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Success and Failures of Combined Modalities in Glioblastoma Multiforme: Old Problems and New Directions

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Glioblastoma multiforme (GBM) is an aggressive intracranial tumor characterized by local and distant brain relapse despite aggressive therapy. Current standard treatment includes surgical resection followed by radiation with concurrent and adjuvant temozolomide as part of a combined modality approach. In this review, the historical basis for the current standard treatment is discussed as well as other recent combined modality successes and failures. An overview of emerging combined modality therapies for GBM is presented including immunotherapy, and rationally designed radiosensitizers. Unanswered questions facing the oncology community regarding the treatment of GBM are also discussed.
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Do not repeat the tactics which have gained you one victory, but let your methods be regulated by the infinite variety of circumstances.

(Sun Tzu 6.28)

Introduction

The therapeutic management of glioblastoma multiforme (GBM) and many other brain tumors is complicated by a unique set of challenges that are rarely seen in combination at other extracranial sites. These challenges consist of (1) *extent of resection*: tumors arising in many regions of the brain and the brainstem are unresectable because of unacceptable levels of morbidity and mortality, and the infiltrative nature of these tumors makes it virtually impossible to resect all viable tumor cells; (2) *blood-brain barrier (BBB) penetration*: many therapeutic agents, regardless of their tumor selectivity and potency, cannot cross the BBB, and in many cases, tumor penetration can be predicted but has not been confirmed in situ; (3) *tissue sensitivity*: cytotoxic agents, especially radiation therapy (RT) and many systemic DNA damaging chemotherapies, can induce significant acute toxicities in brain tissue, as well as profound late effects including cognitive dysfunction, and finally (4) *therapeutic resistance*: although controversial and not necessarily limited to GBMs, these cancers appear to contain substantial radio-resistant and chemo-resistant populations of tumor cells, as well as significant intratumoral heterogeneity at the molecular level. Because of these challenges, it is likely that any significant advance in overall survival (OS) for GBM requires an intensive, combined modality strategy, which addresses a heterogeneous and treatment-refractory disease at the primary site and at distant areas in the brain. Much like Sun Tzu's advice above, a variety of unique tactics are required for this strategy to be successful. In this review, we define and summarize the key elements of combined modality therapy for the treatment of GBM. We then present selected examples of successes and failures along the path to enhance OS for this disease, followed by a discussion of emerging opportunities for new therapy combinations. Finally, we present a series of open questions for consideration in the future for the design of new treatment regimens.

Clinical Case

We begin with a clinical case of GBM that highlights the aggressive and insidious nature of GBM, and why this disease has proved so resistant to treatment. Patient G.S. was initially diagnosed with a left frontal lobe GBM after presenting with several brief episodes of speech impairment in May of 2013. The patient was treated at our center, and the chronological magnetic resonance imaging (MRI) images for this patient are

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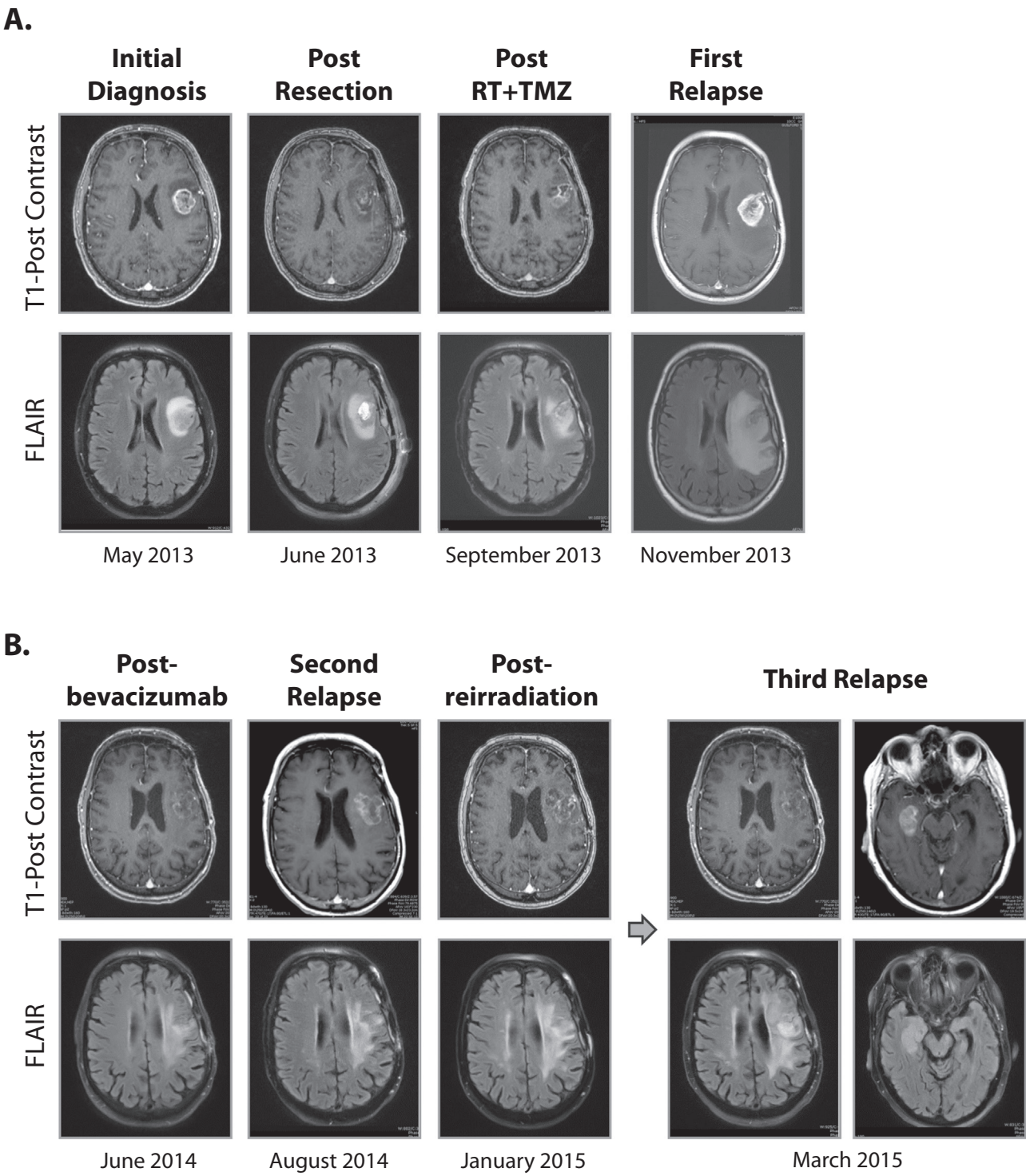

Figure 1 Chronological MRI images from a patient with GBM treated at the Yale Cancer Center with multiply recurrent disease despite aggressive treatment. a) FLAIR and T1 MRI images from the initial treatment course and first relapse approximately 6 months after diagnosis. b) Subsequent MRI images depicting bevacizumab response followed by second relapse, at which time re-irradiation with a novel radiosensitizer was performed. Approximately 6 months later, he developed a distant relapse outside initial and repeat treatment fields.

shown in the Figure. Because of the tumor's location near Broca area, he underwent an awake craniotomy with speech mapping during the procedure, and a radical but subtotal resection was performed. He was then treated with post-operative RT and concurrent, followed by adjuvant, temozolomide (TMZ) chemotherapy (Fig. A). He had his first recurrence approximately 6 months after diagnosis, which occurred within the original T1 postcontrast enhancing site of disease. He was treated on a clinical trial with a novel agent combined with bevacizumab. A posttreatment scan 6 months later revealed near-complete resolution of T1 postcontrast enhancing disease but a persistent fluid-attenuated inversion