Glioblastoma multiforme: A bigger challenge in resource-limited countries

Glioblastoma multiform (GBM), the most common and the most aggressive brain tumor in older adults, once diagnosed kills majority of the patients within the first year despite aggressive surgical resection and high doses of radiation therapy (RT). Initially, nitrosureas such as lomustine were the main chemotherapeutic agents used although they only showed modest success.[1] Since Stupp *et al.* published their breakthrough findings in 2002, the accepted standard therapy worldwide for GBM has been concurrent fractionated RT (60 Gy, 2 Gy × 5 d/wk for 6 weeks) with temozolamide followed by maintenance therapy with temozolamide prolonged the survival with minimal toxicity.[2] Investigators later found that a higher initial Karnofsky performance Score and O6-methylguanine–DNA methyltransferase (MGMT) methylation were associated with better prognosis and longer survival.[3,4]

In this issue of the *Journal*, Kumar *et al.* reported a series consisting of 439 patients with GBM over a period of nine years in their institution where healthcare was not equally accessible or affordable.[5] They divided the group into two groups: Those whose Karnofsky Performance Score was <70 and received RT dose of 30-35 Gy in 10-15 fractions and those with Karnofsky Performance Score ≥70 who received conventional RT dose of 60 Gy in 30 fractions once daily for five days a week with or without adjuvant chemotherapy with temozolamide or lomustine. The authors found that the two-year survival rates were 2.2% and 8.2% with median survivals of 6.3 and 7.9 months, respectively, ($P = 0.0010$). They also found that the main reason for not initiating or discontinuation of RT or adjuvant chemotherapy with either temozolamide or lomustine was secondary to cost and not due to toxicity. The study was limited by its retrospective nature and grouping of patients based solely on performance status with those in poor performance status plus larger tumor burden selectively receiving lower RT doses, thus faring worse. The challenges the authors faced as with many similar resource-limited countries was being unable to provide what is the known best standard of care for their patients. The authors urged that in patients with poor performance status, hypofractionated RT schedule may be considered.

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In a recent publication in Lancet Oncology by Malstrom *et al.* consisting of 291 patients with GBM, the investigators found that the standard fractionated RT (60 Gy administered in 2 Gy fractions over 6 weeks) was associated with poor outcomes, especially in patients older than 70 years. In their study, the median survival in the intent-to-treat population was 8.3 months for temozolomide, 7.5 months for hypofractionated radiation, and 6 months for standard radiation. The authors concluded that both temozolomide and hypofractionated radiotherapy as defined by (34 Gy administered in 3·4 Gy fractions over 2 weeks) should be considered as standard treatment options in elderly patients with glioblastoma.[6] Similarly, Lo *et al.* highlighted their findings during the 2011 American Society of Clinical Oncology annual meeting and concluded hypofractionated radiotherapy to be a safe and effective treatment for glioblastoma, especially in those patients who are elderly or have poor performance status.[7]

In resource-limited countries with high patient volume, late disease presentation, and high treatment abandonment, we are far from being able to provide testing on MGMT promoter methylation status as a useful predictive marker for benefit from temozolomide or various other targeted anti-angiogenic therapies. Would it then be more desirable to consider hypofractionated RT as the standard therapy for those diagnosed with GBM? As Kumar *et al.* have revealed, hypofractionated RT is well-tolerated, and it can also reduce the overall treatment time without negative effects on survival compared with conventional fractionation.

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