Med Oncol (2013) 30:338
DOI 10.1007/s12032-012-0338-1

SHORT COMMUNICATION

Delayed response and survival from NovoTTF-100A in recurrent GBM

J. Lee Villano · Leena E. Williams · Karriem S. Watson · Nandini Ignatius · Marquess T. Wilson · Tibor Valyi-Nagy · Edward A. Michals · Herbert H. Engelhard

Received: 6 November 2012 / Accepted: 14 November 2012

Abstract We present a 48-year-old male with recurrent glioblastoma (GBM) who was enrolled in the NovoTTF-100A landmark phase III study and has been on device for >6 years. During this time, his magnetic resonance images demonstrated initial growth followed by a slow decrease in enhancement with continued residual disease. Long-term survivors in patients with recurrent GBM are rare, especially in the absence of definitive local treatment such as surgery or radiosurgery. We present the clinical, imaging and pathological findings for this patient in relation to use of the NovoTTF-100A device.

J. L. Villano · N. Ignatius
Department of Medicine, University of Illinois Medical Center, Chicago, IL, USA

J. L. Villano · L. E. Williams · K. S. Watson · H. H. Engelhard
Department of Neurosurgery, University of Illinois Medical Center, Chicago, IL, USA

J. L. Villano (✉)
University of Kentucky, 800 Rose St., CC447, Lexington, KY 40536-0093, USA
e-mail: jlvillano@uky.edu

M. T. Wilson
Department of Neurology, University of Illinois Medical Center, Chicago, IL, USA

T. Valyi-Nagy
Department of Pathology, University of Illinois Medical Center, Chicago, IL, USA

E. A. Michals
Department of Radiology, University of Illinois Medical Center, Chicago, IL, USA

Keywords Glioblastoma · Brain tumor · Tumor treatment fields · Recurrent tumor · Survival

Introduction

Patients with recurrent glioblastoma (GBM) have poor outcomes with median survival of <6 months in most series [1]. Reports of patients having prolonged survival with GBM are limited mainly to treatments for primary disease [2–5]. With patients living longer, more investigations are being conducted in second line treatment [1]. The recent phase II (BRAIN) study demonstrated median survival of 9 months with bevacizumab-based treatment [1].

NovoTTF-100A is a recently FDA-approved device that creates electrical fields within the tumor that disrupt cell division during anaphase [6]. Patients wear non-invasive transducer arrays on their scalp during most of the day. A landmark phase III trial in recurrent GBM demonstrated the device has equivalent therapeutic benefit to chemotherapy, with less toxicity and with improved quality of life measures [6].

We report a patient enrolled in this trial that has continued to respond to the NovoTTF-100A device for more than 6 years, representing one of the longest reported survivors of recurrent GBM.

Case report

A 48-year-old Hispanic male presented in February 2004 with a generalized tonic–clonic seizure. MRI of the brain demonstrated an enhancing mass in the right parietal lobe. He initially underwent debulking of the mass, and final

Published online: 10 January 2013

pathology was interpreted as suggestive of infiltrating glioma. Postoperatively, he developed noticeable, 4/5, left hemiparesis with left facial droop. Without a conclusive diagnosis, he was recommended a repeat craniotomy, which he declined (Figs. 1, 2).

Nine months later, based on imaging studies he underwent a second right frontoparietal craniotomy and biopsy with debulking of the mass. He received impregnated carmustine wafers during surgery. Pathological analysis demonstrated GBM having brisk mitotic activity, widespread microvascular proliferation, pseudopalisading necrosis with significant nuclear pleomorphism and atypia. It also had oligodendroglial features, and chromosomal analysis revealed heterozygous deletions of both 1p and 19q chromosomes [7]. Methylation analysis for the promoter region of the *MGMT* gene demonstrated positive methylation.

He was treated with the involved-field cranial irradiation and concomitant daily temozolomide, which he tolerated well. Although he had a delay in starting the maintenance portion, imaging studies following his eleventh cycle demonstrated progression of his enhancing lesion. Almost 2 years after his initial tumor resection, he underwent a third craniotomy for surgical debulking, which demonstrated similar pathology as his second surgery. Five months later, he received radiation boost via Gamma Knife as he showed increased enhancement. Imaging performed 4 months after this procedure revealed progression. He was then enrolled in the Novocure phase III recurrent trial, and on November 15, 2006, he began treatment with the NovoTTF-100A device for 22 h daily. Since starting this treatment, he has been clinically stable. During the initial MRI scans on study, his enhancing lesion grew in size, but did not meet criteria for disease progression, and therefore, he remained in the trial. This was then followed by a period of slow but continued decrease in enhancement that has since stabilized. He remains active and functional and continues using the device.

Discussion

The NovoTTF-100A device is a portable battery-operated device that generates alternating electric fields called tumor treating fields (TTFields). Charged intracellular dipoles such as microtubules are required for cell division and are

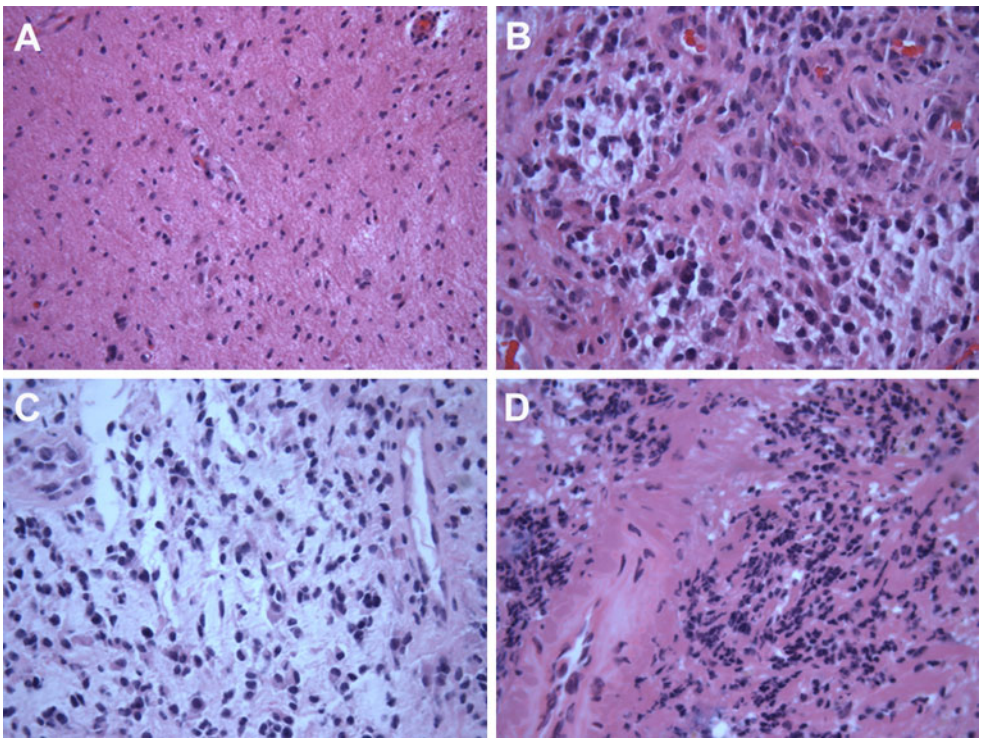

Fig. 1 **a** Hematoxylin and eosin-stained section of brain biopsy specimen from 4/2004 with mildly increased cellularity and glial atypia suggestive of infiltrating glioma (magnification: ×200). **b** Hematoxylin and eosin-stained section of GBM from 11/2004 with increased cellularity, significant glial atypia and pleomorphism, mitotic activity and microvascular proliferation (magnification: ×400). **c** Hematoxylin and eosin-stained section of GBM from 11/2004. Some tumor areas were dominated by tumor cells featuring round nuclei consistent with an oligodendroglioma component (magnification: ×400). **d** Hematoxylin and eosin-stained section of resection specimen from 2/2006 with highly cellular glioma and vascular changes consistent with radiation-related changes (magnification: ×400)

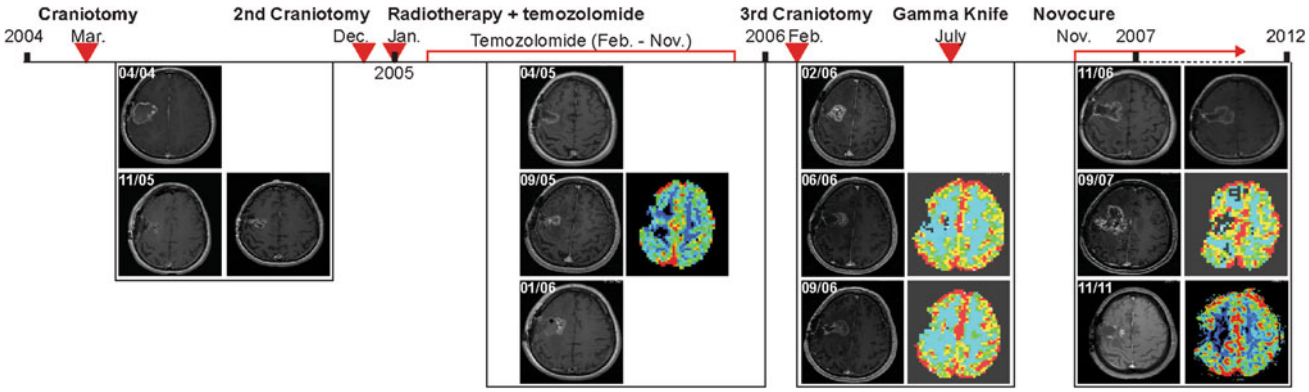

Fig. 2 Results of diagnostic MRI throughout disease course. T1-weighted MRI of the brain with Gadolinium contrast-axial section with accompanied perfusion study at similar structural level. These images corresponds to the timeline-demonstrating therapy and disease activity. In the perfusion study, voxels that are *red* correspond to high blood flow, as seen with the outer cerebral vasculature and growing tumor. *Blue colored* voxels correspond to areas of low blood flow, as seen in white matter, with gradation of blood flow visualized by changes in the *red-to-blue color* spectrum. Note that most recent image does not demonstrate increased perfusion

disrupted by TTFields. This disruption leads to an arrest on cell proliferation with subsequent apoptosis and theoretically provides cytotoxic therapy [6]. The prolonged survival in our patient receiving only TTFields is consistent with these pre-clinical findings.

Our patient's diagnosis of GBM was confirmed by having two independent neuro-pathologic reviews. Histologically, the hallmarks of GBM were present: widespread microvascular proliferation and pseudopalisading necrosis. However, he does have the subclass of GBM-containing oligodendroglial component [7]. Although debated, this is associated with improved outcomes. Our patient's clinical course was progressive, requiring multiple craniotomies, chemotherapy and radiation.

Radiation necrosis also needs be considered. Radiation damage to vascular endothelial cells can result in compromise of the blood–brain barrier. Although radiation necrosis cannot be ruled out, the enhancing lesion on MRI demonstrated increased cerebral blood volume on perfusion studies, which is consistent with recurrent tumor. Also, the resected samples in the two craniotomies following his initial treatment retained active tumor cells. It is notable that patients with methylated *MGMT* gene have increased risk of developing pseudoprogression; however, he started TTF therapy nearly 2 years from receiving his concurrent radiation and temozolomide. Finally, radiation necrosis or pseudoprogression will in time generally have a self-limiting course, although many cases will have disease progression as viable tumor frequently coexists within areas of radiation necrosis, and our patient has been on device for greater than 6 years with imaging evidence of residual enhancement [8]. This leads us to conclude that the imaging findings represent disease progression.

In conclusion, our patient is a unique long-term survivor of GBM with evidence of residual disease. He has received significant amount of treatment, but currently for >6 years is only receiving the NovoTTF-100A device.

Acknowledgments Authors received fund from Novocure clinical trial sponsorship.

Conflict of interest None.

References

1. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27:4733–40.
2. Valery CA, Seilhean D, Boyer O, Marro B, Hauw JJ, Kemeny JL, et al. Long-term survival after gene therapy for a recurrent glioblastoma. Neurology. 2002;58:1109–12.
3. Sperduto CM, Chakravarti A, Aldape K, Burger P, Papermaster GB, Sperduto P. Twenty-year survival in glioblastoma: a case report and molecular profile. Int J Radiat Oncol Biol Phys. 2009;75:1162–5.
4. Combs SE, Thilmann C, Edler L, Debus J, Schulz-Ertner D. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. J Clin Oncol. 2005;23:8863–9.
5. Sonoda Y, Kumabe T, Watanabe M, Nakazato Y, Inoue T, Kanamori M, et al. Long-term survivors of glioblastoma: clinical features and molecular analysis. Acta Neurochir. 2009;151:1349–58.
6. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, 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.
7. Louis DN, International Agency for Research on Cancer, World Health Organization, Deutsches Krebsforschungszentrum Heidelberg. WHO classification of tumours of the central nervous system. Lyon Geneva, Switzerland: International Agency for Research on Cancer, Distributed by WHO Press, World Health Organization; 2007. p. 309.
8. Ruben JD, Dally M, Bailey M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. Int J Radiat Oncol Biol Phys. 2006;65:499–508.