Comment re: Temozolomide Preferentially Depletes Cancer Stem Cells

Roberto Pallini, Nicola Montano and Luigi M. Larocca


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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. 6A 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. 1A 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. 6A of ref. 1 (upper and lower left), the ventricles homolateral to the tumor are not compressed or displaced as expected (Fig. 1C and D); conversely, they seem slightly enlarged. Furthermore, the untreated xenograft in Fig. 6A 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. 6B 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 O6 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. 6A and B of ref. 1. However, Fig. 6D 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.

Roberto Pallini
Nicola Montano
Institutes of Neurosurgery,
Catholic University School of Medicine,
Rome, Italy

Luigi M. Larocca
Institutes of Pathology,
Catholic University School of Medicine,
Rome, Italy

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References