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‘Elderly’ patients with newly diagnosed glioblastoma deserve optimal care

Matthias Holdhoff,

Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1550 Orleans Street, 1M16, Baltimore, MD 21287, USA

Gary L. Rosner,

Division of Biostatistics and Bioinformatics, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Sara Alcorn, and

Department of Radiation Oncology and Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Stuart A. Grossman

Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1550 Orleans Street, 1M16, Baltimore, MD 21287, USA

The treatment of ‘elderly’ patients with newly diagnosed glioblastoma (GBM) has received considerable attention following the recently published results of two randomized, prospective, multicenter trials designed to establish optimal therapy in this patient population [1, 2]. The first trial, NOA-08, randomized 373 patients over the age of 65 years with anaplastic astrocytoma or GBM to either standard radiation (60 Gy in 30 fractions) or dose dense temozolomide (100 mg/m² 1 week on, 1 week off) [1]. The second trial, named the Nordic trial, randomized 342 patients over the age of 60 to three arms: (1) hypofractionated radiation (34 Gy in 10 fractions), (2) standard radiation, and (3) single-agent temozolomide (200 mg/m² for five consecutive days every month) [2]. Both of these studies conclude that temozolomide alone was ‘not inferior’ to radiation, implying that single-agent chemotherapy should be considered as a standard of care in this patient population.

However, the standard of care for patients with newly diagnosed GBM consists of 6 weeks of radiation to 60 Gy with daily concomitant temozolomide, followed by 6 months of adjuvant temozolomide, based on the landmark EORTC/NCIC study published in 2005 [3]. The 5-year follow-up data of this trial demonstrated that radiation with temozolomide provided superior outcomes compared to radiation alone in each accrued age group, including patients age 61–70 (hazard ratio of 0.7 {0.5–0.97}) [4].

	Median survival (months)	2 year survival	3 year survival	4 year survival	5 year survival
Radiation	11.8	5.7 %	2.3 %	2.3 %	0%
Radiation and temozolomide	10.9	21.8 %	12.3 %	8.8 %	6.5 %

From: Stupp et al. Lancet Oncol 2009. Patients over the age of 60

It should be noted that neither the NOA-08 nor the Nordic trial contained a comparison arm of standard radiation and temozolomide. In the Nordic trial, the 60–70 year old patients had a median survival of only 8.3 months if they received hypofractionated radiation and 7.8 months if they received temozolomide alone. These results are inferior to the age-matched results from the EORTC/NCIC trial [3, 4]. In the NOA-08 trial, the definitions for non-inferiority were so broad that radiation alone would have been considered ‘not inferior’ to radiation combined with temozolomide in the pivotal EORTC/NCIC study, based on treatment-specific median survivals reported in the latter study. Furthermore, using a non-inferiority design when predictable treatment crossovers will occur is likely to yield “non-inferior” survival results, which ultimately have little or no impact on medical practice.

Institutional and national bodies that establish clinical practice treatment guidelines will review these two prospective randomized trials. Extreme caution should be used in concluding that temozolomide alone is an acceptable standard in this patient population, since approximately 45 % of all patients with GBM are over the age of 65 [5]. Chronologic age alone is simply insufficient to determine if an individual patient will tolerate combination therapy [6]. Prescribing single agent temozolomide to an older patient with an excellent performance status after a gross total resection of an MGMT promoter-methylated glioblastoma was entirely possible within the context of these research studies and could be viewed as acceptable practice using the conclusions of these studies. However, this approach is unlikely to provide optimal therapy for such a patient. One ongoing trial (EORTC 22061-26062) randomizes elderly patients with glioblastoma to radiation and chemotherapy versus radiation (www.clinicaltrials.gov). Unfortunately, this study will not resolve the outstanding question as it employs a non-standard short-course of radiation in both arms without a standard treatment arm.

As a result, until proven otherwise, older patients with newly diagnosed GBM who are clinically fit should be offered the best available therapy, which as of 2013 remains radiation and temozolomide as defined by the EORTC/NCIC study [3, 4].

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