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## Bevacizumab as an adjuvant therapy for glioblastoma in elderly patients: the facts

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Glioblastoma (GBM) is the most aggressive and common primary brain tumor in adults, recurring in an average of 6.9 months after initial diagnosis even with aggressive treatment (1,2). After initial diagnosis, most patients survive an average of 14 months (3). Since 2005, the standard of care for GBM that has provided a clinically significant survival benefit with minimal toxicity from adjuvant treatments has consisted of surgical resection, followed by conventional radiation therapy (RT) with concomitant and adjuvant temozolomide (TMZ) chemotherapy (4). These treatment guidelines, known as the Stupp protocol, were originally based off a large, randomized controlled trial using data obtained in patients less than 70 years old (4,5). According to the most recent Central Brain Tumor Report of the United States (CBTRUS), GBM is found to have the highest average age-adjusted incident rates in patients age 65 to 84 years old and the lowest 1-, 2-, and 5-year relative survival rates when compared to younger patients diagnosed with a GBM (6). Because of this, many clinical studies have been performed to determine if the guidelines set forth in the Stupp protocol should likewise be applied to elderly patients with an intracranial GBM. Additionally, recent clinical trials testing the popular adjuvant chemotherapy bevacizumab (BEV) in the elderly population will be analyzed.

Compared to the younger population groups, most elderly patients present with diminished functional reserves, have additional comorbidities, and exhibit a slower recovery after surgery (7). Therefore, debate has existed regarding the surgical strategy, if any, for the elderly population. In a recent large-scale retrospective study based on the Surveillance, Epidemiology, and End Results (SEER) registry, gross total resection of GBM improved overall survival (OS), even in the elderly population when compared to subtotal resection or no resection at all (8). A careful preoperative evaluation must be carried out though as elderly patients with a higher Karnofsky Performance Status (KPS) score, tumors in non-eloquent areas, methylated O-6-methylguanine-DNA-methyltransferase (MGMT) promoter status, and without a compromised neurological status are more likely to benefit from aggressive surgical resection (9).

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RT remains a mainstay of treatment in the elderly population undergoing gross total resection of GBM, although the dosing pattern for this population group is under debate. A standard 6-week course of RT in the elderly population is associated with substantial risks of morbidity and early discontinuation, thus leading to investigations into shorter courses of radiation (5). In a recent prospective randomized clinical trial, elderly patients receiving the conventional 6 weeks of RT were compared against elderly patients receiving RT over 3 weeks (10). No difference in survival was found between the standard and the 3-week course of RT. In a more recent randomized controlled trial, elderly patients undergoing a short 1-week course of RT showed no differences in OS, progression-free survival (PFS), nor quality of life when compared to patients receiving 3 weeks or more of RT for GBM (11).

In addition to maximal safe resection and RT, Perry *et al.* showed patients greater than 65 years old with methylated forms of the MGMT promoter also benefit from TMZ in combination with RT (OS 13.5 months) versus RT alone (OS 7.7 months) (12). Patients with GBM with unmethylated forms of the MGMT promoter also showed increased OS to TMZ/RT treatment (OS 10.0 months) *vs.* RT alone (OS 7.9 months). Although TMZ has proven effective and safe, many trials have been performed to determine if other chemotherapeutic agents may provide additional benefit to the elderly population, specifically the anti-angiogenic agent BEV.

Since receiving Food and Drug Administration approval in 2009 for the use in patients with GBM, BEV has safely been used in combination with TMZ and other agents in the treatment of primary and recurrent GBM (13). As an immunotherapy agent, BEV acts by blocking the interaction of vascular endothelial growth factor A (VEGF-A), an important signal protein, with the VEGF and neuropilin receptors (14,15). These receptors, when activated, lead to endothelial cell proliferation with subsequent rapid tumor growth. Although many high-quality, phase 3 randomized control trials have tested the addition of BEV to the treatment regimen for younger patients with GBM, the elderly population has not been well represented (16,17).

In a retrospective study, BEV was shown to be more beneficial in certain groups of patients versus others, namely the elderly and patients with a lower KPS score. In a retrospective study, Nghiemphu *et al.* compared a group of 44 patients with recurrent GBM greater than 55 years old with a KPS less than 80 treated with BEV compared against a control group receiving no additional treatments (18). Results indicated an increased PFS by 2.4 months and OS by 2.9 months in the group treated with BEV. In this study cohort, patients aged greater than 55 years old showed a 1.4-fold higher expression of VEGF-A when compared to younger patients, possibly accounting for the observed increase in PFS and OS. Furthermore, dexamethasone requirements were reduced in patients on BEV.

Results of this study spurred additional studies in the elderly. A retrospective study involving 120 patients was performed by Babu *et al.* in patients greater than 65 years old with a median KPS score of 80 (19). Patients were treated with maximum safe resection, followed by RT and TMZ. Approximately 60% of patients underwent treatment with additional agents, most commonly BEV or Irinotecan. Results indicated patients undergoing gross total resection who were of older age, with a higher baseline KPS score, and who were treated

with BEV to have significantly increased survival when compared to patients undergoing subtotal tumor resection. Furthermore, patients those treated with BEV versus Irinotecan or no agents at all had a significant increase in OS.

A prospective study by Reyes-Botero *et al.* sought to evaluate the effects of BEV in combination with TMZ in a group of 66 patients greater than 70 years old with a KPS <70 as the initial treatment after diagnosis of GBM (20). Comparing this patient group treated with TMZ/BEV combination therapy with a similarly aged group undergoing no surgical, radiation, or chemotherapies for a newly diagnosed GBM revealed an increase in the OS by 12 weeks. In fact, one third of patients became autonomous and capable of self-care (KPS >70). Although TMZ/BEV combination therapy may sound promising in this population group, a study performed years prior using only TMZ in the same population group yielded similar improvement in OS with the same proportion of patients becoming autonomous and capable of self-care (21). Since TMZ is less effective in patients harboring a non-methylated MGMT promoter, additional patients may benefit when BEV is combined with TMZ therapy (20,21).

To truly determine if past retrospective and prospective studies performed with BEV benefitted the elderly population, Wirsching *et al.* performed the first randomized control study in a group of 75 elderly patients with GBM treated with RT combined with BEV to patients receiving hypofractionated RT only (22). Patients greater than 65 years old with a KPS of >60 were enrolled in this trial who had undergone surgical resection of GBM within the last 28 to 49 days. Patients selected for this trial had a non-methylated form of the MGMT promoter since previous studies have already shown elderly patients with a methylated form of MGMT are best treated with TMZ therapy with or without hypofractionated RT (5). Patients receiving BEV in combination with RT had a longer PFS by 2.8 months when compared to patients receiving hypofractionated RT only, but there was no significant difference in OS, with both groups tested having an OS of slightly over 12 months. Analyzing the results further indicated patients with the receptor tyrosine kinase I methylation subtype and proneural gene expression gene subtype had the strongest association of improved PFS from BEV treatment.

Although increased OS could not be supported with the first randomized controlled trial performed by Wirsching *et al.*, PFS was seen to be improved in each clinical trial of elderly patients with GBM treated with BEV. In addition to PFS, BEV also has a notable steroid-sparing effect because of blood brain barrier and blood tumor barrier restoration that may help elderly patients wean off steroids sooner, thus improving quality of life (20). In addition, the amount of symptomatic radiation necrosis in the elderly patients may also be reduced with the BEV adjuvant therapy (23). Although PFS may be increased, the risk of adverse events associated with BEV needs to be considered, especially in the elderly population. In the randomized clinical trials above, patients on BEV experienced an increased amount of hypertension, proteinuria, pulmonary embolism, deep venous thrombosis, and wound healing complications (16,17). Additional randomized clinical trials specifically investigating the elderly population with GBM are needed to guide practitioners to deliver the best pharmacological therapies while minimal risk to these patients.

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