ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Clinical Professor of Neurological Surgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Neuro-Oncology

Editor
Mitsutoshi Nakada, MD
Kanazawa University, Ishikawa, Japan

SNI
Open Access

Case Report

Clinically useful tumor fluorescence greater than 24 hours after 5-aminolevulinic acid administration

Sameah Haider, Travis Matthew Hamilton, Rachel J. Hunt, Ian Y. Lee, Adam M. Robin

Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, United States.

E-mail: Sameah Haider - shaider1@hfhs.org; Travis Matthew Hamilton - thamilt8@hfhs.org; Rachel J. Hunt - rhunt2@hfhs.org; Ian Y. Lee - ilee1@hfhs.org; *Adam M. Robin - arobin1@hfhs.org

***Corresponding author:**
Adam M. Robin,
Department of Neurosurgery,
Henry Ford Hospital, Detroit,
Michigan, United States.

arobin1@hfhs.org

Received : 19 August 2021
Accepted : 05 February 2022
Published : 25 March 2022

DOI
10.25259/SNI_836_2021

Quick Response Code:

ABSTRACT

Background: 5-aminolevulinic acid (5-ALA) is a valuable surgical adjuvant used for the resection of glioblastoma multiforme (GBM). Since Food and Drug Administration approval in 2017, 5-ALA has been used in over 37,000 cases. The current recommendation for peak efficacy and intraoperative fluorescence is within 4 h after administration. This narrow time window imposes a perioperative time constraint which may complicate or preclude the use of 5-ALA in GBM surgery.

Case Description: This case report describes the prolonged activity of 5-ALA in a 66-year-old patient with a newly diagnosed GBM lesion within the left supramarginal gyrus. An awake craniotomy with language and sensorimotor mapping was planned along with 5-ALA fluorescence guidance. Shortly, after receiving the preoperative 5-ALA dose, the patient developed a fever. Surgery was postponed for an infectious disease workup which proved negative. The patient was taken to surgery the following day, 36 h after 5-ALA administration. Despite the delay, intraoperative fluorescence within the tumor remained and was sufficient to guide resection. Postoperative imaging confirmed a gross total resection of the tumor.

Conclusion: The use of 5-ALA as an intraoperative adjuvant may still be effective for patients beyond the recommended 4-h window after initial administration. Reconsideration of current use of 5-ALA is warranted.

Keywords: 5-ALA, 5-Aminolevulinic acid, GBM, Glioblastoma multiforme

INTRODUCTION

High-grade gliomas (HGG) represent the most common primary intracranial tumor with an estimated 13,000–17,000 newly diagnosed cases each year.[17,20,21,29] Despite modest survival benefit with adjuvant therapies such as chemo-radiation and tumor-treatment fields, long-term prognosis with HGG is invariably discouraging with 1- and 2-year survival rates of 38% and 16%, respectively.[3] The preponderance of evidence suggests that the extent of resection (EOR) correlates strongly with survival. The use of advanced surgical adjuncts, such as intraoperative magnetic resonance imaging (MRI), and fluorescence-guided surgery (FGS), has shown promising results. Numerous RCTs have demonstrated that both tools increase EOR with an associated increase in progression-free survival.[18,22,24]

Since the US Food and Drug Administration's approval of 5-aminolevulinic acid (5-ALA) in February 2017, over 37,000 patients with glioblastoma multiforme (GBM) have been operated

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, transform, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.
©2022 Published by Scientific Scholar on behalf of Surgical Neurology International

on with the aid of FGS. The current recommended dose of 5-ALA is 20 mg/kg body-weight, administered orally 2–4 h before induction of anesthesia.[15] These recommendations arise from preclinical animal studies[23] and Phase I and 2 dose-escalation trials,[4,15,16] with additional support from a randomized, prospective, and double-blind study of alternative dosage regimens for HGG resection.[25]

5-ALA is a prodrug with selective intracellular conversion to protoporphyrin IX, the fluorescent downstream metabolite of 5-ALA that preferentially accumulates in high-grade tumor cells to glow under blue-light illumination.[8,12,16,23] *In vivo* animal studies report peak fluorescence between 1.5 and 4 h after administration,[19,23] yet, clinical experience has demonstrated visually discernible tumor fluorescence even 12–16 h after initial dosing.[7,13,28] While those instances of prolonged fluorescence have been informally described, we present the first reported case of clinically useful intraoperative tumor fluorescence >24 h after 5-ALA administration, without redosing.

CLINICAL PRESENTATION

A 66-year-old right-handed male initially presented with mild cognitive difficulty, dysphasia and progressive difficulty walking. On examination, a subtle neglect, acalculia, extinction to double simultaneous stimuli, and right-sided apraxia were noted. Evaluation with MRI demonstrated a partially cystic contrast-enhancing mass in the dominant supramarginal gyrus with fluid-attenuated inversion recovery positive signal intensity extending above to the superior parietal lobule, suggestive of glioma [Figure 1]. An electroencephalogram showed cortical irritability on the left but no definite seizures. His symptoms improved with levetiracetam and dexamethasone, which he continued until surgery. Given the eloquent location of his tumor, the surgical plan included an awake language and sensorimotor mapping using phase reversal and cortical and subcortical motor-evoked potentials to preserve function. We also elected to make use of 5-ALA and intraoperative MRI to maximize resection.

On arrival to the preoperative area, a 20 mg/kg oral dose of 5-ALA was given at 5:50 AM, within 2 h of surgery. Before transport to the operative suite, the patient developed a fever of 38.8°C, which increased to 39.4°C on repeat evaluation. After consultation with our clinical trials team and anesthesia, surgery was deferred in favor of further evaluation of the cause of the fever. He was transferred to the intensive care unit and kept under light precautions in the interim. His fever was self-limiting. Further evaluation revealed no infectious etiology. Surgery was rescheduled for the following morning at 9:30 AM, more than 24 h after administration of 5-ALA.

During surgery, cortical mapping demonstrated several areas critical for language function. The non-enhancing lesion was found to be in an area that, when stimulated, resulted in movement of the opposite arm and face as well as dysesthetic pain in a similar distribution. After cortical mapping and partial white light resection, the first utilization of fluorescence came a full 32 h after 5-ALA administration [Figure 2]. The cystic enhancing and fluorescent tumor were removed and sent for pathologic analysis

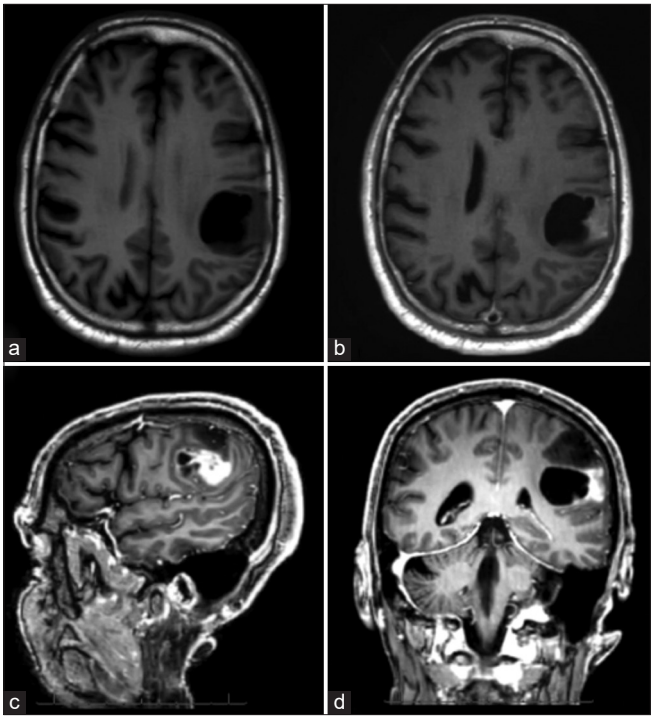

Figure 1: Preoperative magnetic resonance imaging (MRI) of the brain with and without contrast demonstrating contrast-enhancing left parietal cystic lesion. (a) Axial MRI T1-weighted, (b) axial T1-weighted with gadolinium, (c) sagittal T1-weighted with gadolinium, and (d) coronal T1-weighted with gadolinium.

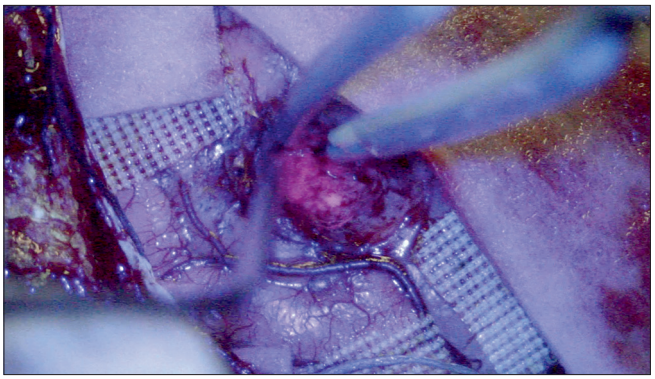

Figure 2: Intraoperative view of fluorescent, pathologic tissue visualized through a small corticotomy window. Photo taken at the onset of the resective portion of the surgery, approximately 33 h after administration of 5-aminolevulinic acid. Normal brain parenchyma did not fluoresce and all pathologic specimens that fluoresced were positive for tumor.

[Figure 3]. Further molecular characterization demonstrated: Grade 3 Diffuse Astrocytoma; IDH wild-type, MIB index 7%; and MGMT promotor methylation. Postoperatively, no focal neurological deficits were identified. MRI obtained on postoperative day 2 showed resection of the enhancing lesion and non-enhancing residual T2 hyperintense suspected disease at the superior margin [Figure 4].

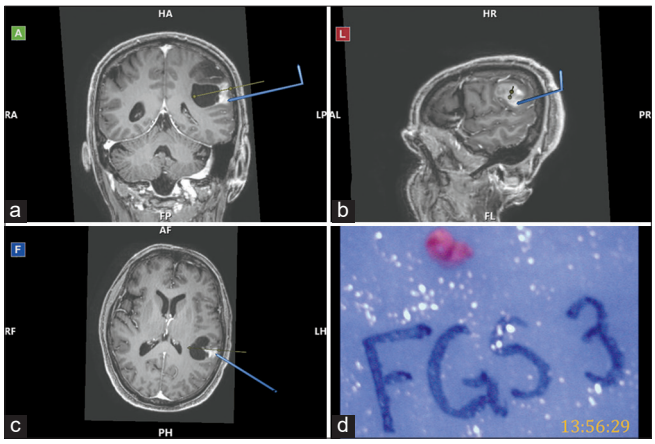

Figure 3: Intraoperative navigation depicting location of biopsy sample and visualized fluorescence under blue-light illumination in the (a) coronal plane, (b) sagittal plane, (c) axial plane, and (d) microscope luminescence control window. The time stamp indicates approximately 32 h after initial administration of 5-aminolevulinic acid. The blue lines in (a), (b), and (c) indicate location of fluorescent biopsy sample depicted in (d).

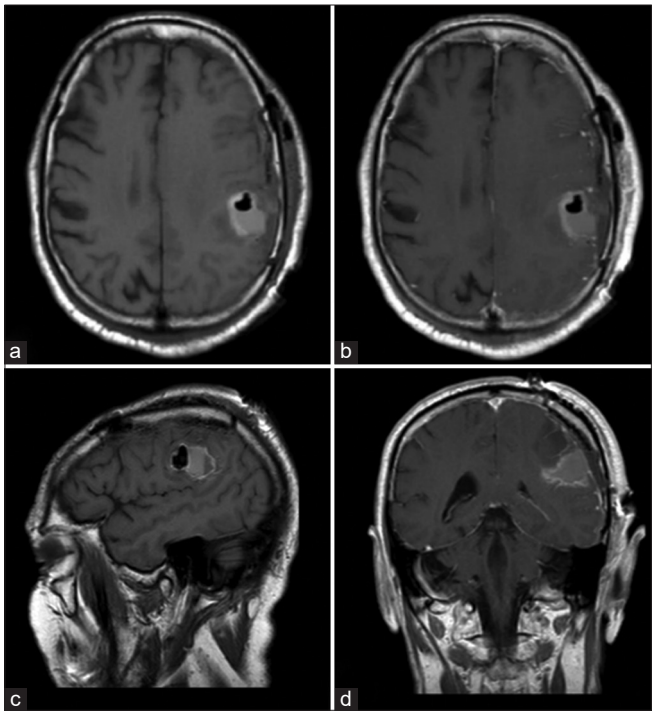

Figure 4: Postoperative T1-weighted (a and c) pre-contrast and (b and d) post-contrast magnetic resonance imaging demonstrating complete removal of the contrast-enhancing tumor.

IRB approval was not obtained as this is a case report, negating the requirements for review. The patient's identity was not disclosed or compromised.

DISCUSSION

The use of 5-ALA FGS as an adjunct for visualization and resection of GBM was approved in June 2017. Since then, there have been multiple articles reporting the efficacy, dosing, and outcomes relative to the volume of tumor resected.[5,8] However, there is limited information regarding the upper temporal limits of sufficient brain tissue fluorescence at the recommended dose of 20 mg/kg.

The rationale for exogenous 5-ALA administration 2–4 h before anesthetic induction is predicated on both the aforementioned dose-response studies and the likelihood that anesthetic administration, patient positioning, setup, craniotomy, and initial macroscopic white-light tumor debulking constitute the initial 3–4 h time period after 5-ALA administration, with the anticipated microscopic blue-light tumor resection occurring in the 4–7 h time frame after dosing.[2,26,27] Expert opinion has further cautioned that if surgery is unexpectedly delayed, one should not cancel surgery strictly on the basis of non-adherence to the classically described fluorescence time window.[28]

ALA is an endogenous metabolite of the mitochondria, which is further metabolized to produce protoporphyrin IX (PpIX). Exogenous/oral 5-ALA is thought to be preferentially metabolized by cells that undergo a high rate of proliferation (i-67, MIB-1 index, and WHO grade).[10,15] The accumulation of the metabolite PpIX allows for intraoperative fluorescence under deep blue light (wavelength filter of 375–440 nm), thereby providing differentiation of high-grade glial tissue from normal parenchyma. The current recommended time to surgery after oral administration of 5-ALA is 2–4 h. Industry-sponsored clinical studies have shown a mean half-life of 0.9 (0.8–1.3) h at the recommended dose, while the maximum concentration of PpIX metabolite was found to occur at a median value of 4 (1.2–7.8) h.[14] Dose-dependent analysis performed by Michael *et al.* also suggests that increasing doses of 5-ALA are associated with higher rates of gross total resection with lower residual tumor volume when compared to standard dosing in patients with GBM. However, to the best of the authors' knowledge, there are no studies comparing the fluorescence intensity of brain tissue as a function of time after administration or plasma concentration of 5-ALA.[15,16]

There are many factors that can affect the active metabolic plasma concentration of 5-ALA, including antibiotics and seizure medications such as phenytoin.[6,16] However, our patient did not receive antibiotics before his fever episode instead receiving a standard perioperative first-generation

cephalosprin shortly before incision on the day of the surgery. The patient had no remote history of medication use that would affect elimination (including Keppra), nor evidence of hepatorenal dysfunction that would prolong the excretion of 5-ALA. *In vitro* studies of the WHO Grade 3, human glioma cell lines have shown that *IDH1* mutation is associated with a delay in 5-ALA metabolism and consequent fluorescent activity; however, our patient was found to be *IDH1* wild-type. [Figure 3] depicts a fluorescent tissue sample at 32 h post 5-ALA dosing, the longest reported example of its kind.

Irrespective of the degree of metabolic clearance, tumor fluorescence with 5-ALA is often heterogeneous.[5] Solid tumor will fluoresce as red, whereas vaguely fluorescent pink tissue beyond the border of MRI T1-Gd enhancement has been described to represent infiltrating tumor both with positive predictive values >92%.[5,7] [Figure 2] depicts tumor fluorescence between 24 and 33 h after initial 5-ALA dose. Factors that may limit visualization of tissue fluorescence include the depth and breadth of the surgical bed and their subsequent impact on the amount of excitatory blue light that can be delivered to the metabolite PpIX-containing tumor tissues. In addition, photobleaching with prolonged illumination can limit visualization of fluorescent tumor.[1,2,9,11] While the ongoing degradation of photoactive PpIX cannot be excluded, the resection of weakly fluorescent and non-fluorescent tissue should still be considered with MRI, intraoperative neuronavigation, and direct visualization of abnormal tissue without damage to eloquent brain tissue.

CONCLUSION

The prospect of working outside the recommended 2–4 h time frame from the administration of 5-ALA to induction of anesthesia allows for greater flexibility in the event of unanticipated scheduling constraints. Our findings also raise the plausibility of whether patients may take 5-ALA the evening before surgery as opposed to 3–5:00 AM the day of surgery. Further evaluation of the temporal characteristics of tissue fluorescence following 5-ALA administration in humans undergoing brain tumor resections would be of value.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Belykh E, Miller EJ, Patel AA, Bozkurt B, Yağmurlu K, Robinson TR, *et al*. Optical Characterization of Neurosurgical Operating Microscopes: Quantitative Fluorescence and Assessment of PpIX Photobleaching, Scientific Reports; 2018. p. 8.
2. Broekx S, Weyns F, De Vleeschouwer S. 5-Aminolevulinic acid for recurrent malignant gliomas: A systematic review. Clin Neurol Neurosurg 2020;195:105913.
3. Cantrell JN, Waddle MR, Rotman M, Peterson JL, Ruiz-Garcia H, Heckman MG, *et al*. Progress toward long-term survivors of glioblastoma. Mayo Clin Proc 2019;94:1278-86.
4. Cozzens JW, Lokaitis BC, Moore BE, Amin DV, Espinosa JA, MacGregor M, *et al*. A phase 1 dose-escalation study of oral 5-aminolevulinic acid in adult patients undergoing resection of a newly diagnosed or recurrent high-grade glioma. Neurosurgery 2017;81:46-55.
5. Díez Valle R, Hadjipanayis CG, Stummer W. Established and emerging uses of 5-ALA in the brain: An overview. J Neurooncol 2019;141:487-94.
6. Gleolan Package Insert. Lexington, KY: NX Development Cop.; 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208630s003lbl.pdf. [Last accessed on 2021 Aug 19].
7. Hadjipanayis CG, Widhalm G, Stummer W. What is the surgical benefit of utilizing 5-aminolevulinic acid for fluorescence-guided surgery of malignant gliomas? Neurosurgery 2015;77:663-73.
8. Haider SA, Lim S, Kalkanis SN, Lee IY. The impact of 5-aminolevulinic acid on extent of resection in newly diagnosed high grade gliomas: A systematic review and single institutional experience. J Neurooncol 2019;141:507-15.
9. Haj-Hosseini N, Richter J, Andersson-Engels S, Wårdell K. In: Kollias N, Choi B, Zeng H, Malek RS, Wong BJ, Ilgner JF, *et al*., editors. Photobleaching Behavior of Protoporphyrin IX during 5-Aminolevulinic Acid Marked Glioblastoma Detection. San Jose, CA: SPIE; 2009. p. 716131
10. Jaber M, Wölfer J, Ewelt C, Holling M, Hasselblatt M, Niederstadt T, *et al*. The value of 5-aminolevulinic acid in low-grade gliomas and high-grade gliomas lacking glioblastoma imaging features: An analysis based on fluorescence, magnetic resonance imaging, 18F-fluoroethyl tyrosine positron emission tomography, and tumor molecular factors. Neurosurgery 2016;78:401-11; discussion 411.
11. Kaneko S, Kaneko S. Fluorescence-guided resection of malignant glioma with 5-ALA. Int J Biomed Imaging 2016;2016:6135293.
12. Kim JE, Cho HR, Xu WJ, Kim JY, Kim SK, Kim SK, *et al*. Mechanism for enhanced 5-aminolevulinic acid fluorescence in isocitrate dehydrogenase 1 mutant malignant gliomas. Oncotarget 2015;6:20266-77.
13. Maragkos GA, Schüpper AJ, Lakomkin N, Sideras P, Price G, Baron R, *et al*. Fluorescence-guided high-grade glioma surgery more than four hours after 5-aminolevulinic acid administration. Front Neurol 2021;12:644804.
14. Marzella L. Division Director Summary Review NDA 208630; 2017.
15. Michael AP, Watson VL, Ryan D, Delfino KR, Bekker SV,

Cozzens JW. Effects of 5-ALA dose on resection of glioblastoma. J Neurooncol 2019;141:523-31.
16. NX Development Corporation; 2017. Available from: https://www.nx-development-briefing-information-for-the-may-10--2017-meeting-of-the-medical-imaging-drugs-advisory-committee.pdf
17. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, *et al*. The epidemiology of glioma in adults: A "state of the science" review. Neuro Oncol 2014;16:896-913.
18. Pichlmeier U, Bink A, Schackert G, Stummer W, ALA Glioma Study Group. Resection and survival in glioblastoma multiforme: An RTOG recursive partitioning analysis of ALA study patients. Neuro Oncol 2008;10:1025-34.
19. Predina JD, Runge J, Newton A, Mison M, Xia L, Corbett C, *et al*. Evaluation of aminolevulinic acid-derived tumor fluorescence yields disparate results in murine and spontaneous large animal models of lung cancer. Sci Rep 2019;9:7629.
20. Price RL, Chiocca EA. Evolution of malignant glioma treatment: From chemotherapy to vaccines to viruses. Neurosurgery 2014; 61 Suppl 1:74-83.
21. Rasmussen BK, Hansen S, Laursen RJ, Kosteljanetz M, Schultz H, Nørgård BM, *et al*. Epidemiology of glioma: Clinical characteristics, symptoms, and predictors of glioma patients grade I-IV in the the Danish neuro-oncology registry. J Neurooncol 2017;135:571-9.
22. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V. Intraoperative MRI guidance and extent of resection in glioma surgery: A randomised, controlled trial. Lancet Oncol 2011;12:997-1003.
23. Stummer W, Stocker S, Novotny A, Heimann A, Sauer O, Kempski O, *et al*. *In vitro* and *in vivo* porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid. J Photochem Photobiol B 1998;45:160-9.
24. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, *et al*. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: A randomised controlled multicentre phase III trial. Lancet Oncol 2006;7:392-401.
25. Stummer W, Stepp H, Wiestler OD, Pichlmeier U. Randomized, prospective double-blinded study comparing 3 different doses of 5-aminolevulinic acid for fluorescence-guided resections of malignant gliomas. Neurosurgery 2017;81:230-9.
26. Suero Molina E, Wölfer J, Ewelt C, Ehrhardt A, Brokinkel B, Stummer W. Dual-labeling with 5-aminolevulinic acid and fluorescein for fluorescence-guided resection of high-grade gliomas: Technical note. J Neurosurg 2018;128:399-405.
27. Teng L, Nakada M, Hayashi Y, Yoneyama T, Zhao SG, Ham JI. Current applications of 5-ALA in glioma diagnostics and therapy. In: Lichtor T, editor. Clinical Management and Evolving Novel Therapeutic Strategies for Patients with Brain Tumors. Chennai: InTech; 2013.
28. Tonn JC, Stummer W. Fluorescence-guided resection of malignant gliomas using 5-aminolevulinic acid: Practical use, risks, and pitfalls. Clin Neurosurg 2008;55:20-6.
29. Walid MS. Prognostic factors for long-term survival after glioblastoma. Perm J 2008;12:45-8.

How to cite this article: Haider S, Hamilton TM, Hunt RJ, Lee IY, Robin AM. Clinically useful tumor fluorescence greater than 24 hours after 5-aminolevulinic acid administration. Surg Neurol Int 2022;13:99.