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Amino Acid PET Imaging of the Early Metabolic Response During Tumor-Treating Fields (TTFields) Therapy in Recurrent Glioblastoma

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Abstract

Tumor-Treating Fields (TTFields) therapy is a relatively new treatment approach for malignant gliomas. We evaluated if amino acid positron emission tomography (PET) can detect an objective metabolic response to TTFields therapy in recurrent glioblastomas. PET scanning with alpha[C-11]-methyl-L-tryptophan (AMT) before and 2–3 months after the start of TTFields treatment showed an interval decrease of tryptophan uptake in the whole tumor (2 patients) or in a portion of the tumor (1 patient). These data demonstrate that TTFields therapy can induce an early metabolic response in recurrent glioblastoma, and this treatment response can be detected by amino acid PET.

Keywords

Recurrent glioblastoma; molecular imaging; amino acid PET; Optune therapy; alternating electric fields; tumor-treating fields

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REFERENCES

1. Alkonyi B, Barger GR, Mittal S, et al. Accurate differentiation of recurrent gliomas from radiation injury by kinetic analysis of alpha-¹¹C-methyl-L-tryptophan PET. *J Nucl Med* 2012;53:1058–1064. [PubMed: 22653792]
2. Kamson DO, Mittal S, Robinette NL, et al. Increased tryptophan uptake on PET has strong independent prognostic value in patients with a previously treated high-grade glioma. *Neuro Oncol* 2014;16:1373–1383. [PubMed: 24670609]
3. Bosnyak E, Kamson DO, Robinette NL, et al. Tryptophan PET predicts spatial and temporal patterns of post-treatment glioblastoma progression detected by contrast-enhanced MRI. *J Neurooncol* 2016;126:317–325. [PubMed: 26514361]
4. Kirson ED, Dbaly V, Tovarys F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A* 2007;104:10152–10157.
5. Mittal S, Klinger NV, Michelhaugh SK, et al. Alternating electric tumor treating fields for treatment of glioblastoma: rationale, preclinical, and clinical studies. *J Neurosurg* 2017 2 24:1–8. doi: 10.3171/2016.9.JNS16452.
6. Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A system for glioblastoma: The Patient Registry Dataset (PRiDe). *Semin Oncol* 2014;41 Suppl 6:S4–S13. [PubMed: 25213869]
7. Stupp R, Wong ET, Kanner AA, Steinberg D, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer* 2012;48:2192–2202. [PubMed: 22608262]
8. Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. *JAMA* 2015;314:2535–2543. [PubMed: 26670971]
9. Villano JL, Williams LE, Watson KS, et al. Delayed response and survival from NovoTTF-100A in recurrent GBM. *Med Oncol* 2013;30:338. [PubMed: 23307238]
10. Vymazal J, Wong ET. Response patterns of recurrent glioblastomas treated with tumor-treating fields. *Semin Oncol* 2014;41 Suppl 6:S14–24.

Figure 1.

MRI (post-gadolinium T1-weighted [T1-Gad] and non-contrast T2 images) and alpha[C-11]-methyl-L-tryptophan (AMT)-PET/T1-Gad MR fusion images of a 45 year-old woman who showed MRI signs of tumor progression 2 months after completion of chemoradiation following resection of a left temporal lobe glioblastoma. Maintenance temozolomide therapy was continued and Tumor-Treating Fields (TTFields) therapy was started following an AMT-PET scan acquired under a research protocol approved by the Institutional Review Board.¹⁻³ AMT Standardized Uptake Value [SUV] in the contrast-

enhancing mass was 5.0, consistent with active tumor.² After 3 months of TTFields treatment, follow-up AMT-PET scan showed decreased tumoral SUV (3.7). T1-Gad MRI showed stable contrast enhancement during the same period and in subsequent follow-up scans.

TTFields therapy for newly diagnosed and recurrent glioblastomas applies low intensity, intermediate frequency (100 kHz-1 MHz), alternating electric fields that have anti-proliferative properties.^{4,5} The treatment is delivered by the Optune® device with a recommended usage of at least 18 hours per day (75% compliance).⁶ In a phase III clinical trial for recurrent glioblastomas, TTFields treatment showed equivalent efficacy when compared to active chemotherapy.⁷ A randomized clinical trial also demonstrated a 5-month overall survival benefit from maintenance TTFields therapy plus temozolomide as compared to temozolomide alone in supratentorial newly-diagnosed glioblastoma following completion of chemoradiation.⁸ Imaging studies evaluating response to TTFields treatment have been limited and confined to MRI.^{9,10} The overall MRI tumor response rate was approximately 15%, and radiographic response developed slowly with a median of 5 months. Overall survival was longer in responders than in non-responders. The present case and two additional patients, shown on Figures 2 and 3, demonstrate that amino acid PET may be more sensitive than MRI to detect early therapeutic responses to TTFields therapy, as metabolic effects can develop within 3 months after treatment initiation.

Figure 2.

MRI (T1-Gad and T2) and AMT-PET/T1-Gad MR fusion images of a 64 year-old man with an aggressive right frontal glioblastoma that progressed during post-surgical chemoradiation (proven by histopathology). TTFields treatment was started shortly after MRI and AMT-PET scans were consistent with further tumor progression. Baseline AMT-PET showed an SUV of 4.3 that decreased to 3.7 two months later. MRI contrast enhancement was unchanged. Because of persistent MRI abnormalities, bevacizumab was added 1 month later while TTFields was continued. A second follow-up AMT-PET 6 months later showed a further

decrease of SUV (below 3.0) along with interval decrease of contrast enhancement and decreased T2 signal.

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Figure 3.

Heterogeneous metabolic response to TTFields treatment in a 51 year-old man with a recurrent left frontal glioblastoma progressing 4 months after completion of chemoradiation while on maintenance temozolomide. MRI (T1-Gad and T2) and AMT-PET/T1-Gad MR fusion images obtained at baseline and after 3 months of TTFields therapy suggested some progression. However, there were intratumoral differences in metabolic changes. While the lower tumor portion showed an expansion of the area with contrast enhancement and high

AMT uptake (1st and 2nd image panels), the upper tumor portion showed an interval decrease of AMT SUV from 4.9 to 3.8 (3rd and 4th panels).

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