnetic resonance images (MRI; TR/TE 4,000/73 ms). In Fig. 6*A* of their report, the hyperintense signal of the xenograft is similar to cerebrospinal fluid (CSF). At this TR/TE value, a glial tumor without necrotic or cystic areas is expected to be less hyperintense than CSF (Fig. 1*A* and *B, arrow*). Although the MRI appearance may depend on transplantation techniques, the hyperintense signal of the xenografts seems related to regressive phenomena (5). In Fig. 6*A* of ref. 1 (*upper* and *lower left*), the ventricles homolateral to the tumor are not compressed or displaced as expected (Fig. 1*C* and *D*); conversely, they seem slightly enlarged. Furthermore, the untreated xenograft in Fig. 6*A* of ref. 1 (*upper left*) shows an extra-axial CSF collection that does not favor the presence of an underlying mass lesion.

Glioblastoma cancer stem cells (CSCs) are known to generate tumors *in vivo* that phenocopy the parent tumor, although vascularity and heterogeneity may be less prominent. In Fig. 6*B* and *C* of ref. 1, however, the xenografts lack glioblastoma features resembling foci of anaplastic astrocytoma, therefore suggesting that the grafted CSCs may have lost the grade of malignancy of parental glioblastoma.

Pretreatment with temozolomide dose-dependently reduced the size of tumor xenografts irrespective of the O^6 methylguanine-DNA methyltransferase (MGMT) status of the CSCs. Indeed, tumor size substantially decreased in mice injected with CSCs exposed to 50 μmol/L of temozolomide relative to the 5 μmol/L dose, as shown in Fig. 6*A* and *B* of ref. 1. However, Fig. 6*D* of ref. 1 shows that proliferation of R28 cells does not significantly differ between 5 and 50 μmol/L of temozolomide. Changing the interpretation of Beier and colleagues, we propose that early after implantation 50 μmol/L-temozolomide treatment had been more effective than 5 μmol/L but 12 weeks later the tumors proliferated with similar rates. Beier and colleagues show that temozolomide-treated CD133+ glioblastoma cells actually continue to proliferate *in vitro*. The same may happen when xenografting the cells. Obtaining any data on cell death would have been beneficial. Future studies are needed to fully understand the effects of temozolomide and other therapies on different tumor cell populations in this heterogenous disease.

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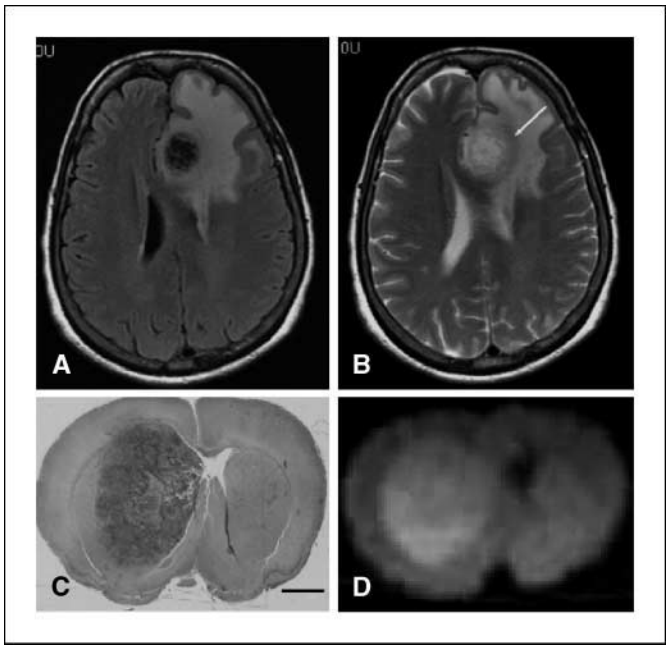

Figure 1. Human glioblastoma (*A* and *B*) and intracerebral xenograft (*C* and *D*). *A,* T2-weighted MRI (TR/TE 1800/16 msec). *B,* T2-weighted MRI (TR/TE 4200/99 msec). *C,* histological section of U87MG glioblastoma xenograft. Hematoxylin-eosin. *Bar*, 1,350 μm. *D,* gadolinium-enhanced T1-weighted MRI.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

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