Bevacizumab for newly diagnosed glioblastoma

- Evaluating treatment outcome of Glioblastoma with Stupp's regimen: an experienced in single Institute
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Bevacizumab, a medication that targets blood vessel formation, has been studied for its potential use in the treatment of newly diagnosed glioblastoma, a type of aggressive brain cancer. However, its role in the treatment of newly diagnosed glioblastoma remains a topic of ongoing research and debate within the medical community.

Here are some key points regarding the use of bevacizumab for newly diagnosed glioblastoma:

Clinical Trials: Bevacizumab has been evaluated in clinical trials as part of treatment regimens for newly diagnosed glioblastoma. These trials aimed to determine whether adding bevacizumab to standard treatments, such as surgery, radiation therapy, and chemotherapy (temozolomide), could improve outcomes for patients.

Mixed Results: The results of clinical trials investigating bevacizumab for newly diagnosed glioblastoma have been mixed. While some studies have reported potential benefits in terms of progression-free survival and radiographic response, others have not shown a significant overall survival advantage.

Controversy: The use of bevacizumab in newly diagnosed glioblastoma has been a subject of controversy in the medical community. Some experts argue that the drug may provide temporary relief from symptoms and reduce tumor-related swelling (edema), but it may not significantly extend overall survival or improve long-term outcomes.

Clinical Decision-Making: The decision to use bevacizumab for newly diagnosed glioblastoma is typically made on an individual basis, taking into account the patient's specific circumstances, tumor characteristics, and treatment goals. It is often considered when other treatment options have limited effectiveness or when the patient experiences significant symptoms related to the tumor.

Potential Side Effects: Bevacizumab, like all medications, can have side effects. Common side effects

may include high blood pressure, bleeding, clotting disorders, and gastrointestinal problems. Patients should be closely monitored for these and other potential side effects while on treatment.

Ongoing Research: Research into the use of bevacizumab and other targeted therapies for glioblastoma is ongoing. New treatment approaches and combinations are continually being explored in clinical trials to determine their effectiveness.

The AVAglio trial has reported an improvement of quality of life, while the RTOG 0825 did not, and suggested a negative impact on neurocognitive functions. The GLARIUS trial, focusing on newly diagnosed glioblastoma without MGMT methylation, suggested an advantage for bevacizumab plus irinotecan. The Phase III CENTRIC trial has excluded any role for cilengitide in addiction to standard treatment in newly diagnosed glioblastoma [1)].

The administration of bevacizumab via convection-enhanced delivery (CED) increases survival over that of treatment with IV bevacizumab. Thus, CED of bevacizumab alone or in combination with chemotherapy can be an effective protocol for treating gliomas [2)].

A study by Weller et al. demonstrated that while bevacizumab was associated with a significant advantage in terms of progression-free survival for a specific subtype of glioblastoma (proneural IDH wild-type tumors), it did not confer a significant overall survival benefit in this patient population. These findings were consistent across different analyses and subgroups, highlighting the complexities of treatment response in glioblastoma patients with varying genetic profiles [3)].

CDKN1A, also known as p21 or Waf-1, is a protein that plays a crucial role in controlling various aspects of cell behavior, such as regulating cell growth, causing cells to stop dividing, promoting their differentiation into specialized cell types, and even triggering cell death (apoptosis). In the context of cancer, CDKN1A acts as a tumor suppressor by inhibiting the uncontrolled growth of cancer cells.

In this study, the researchers focused on a specific genetic variant of CDKN1A known as c.93C > A, which involves a change in the DNA code at position 93, resulting in the substitution of one amino acid (serine) with another (arginine) at position 31 in the p21 protein. This genetic variation is known to exist naturally in human populations and has been linked to certain types of cancer.

The study involved 139 adult Chinese patients in Taiwan who had been diagnosed with glioblastoma multiforme (GBM), a particularly aggressive form of brain cancer. To investigate the presence of the c.93C > A polymorphism, the researchers extracted genomic DNA from tumor samples obtained from these patients. They used a laboratory technique called polymerase chain reaction (PCR) followed by restriction fragment length polymorphism analysis (RFLP) to identify whether patients had specific genetic variations at this site.

The distribution of these genetic variations among the GBM patients was as follows: 23.02% had two copies of the serine allele (Ser/Ser), 27.34% had two copies of the arginine allele (Arg/Arg), and 49.64% had one copy of each allele (Ser/Arg).

The study's findings revealed that the presence of the CDKN1A c.93C > A polymorphism was not directly associated with overall survival in GBM patients. However, a significant observation was made regarding survival benefits in individuals with Arg/Arg and Arg/Ser genotypes who received a combined treatment approach involving concurrent chemoradiotherapy (CCRT) and bevacizumab, compared to those who underwent CCRT alone.

In essence, this research suggests that the presence of the CDKN1A c.93C > A polymorphism may have implications for the development and prognosis of GBM. It indicates that individuals with specific genetic variants may respond differently to treatment with bevacizumab, a medication used in the management of GBM. While further research is needed to fully understand the underlying mechanisms, these findings offer insights into the potential use of genetic information for predicting how GBM patients may respond to certain therapies, particularly bevacizumab, and could aid in tailoring treatment strategies for better outcomes [4)].

The recommended treatment for MGMT promoter unmethylated glioblastoma (Glioblastoma) is radiation therapy with concurrent/adjuvant temozolomide (TMZ).

Although overall survival (OS) is the standard for determining Glioblastoma treatment efficacy, using OS as an endpoint when studying new therapeutic strategies can be problematic because of potential influence of therapies prior to or subsequently following the therapy being studied. For example, it is difficult to definitively conclude that bevacizumab has no efficacy in Glioblastoma when a large percentage of patients in the placebo arms in both III trials studying efficacy of bevacizumab (i.e. AVAglio and RTOG 0825) eventually crossed over and received bevacizumab (31% in AVAglio) [5)] and 48% in RTOG-0825 [6)]. If bevacizumab increased OS when given at any time during treatment, we may expect both treatment arms to have similar median OS since most patients eventually were treated with bevacizumab, disguising any therapeutic effects of the drug. Together, these results suggest OS may not be a suitable endpoint when studying new therapeutics or when there is a high chance of cross over in the control arm [7)].

Trials

AVAglio: a phase III trial with the addition of bevacizumab to the Stupp regimen for newly diagnosed GBM [8)] and RTOG 0825 (another trial of similar design) showed improved PFS, but no significant improvement on OS [9)].

Yang et al. analyzed four clinical trials, including 607 patients, to investigate the efficacy and safety of bevacizumab when combined with chemotherapy for the treatment of glioblastomas. Results demonstrated that bevacizumab when combined with chemotherapy improved progression-free survival (HR = 0.66; 95% CI 0.56-0.78; $p < 0.00001$) compared with bevacizumab or chemotherapy alone. Furthermore, overall survival showed insignificant difference between two arms (HR 0.99; 95% CI 0.8-1.21; $p = 0.92$). However, we found that patients treated with bevacizumab-containing therapy reported increased objective response rate (OR 1.85, 95% CI 1.17-2.93; $p = 0.009$), but more treatment-related adverse events (OR 1.75; 95% CI 1.09-2.83; $p = 0.02$) [10)].

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