Editorial

Deferoxamine may enhance 5-aminolevulinic acid-based fluorescence in glioma surgery

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Glioblastoma multiforme (GBM) is one of the most malignant brain tumors, because of its proliferative and invasive characteristics. The median survival is 12–16 months, despite multidisciplinary therapies, including surgery, radiation, and chemotherapy (1,2). GBM tumor cells migrate into the brain parenchyma far from the tumor mass and recurrence is common along the periphery of the tumor removal cavity, even in cases where the enhanced lesion has completely disappeared postoperatively (2). However, it is difficult to evaluate tumor spread of GBM on magnetic resonance imaging (MRI). We have previously reported a positron emission tomography (PET) study in which we compared the methionine (MET) uptake area to the area of gadolinium (Gd) enhancement on MRI in patients with GBM (3). We showed that the MET uptake area completely enveloped the Gd-enhanced area. In most cases, the MET uptake area enclosed the outer region of the Gd-enhanced area, with an additional 30 mm expansion. In contrast, the Gd-enhanced area coincided with only 58.6% of the MET-uptake area on average. Based on these results, we identified three cases of possible GBM recurrences after complete resection; they presented as new Gd-enhanced lesions in the MET uptake area at the edge of the surgical removal cavity (3). Hence, MET-PET may be useful for predicting local recurrence, given the metabolic abnormalities in residual tumor cells even before local tumor recurrence could be discerned on MRI (4).

The resection rate is one of the prognostic factors in GBM. It has been reported that resection of >78% of GBM lesions could improve survival; moreover, aggressive resection of 95–100% of the tumor increases survival in a stepwise fashion (5). Accordingly, it seems necessary to remove the infiltrating tumor along with the surrounding normal brain tissue, in order to achieve gross total resection.

It is considered that 5-aminolevulinic acid (5-ALA) may be useful for discriminating high-grade glioma from normal brain tissues during surgery. A randomized controlled trial showed that 5-ALA fluorescence-guided resection of glioblastoma improved patients' 6-month progression-free survival as compared to those undergoing microsurgical resection under conventional white light (6). Subsequently, analysis of data from a randomized controlled trial provided level 2b evidence supporting the benefit of resection under 5-ALA fluorescence guidance on overall survival (7).

We have previously reported the sensitivity, specificity, positive-predictive value, and negative-predictive value of 5-ALA for identifying more than 50% of olig2-positive cells remaining in the wall of the removal cavity, as examined on immunohistochemistry of the postoperative surgical specimens, as 90.9%, 44.4%, 66.7%, and 80%, respectively (8). In other words, it is not possible to identify all the tumor cells with conventional usage of 5-ALA.

Glioblastoma stem cells (GSCs) have been reported to play a crucial role in the initiation, progression, resistance

to therapy, and recurrence of GBM (9,10). In our recurrent cases, it appears that GSCs must have remained around the removal cavity, acting as the major source of the recurrence, after escaping the effect of multimodal therapies (2). GBM is considered to be composed of heterogeneous populations of tumor cells and to include specific subpopulations, i.e., GSCs and non-GSCs. Wang *et al*. showed that GSCs are less able to accumulate protoporphyrin IX (PpIX) than non-GSCs, and a subset of side population (SP)-defined C6 glioma cells, which are GSCs, most likely escapes from detection and resection under 5-ALA-based photodynamic diagnosis (PDD) (11). Additionally, they demonstrated that a subpopulation of C6 SP-defined GSCs possessing low PpIX fluorescence exhibit markedly higher tumorigenic activity and much more rapid progression of tumors than that of SP-derived cells possessing high PpIX fluorescence. In contrast, main population (MP)-derived cells, i.e., non-GSCs showing low PpIX fluorescence, did not present rapid progressions. This phenomenon indicates that more aggressive tumor cells can elude 5-ALA-based resection, and lead to tumor recurrence. This leads to the question of how SP-derived cells with low PpIX fluorescence can be removed. To achieve this, Wang *et al*. propounded deferoxamine (DFO) treatment. The agent has a specific affinity for free iron in the blood stream, resulting in the suppression of the metabolism of PpIX to heme by an iron-chelation effect. Valdés *et al*. have shown that DFO-mediated iron chelation increases 5-ALA-mediated PpIX accumulation in U251 malignant glioma cells in vivo (12). Wang *et al*. hypothesized that DFO may suppress this PpIX metabolism process, resulting in the restoration of PpIX accumulation in GSCs (11). They then demonstrated that DFO treatment significantly increased the percentage of PpIX fluorescence-positive cells among C6 SP-derived cells, as compared to that in MP-derived cells (11). They certainly showed a distinctive decrease in the frequency of cells with poor PpIX accumulation using this DFO treatment. However, the DFO-induced enhancement effect was not observed in MP-derived cells. They first reported that DFO-mediated iron chelation could enhance PpIX accumulation in C6 SP-defined GSCs. Further clinical studies are required to test the applicability of DFO in the enhancement of PpIX accumulation in GSCs in GBM (11). Because DFO has been clinically used as treatment for hemochromatosis, to reduce liver iron concentration without significant side effects (13,14), this agent could be applied in glioma surgery in future.

At the molecular level, what causes the low accumulation of PpIX in C6 SP-defined GSCs? In a search for iron metabolism-associated genes, *HO-1*, which encodes a rate-limiting enzyme for heme degradation and which functions as an inducible protective gene against cellular stress and oxidative injury, was identified (15). Semi-quantitative RT-PCR analysis of *HO-1* revealed significantly enhanced expression in C6 SP-derived cells treated with 5-ALA, as comparing to that without 5-ALA treatment. This difference was not observed in C6 MP-derived cells. Accordingly, C6 SP-derived cells, namely GSCs, in the GBM may strongly express *HO-1* under 5-ALA treatment, which could accelerate PpIX/heme metabolism, leading to poor accumulation of 5-ALA. Elevated expression of *HO-1* was seen in human GBMs as compared to non-tumorous tissue or low grade gliomas, based on publicly available datasets, including the TCGA_GBM HG-U133A platform, Rembrandt, and Gravendeel datasets. In addition, *HO-1* was verified as a prognostic factor in GBMs based on Kaplan-Meier survival analysis. In fact, the lower expression group showed significantly longer survival than did the high expression group in all datasets. Taken together, administration of 5-ALA could activate *HO-1*, leading to reduced accumulation of PpIX through accelerated metabolism of PpIX to heme in GSCs.

In conclusion, Wang *et al*. showed that an iron chelator could be used to improve 5-ALA-based PDD of SP-defined GSCs in glioma. Clinical usage of a combination of 5-ALA and DFO may be valuable in glioma surgery.

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