



Commentary

Intracranial Glioblastomas: New Hope for an Effective Treatment

Arthur J.L. Cooper

Department of Biochemistry and Molecular Biology, New York Medical College, 15 Dana Road, Valhalla, NY 10595, United States



According to the National Brain Tumor Society, over 120 different types of human brain tumors have been described, the most common of which are gliomas arising from glial (supportive) cells. Approximately two-thirds of brain tumors are benign, but about one third are malignant. The most common adult-onset primary (i.e., arising from the brain itself) malignant brain tumor is glioblastoma multiforme (GBM), accounting for about 20% of all intracranial tumors. Because by the time the cancer is discovered the tumor has usually metastasized to other parts of the brain, it is extremely rare for the patient to be cured by surgical resectioning. Thus, in addition to surgery, first lines of defense are radiation therapy, anti-angiogenic agents and chemotherapy. Despite these heroic efforts the prognosis is grim, with GBM patients often dying within months of first diagnosis. In a recent study of 503 patients it was shown that median survival time is 25 months after first diagnosis and 12 months after first resectioning (Ringel et al., 2015). In other studies, median survival was reported to be 15 months for newly-diagnosed GBM and 5–7 months for recurrent/relapsed GBM (reviewed by Henriksson et al., 2011). Current standard of care (radiotherapy plus temozolomide followed by 6 cycles of adjuvant temozolomide) provides 2- and 5-year survival rates of 27 and 10% for patients with newly diagnosed GBM (Stupp et al., 2009). The annual incidence (as of 2008) in the “World Standard Population” is estimated to be 3.8/100,000 in males, 3.1 in females, but slightly higher in the developed world, and with a median age of onset of about 64 years (Ahmed et al., 2014). Mean survival time following diagnosis of patients with GBM has improved only marginally within the last 50 years. Thus, new strategies to treat GBM are urgently needed.

The work by Sharpe et al. (2015–in this issue) may provide just such a strategy. The rationale is relatively simple yet elegant. DNA repair mechanisms in mitochondria are limited and are not active in cells containing damaged mitochondrial DNA (mtDNA). Inasmuch as intact mitochondria are essential for the maintenance of cellular function and replication of cancer stem cells, these organelles may be particularly useful targets in cancer therapy (Deus et al., 2015). Monoamine oxidase-B (MAOB) in the brain is highly enriched in glial mitochondria (Ekblom et al., 1993). Moreover, MAOB levels are higher in the mitochondria of glioblastoma cells compared to those of normal astrocytes. Therefore, MAOB is a potential chemotherapeutic target in glioblastoma cells.

It is well known that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) crosses the blood–brain-barrier (BBB) and is oxidized by MAOB to 1-methyl-4-phenyl-2,3-dihydropyridinium (MPDP⁺), followed by a second oxidation catalyzed by Coenzyme Q to 1-methyl-4-phenylpyridinium (MPP⁺) – a neurotoxin that targets the substantia nigra and causes Parkinson-like symptoms in humans and experimental animals (e.g., Hare et al., 2013). Sharpe et al. have designed a compound that incorporates a “seeker” moiety similar to MPTP, but which, unlike MPTP, is not noticeably toxic to normal neural cells, and which carries a nitrogen mustard “warhead” [–N(CH₂CH₂Cl)₂]. This compound is N,N-bis(2-chloroethyl)-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)propanamide (MP-MUS), which was shown to be an excellent substrate of MAOB and more selective toward MAOB than toward MAOA. MP-MUS, in a similar fashion to MPTP, readily crosses the BBB and is consecutively oxidized by MAOB and Coenzyme Q to a pyridinium compound (in this case, P⁺-MUS). P⁺-MUS, like MPP⁺, is highly lipophilic and accumulates in the mitochondrial matrix (Sharpe et al., 2015a). Loss of chloride ion from P⁺-MUS results in conversion of the mustard moiety to a highly reactive substituent (either a 3-membered aziridinium or a 5-membered dihydrooxazolium), which has the ability to cause massive oxidative stress and DNA breaks in the targeted mitochondria (Sharpe et al., 2015–in this issue).

Preliminary findings with MP-MUS reported by Sharpe et al. (2015–in this issue) are highly encouraging. The authors showed that incubating cultures of human glioblastoma cells with MP-MUS significantly decreased the mitochondrial membrane potential, whereas selegiline, a specific inhibitor of MAOB, did not. Treatment with MP-MUS resulted in an increase in mtDNA damage, an increase in reactive oxygen species (ROS) and an increase in MAOB – until the cells began to die. In response to MP-MUS treatment, the cells upregulated mitochondrial biogenesis, but the mitochondria were poorly energized and cell viability declined. Incubation of the human glioblastoma cells with selegiline protected against the toxic effects of MP-MUS, indicating that the cellular/mitochondrial damage is indeed due to activation of the MP-MUS prodrug to a mitochondrial toxicant via the action of MAOB.

In a second series of experiments, Sharpe et al. investigated the effect of MP-MUS treatment on primary human glioma xenografts in a Nu/Nu mouse model. Tumor volumes shrank in the MP-MUS treatment group after the first injection, whereas tumors grew steadily in the saline-treated controls, and, interestingly, tumors could not be detected in two of the MP-MUS-treated animals. No evidence was found for Parkinson-like symptoms or damage to the substantia nigra in the MP-MUS-treated mice. The xenografts that were not completely destroyed by the MP-MUS treatment exhibited marked increases in MAOB, ROS, oxidative stress

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E-mail address: arthur_cooper@nymc.edu.

markers and mtDNA damage compared to the xenografts in the control mice. No organ specific toxicities were noted for MP-MUS-treated mice.

Finally, the authors investigated the effects of MP-MUS on morbidity and mortality in an intracranial mouse model of primary human GBM. Primary human GBM cells encased in a Matrigel matrix were injected into one hemisphere of NOD/SCID mice. The first of three tail-vein injections of saline MP-MUS was carried out on day 115 post-engraftment. By day 248, 50% of the control mice had died, whereas none of the MP-MUS-treated had died, with only one of the treated mice exhibiting symptoms during the entire study period. Moreover, infiltration of the human GBM cells into the contralateral hemisphere was noted in 10 of 11 control mice. In contrast, GBM cells were noted in the ipsilateral hemispheres of only 6 of the 11 treated mice, but no GBM cell infiltrates were noted in their contralateral hemispheres.

In conclusion, Sharpe et al. have demonstrated that MP-MUS is remarkably selective, targeting the mitochondria via MAOB of human glioblastoma cells both in culture and in vivo, with no discernible organ toxicity. As the authors note, the upregulation of MAOB in the cancer cells is a maladaptive response, which may actually increase the effectiveness of MP-MUS as a chemotherapeutic agent. The authors indicate that additional work is under way to perform more detailed toxicological/pharmacodynamic tests and to fine-tune the manufacturing process, and perhaps design additional warheads. The authors' concluding words are: "we are hopeful to see this drug in clinical trials in the next 18 months". Based on the preliminary data presented by Sharpe et al., MP-MUS is a lead compound in a new strategy that promises to be highly effective in combating the terrible scourge of GBM.

Disclosure

The author discloses no conflict of interest.

References

- Ahmed, R., Oborski, M.J., Hwang, M., Lieberman, F.S., Mountz, J.M., 2014. Malignant gliomas: current perspectives in diagnosis, treatment, and early response assessment using advanced quantitative imaging methods. *Cancer Manag. Res.* 6, 149–1470.
- Deus, C.M., Santos, G.L., Loureiro, R., Vega-Naredo, I., Faneca, H., Oliveira, P.J., 2015. Shutting down the furnace: preferential killing of cancer cells with mitochondrial-targeting molecules. *Curr. Med. Chem.* (Feb 9, Epub ahead of print).
- Ekblom, J., Jossan, S.S., Bergström, M., Orelund, L., Walum, E., Aquilonius, S.M., 1993. Monoamine oxidase-B in astrocytes. *Glia* 8, 122–132.
- Hare, D.J., Adlard, P.A., Doble, P.A., Finkelstein, D.I., 2013. Metallobiology of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity. *Metallomics* 5, 91–109.
- Henriksson, R., Asklund, T., Poulsen, H.S., 2011. Impact of therapy on quality of life, neurocognitive function and their correlates in glioblastoma multiforme: a review. *J. Neuro-Oncol.* 104, 639–646.
- Ringel, F., Pape, H., Sabel, M., Krex, D., Bock, H.C., Misch, M., Weyerbrock, A., Westermaier, T., Senft, C., Schucht, P., Meyer, B., Simon, M., 2015. SN1 study group. Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. *Neuro-Oncology* (Aug 4. pii: nov145. [Epub ahead of print]).
- Sharpe, M.A., Han, J., Baskin, A.M., Baskin, D.S., 2015. Design and synthesis of a MAOB-selectively activated prodrug based on MPTP: a mitochondria-targeting chemotherapeutic agent for treatment of human malignant gliomas. *ChemMedChem* 10, 621–628.
- Sharpe, M.A., Livingston, A.D., Gist, T.L., Ghosh, P., Han, J., Baskin, D.S., 2015. Successful treatment of intracranial glioblastoma xenografts with a novel monoamine oxidase B-activate pro-drug. *EBioMedicine* 2, 1122–1132 (in this issue).
- Stupp, R., Hegi, M.E., Mason, W.P., van den Bent, M.J., Taphoorn, M.J., Janzer, R.C., Ludwin, S.K., Allgeier, A., Fisher, B., Belanger, K., Hau, P., Brandes, A.A., Gijtenbeek, J., Marosi, C., Vecht, C.J., Mokhtari, K., Wesseling, P., Villa, S., Eisenhauer, E., Gorlia, T., Weller, M., Lacombe, D., Cairncross, J.G., Mirimanoff, R.O., European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups, National Cancer Institute of Canada Clinical Trials Group, 2009. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 10, 459–466.