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Role of 5-ALA in improving extent of tumour resection in patients with Glioblastoma Multiforme

Muhammad Waqas
Aga Khan University

Inamullah Khan
Aga Khan University

Muhammad Shahzad Shamim
Aga Khan University, shahzad.shamim@aku.edu

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Muhammad Waqas, Inamullah Khan, Muhammad Shahzad Shamim

Abstract

Goal of surgery for patients with Glioblastoma Multiforme (GBM) is gross total resection with no new neurological deficits. Surgical resection is often restricted due the difficulty in differentiating the tumour from surrounding normal brain using either naked eye, or standard intra-operative white light microscopy. GBM uptakes orally administered 5-ALA becomes fluorescent when viewed by a special light, and this property has been used to improve intra-operative tumour identification. This technique should therefore allow better extent of tumour resection. The hypothesis has been tested through several studies and even though most studies are of low quality, they strongly favour the use of 5- ALA in improving the extent of resection when compared to white light microscopy. A systematic review on the topic had a similar conclusion. Few studies have also hinted on a high false negative rate with the use of this technique.

Keywords: Glioblastoma, 5-ALA, Extent of Resection, Overall Survival.

Introduction

Glioblastoma Multiforme (GBM) is a malignant brain tumour of glial origin that carries a poor prognosis. Despite all the surgical and medical advancement in the treatment of GBM, median survival has not exceeded 15 months, although survival may range between 3 months to 2 years.[1] In some cases of secondary GBM, survival has also been reported for up to 10 years.[2] Surgical approach aimed at gross total resection enhances the efficacy of adjuvant treatment and prolongs the survival in such patients.[3] Nearly 80% of recurrence develop within 2cm of the resection margin.[3] Various modalities have been tried in order to improve extent of tumour resection, including neuronavigation, intra-operative ultrasound, intra-operative MRI (iMRI), awake craniotomy and more recently, 5-aminolevulinic acid (5-ALA) fluorescence guidance.

Aga Khan University Hospital, Karachi, Pakistan.
Correspondence: Muhammad Shahzad Shamim.
Email: shahzad.shamim@aku.edu

5-ALA was approved by the European Medicines Agency (EMA) in 2007, although Food and Drug Administration (FDA) is yet to approve it. It is a biochemical precursor for the heme group and its oral administration leads to its accumulation in glioblastoma cells causing florescence under modified microscopy.[4] This florescence helps the visualization of GBM by the operating surgeon, and its differentiation from normal brain tissue. In this review we look at the use of 5-ALA in procedures aimed at complete resection and effects on improvement in survival compared to conventional surgeries.

Review of Evidence

We searched PubMed database for articles assessing the use of 5-ALA in enhancing extent of resection for GBM. No limit was set on the date of publication and the review was completed in December 2016. Stummer et al., in his landmark paper published in 2006 reported the first phase III trial for 5-ALA and reported complete tumour resection in 65% patients when 5-ALA assisted margin identification was used, compared with 36% in patients undergoing conventional resection.[5] They interpreted that significantly better intra-operative tumour identification, and tumour resection was achieved using 5-ALA fluorescence guidance, especially in contrast enhancing tumours. Six months progression free survival in 5-ALA assisted procedures was reported at 41.0% compared to 21.1% with conventional procedures (p=0.0003).[5] In 2008, Stummer et al., also reported that complete resection using intra-operative 5-ALA significantly prolonged survival in patients with GBM.[6]

Another multicenter, prospective observational study reported complete resection in 54% of patients with GBM when 5-ALA was used, even though the surgeons found the fluorescence to be suboptimal in 40% of the surgeries. They also observed that complete resection was not affected by patients' characteristics such as age, gender, care center, comorbidities, location or histological grade of the tumour. Their mean progression free survival was 6.9 months, while the overall survival was 14.2 months. The overall or

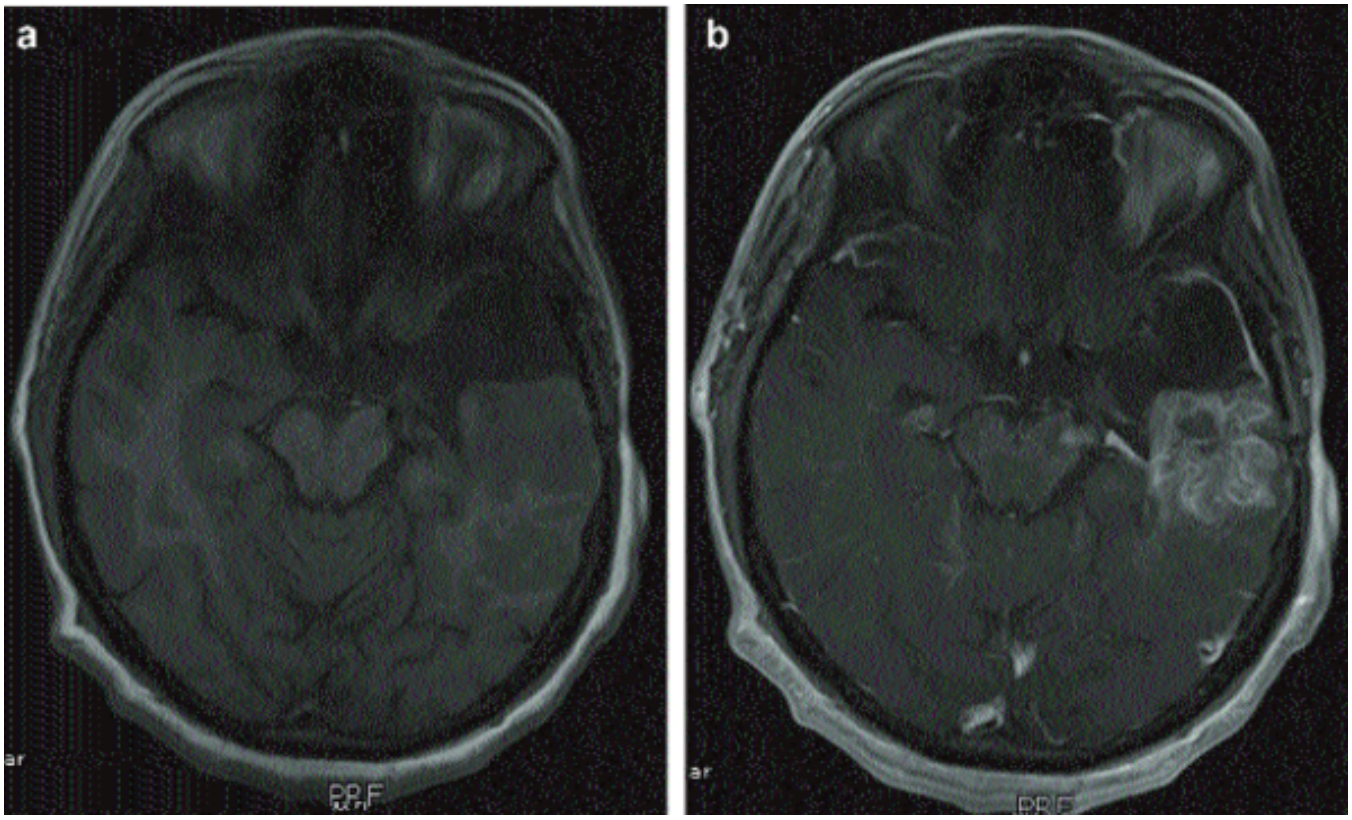

Figure-1: a, b) MRI T1WI pre and post contrast axial images showing a potentially resectable right temporal GBM.

progression free survival had no statistically significant association with the extent of resection.[7]

A 2014 study reported the comparison between extent of resection with the help of 5-ALA and neuronavigation guidance. Although 98% tumour resection was achieved in 90% patients, in 43% patients fluorescent defined margins of tumour exceeded the margins identified by neuronavigation leading to more complete resection. The difference in borders was more frequent in recurrent (60%) and larger (57%) tumours. These findings clearly establish the superiority of 5-ALA over standard neuronavigation.[8]

Another paper in 2015 combined 5-ALA guidance with iMRI to explore further improvement in extent of resection. The fluorescence correctly identified tumour presence in 96% of the cases, although lack of fluorescence correctly identified the absence of tumour in only 12.5% of the cases. They concluded that addition of iMRI might even further improve extent of resection over using 5-ALA alone.[9]

Other papers have also reported better extent of resection for GBM patients with 5-ALA guidance, which also improves progression free survival.[10] However, the evidence to support improvements in overall survival, remains inconclusive.[11]

Regarding safety and adverse effects with the use of 5-ALA, no study reports significant side effects with the therapy. Photosensitivity, a feared side effect is not mentioned by any of the studies, keeping in mind a controlled environment with no direct sunlight and a low lit room environment in the first 24 hours post procedure.[12] An insignificant increase in liver enzymes is reported in the first month post-surgery, but the levels subsequently return to normal. Mild leukocytosis, anaemia and thrombocytopenia may also be noticed with spontaneous recovery.[6] Cost however remains a major concern with 5-ALA use.

Conclusion

Most of the studies strongly favour the use of 5- ALA in improving the extent of resection when compared to white light intra-operative microscopy. A few studies have also suggested a high false negative rate with the use of this technique.

References

1. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001; 5: 190-8.
2. Johnson DR, Ma DJ, Buckner JC, Hammack JE. Conditional probability of long?term survival in glioblastoma. Cancer. 2012; 118: 5608-13.
3. Eljamel MS. Brain photodiagnosis (PD), fluorescence guided resection (FGR) and photodynamic therapy (PDT): past, present and future Photodiagnosis Photodyn Ther. 2008; 5: 29-35.
4. 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. Journal of Photochemistry and Photobiology B: Biology. 1998; 45: 160-9.
5. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. The Lancet Oncology 2006; 7: 392-401.
6. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery. 2008; 62: 564-76.
7. Teixidor P, Arráez MÁ, Villalba G, Garcia R, Tardáguila M, González JJ, et al. Safety and efficacy of 5-aminolevulinic acid for high grade glioma in usual clinical practice: a prospective cohort study. PloS one. 2016; 11: e0149244.
8. Puppa AD, Ciccarino P, Lombardi G, Rolma G, Cecchin D, Rossetto M. 5-aminolevulinic acid fluorescence in high grade glioma surgery: surgical outcome, intraoperative findings, and fluorescence patterns. BioMed Research International. 2014; 2014.
9. Hauser SB, Kockro RA, Actor B, Sarnthein J, Bernays RL. Combining 5-aminolevulinic acid fluorescence and intraoperative Magnetic Resonance Imaging in glioblastoma surgery: a histology-based evaluation. Neurosurgery. 2016; 78: 475-83.
10. Kaneko S, Kaneko S. Fluorescence-guided resection of malignant glioma with 5-ALA. Int J Biomed Imaging. 2016; 2016: 6135293. doi: 10.1155/2016/6135293.
11. Barone DG, Lawrie TA, Hart MG. Image guided surgery for the resection of brain tumours. The Cochrane Library. 2014. Jan 28; (1): CD009685.
12. Honorato-Cia C, Martinez-Simón A, Cacho-Asenjo E, Guillén-Grima F, Tejada-Solís S, Diez-Valle R. Safety profile of 5-aminolevulinic acid as a surgical adjunct in clinical practice: a review of 207 cases from 2008 to 2013. J Neurosurg Anesthesiol. 2015; 27: 304-9.