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Extreme hypofractionation for newly diagnosed glioblastoma: rationale, dose, techniques, and outcomes

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See article by Azoulay et al. in this issue, pp. 1182–1189.

Although the typical reported survival for newly diagnosed glioblastoma patients treated on prospective trials is approximately 16 months,[1] the median survival in a large population-based analysis was only 8.1 months.[2]These data provide the sobering realization that a standard 6-week course of chemoradiotherapy accounts for 10–20% of the remaining lifespan of these patients. To decrease this "temporal toxicity," prior studies have evaluated abbreviated fractionation schedules in the elderly or those with a poorer performance status. Very few earlier approaches utilized extreme hypofractionation, which necessitates stereotactic techniques. There are, of course, several obvious patient-centric benefits of such an approach: increased convenience for the patient/caregivers, reduced transportation needs, reduced overall cost, improved treatment compliance, and better patient satisfaction. There might be biological benefits as well, such as overcoming tumor radioresistance and reducing the lymphopenic effects of standard fractionation.

In this issue, Azoulay and colleagues report outcomes of a phase I/II stereotactic radiosurgery (SRS) trial for newly diagnosed unifocal supratentorial glioblastoma (<150 cc).[3] Dose escalation from 25 to 40 Gy in 5 fractions using a standard 3 + 3 design was employed. The treated volume consisted of the resection cavity and residual enhancing tumor with a 5 mm anatomically constrained expansion; there was no inclusion of the peritumoral edema. Patients received standard-dose temozolomide for the duration of SRS and standard adjuvant temozolomide. Thirty patients (median age = 66 y; median tumor volume = 27 cc) were accrued. No grades 3–5 adverse radiation effects (ARE, the imaging correlate of radiation necrosis) were reported; pseudoprogression occurred in 5 patients (17%) at a median of 3 months. Two dose-limiting toxicities occurred at the 40 Gy dose level (grades 4 and 5). A large proportion of patients (n = 26; 86%) required bevacizumab for symptomatic pseudoprogression, ARE, or progression. The median progression-free survival (PFS) and overall survival (OS) were 8.2 and 14.8 months, respectively.

This report builds on a number of previously published extreme hypofractionated schedules (Table 1). Perhaps the first report was by Souhami et al, who, in 1987, initiated fractionated stereotactic radiotherapy for tumors involving senitive brain structures. Fifteen patients were treated with 6 fractions of 700 centigray.[4] Given the small numbers of patients in each of the studies, variations in eligibility criteria and accepted tumor volumes, differences in allowance of concurrent and adjuvant chemotherapy, variations in use of bevacizumab, and substantial differences among the treatment volumes and dose and fractionation schedules utilized, as well as the influence of performance status, extent of resection, and molecular variables such as isocitrate dehydrogenase status and O^6-methylguanine-DNA methyltransferase status, no comparative analysis of survival outcomes can be performed across these studies. However, two key areas deserve specific attention: target volume delineation and margins and the overall fractionation schedule.

Target volume delineation varies between a 2-phase (first phase targeting peritumoral edema and the second targeting the resection cavity and residual tumor) and a single phase approach (resection cavity and residual tumor without peritumoral edema), with varying expansions and no unified consensus between cooperative group trials.[5] Most centers report using institution-defined margins rather than strict adherence to cooperative group paradigms.[5]This study used only a 5 mm expansion, one of the most restricted margins used to date. Therefore, patterns-of-failure data will be important to consider with updates from this patient cohort, especially at the lower dose levels. This is especially important in light of the emergence of surgical studies that demonstrate that aggressive glioblastoma resection, including the fluid attenuated inversion recovery (FLAIR) abnormality, improves survival.[6] Therefore, the aggressive radiotherapy margin reductions should be pursued cautiously. Conversely, restricted expansion margins (without inclusion of the peritumoral edema but generous expansions from the resection cavity) have been reported to result in improved quality of life, PFS, and OS in a small phase III randomized trial.[7] These small margins will effectively reduce extraneous radiation exposure of normal brain and may decrease neurocognitive side effects. Advanced imaging to

Table 1 Select clinical studies evaluating hypofractionated schedules for newly diagnosed glioblastoma patients

Author and Year	Study Type	N	Concurrent Chemotherapy	Median Treatment Volumes (cc)	Target Volume Delineation	Tested Fractionation Schedules	Maximum BED_{10}	Maximum EQD_2
Floyd et al, 2004	Pilot	18	None	-	PTV1 = tumor resection cavity, residual enhancing tumor PTV2 = peritumoral edema	PTV1: 50 Gy / 10 fx PTV2: 30 Gy / 10 fx	75.0 Gy	62.5 Gy
Chen et al, 2011	Phase I	16	Temozolomide	87	GTV = tumor resection cavity, residual enhancing tumor CTV = GTV + FLAIR volume PTV1 = GTV + 5 mm PTV2 = CTV + 5 mm	PTV1: 60 Gy / 10–20 fx PTV2: 30–45 Gy / 10–20 fx	96.0 Gy	80.0 Gy
Reddy et al, 2012	Phase II	24	Temozolomide	97.9	GTV = tumor resection cavity, residual enhancing tumor CTV = GTV + FLAIR volume PTV1 = GTV + 5 mm PTV2 = CTV + 5 mm	PTV1: 60 Gy / 10 fx PTV2: 30 Gy / 10 fx	96.0 Gy	80.0 Gy
Iuchi et al, 2014	Phase II	46	Temozolomide	80.9	GTV = tumor resection cavity, residual enhancing tumor PTV1 = GTV + 5 mm PTV2 = PTV1 + 15 mm PTV3 = FLAIR signal	PTV1: 68 Gy / 8 fx PTV2: 40 Gy / 8 fx PTV2: 32 Gy / 8 fx	125.8 Gy	104.8 Gy
Ney et al, 2014	Phase II	30	Temozolomide + bevacizumab	131.1	GTV = tumor resection cavity, residual enhancing tumor GTV2 = FLAIR signal PTV1 = GTV1 + 10 mm PTV2 = GTV2 + 10 mm	PTV1: 60 Gy / 10 fx PTV2: 30 Gy / 10 fx	96.0 Gy	80.0 Gy
Omuro et al, 2014	Phase II	40	Temozolomide + bevacizumab	All <60	GTV = tumor resection cavity, residual enhancing tumor GTV2 = FLAIR signal CTV1 = GTV + 5 mm CTV2 = GTV2 + 20 mm PTV1 = CTV1 + 5 mm PTV2 = CTV + 5 mm	PTV1: 36 Gy / 6 fx PTV2: 24 Gy / 6 fx	57.6 Gy	48 Gy
Azoulay et al, 2020	Phase I/II	30	Temozolomide	60	GTV = tumor resection cavity, residual enhancing and nonenhancing tumor CTV = GTV + 5 mm PTV = CTV	25–40 Gy / 5 fx	72.0 Gy	60 Gy

GTV = gross tumor volume, CTV = clinical target volume, PTV = planning target volume, fx = fraction, BED = biologically effective dose, EQD2 = equivalent dose at 2 Gy/fraction.

ensure coverage of the hyperperfused and hypercellular regions which represent the highest risk for tumor recurrence will be important as margins continue to shrink.[8]

The maximum tolerated dose in this trial, 40 Gy in 5 fractions, represents a biologically effective dose of 72 Gy (Table 1), delivered in one week. As tumor kinetic models of glioma stem cells and nonstem cancer cells demonstrate radioresistance to fractionated treatment,[9] a stereotactic approach with high dose per fraction and reduced treatment time may overcome this biological barrier. In addition, chemotherapy and corticosteroids, with traditional fractionated radiotherapy, frequently result in long-lasting CD4 count reduction, which is associated with increased mortality from tumor progression.[10] Constraining radiotherapy volumes represents one method of reducing the risk of treatment-related lymphopenia[11]; and advanced techniques, such as proton therapy, may help reduce this even further. Modeling experiments have demonstrated that a conventionally fractionated course over 6 weeks results in exposure of 99% of the circulating blood to ≥0.5 Gy.[12] Therefore, an approach which employs the highest tolerable dose per fraction, with the smallest acceptable treatment margin, over the shortest period of time would be the most biologically effective and least immunosuppressive approach. This must, of course, be balanced against associated risks. Hypofractionation, especially of large targets, is known to induce radionecrosis. In this context, the almost 90% utilization of bevacizumab must be borne in mind. In fact, it is quite likely that as in a previously published trial, which also employed extreme hypofractionation, bevacizumab might be a necessary component of such an aggressive approach.[13] Courtesy of the publication by Azoulay and colleagues, we seem to at least have the framework for an optimal fractionation schedule for further study.

So what future directions could be developed? First, for patients with smaller volume disease and the need for avoiding immunosuppression, this is a relatively easy option to implement. Second, with the avoidance of lymphopenia with such an approach, as well as the higher likelihood of unleashing neoantigens, SRS could be better suited for a combinatorial approach with immune

checkpoint inhibitors (and the use of bevacizumab in this context would be an additional positive variable). Therefore, although not immediately practice changing, this approach deserves further clinical trial evaluation.

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