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[Intervention Review]

Anti-PD-1 and anti-PD-L1 antibodies for glioma

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ABSTRACT

Background

Glioblastoma multiforme (GBM) is the most common and aggressive adult glioma (16-month median survival). Its immunosuppressive microenvironment limits the efficacy of immune checkpoint inhibitors (ICIs).

Objectives

To assess the effects of the ICIs antibodies anti-programmed cell death 1 (anti-PD-1) and anti-programmed cell death ligand 1 (anti-PD-L1) in treating adults with diffuse glioma.

Search methods

We searched CENTRAL, MEDLINE, Embase, and clinical trials registers on 8 March 2024.

Selection criteria

We included randomised controlled trials (RCTs) evaluating adults with diffuse glioma treated with anti-PD-1/PD-L1 compared to placebo or other therapies used alone or with other ICIs. Primary outcomes were overall survival (OS), progression-free survival (PFS), and serious adverse events (SAE). Secondary outcomes were overall response rate (ORR), quality of life (QoL), and less serious AEs.

Data collection and analysis

We followed standard Cochrane methods.

Main results

We included seven RCTs evaluating anti-PD-1 treatment in recurrent (N = 4) and newly diagnosed (N = 3) grade 4 glioma participants. The analysis encompassed 1953 participants; sample sizes ranged from 35 to 716. Meta-analyses were not possible due to heterogeneity and the small number of studies. Most trials had high risk of bias.

Nivolumab versus bevacizumab in people with recurrent GBM (1 trial, 369 participants)

Nivolumab probably does not increase OS (hazard ratio (HR) 1.04, 95% confidence interval (CI) 0.83 to 1.30; 1.3% more, 95% CI 6.30 fewer to 7.80 more; 369 participants; moderate-certainty evidence) or PFS (HR 1.97, 95% CI 1.57 to 2.48; 16.40% more, 95% CI 12.40 more to 19.00 more; 369 participants; moderate-certainty evidence). The evidence for SAE is very uncertain (risk ratio (RR) 1.20, 95% CI 0.74 to 1.92; 347 participants). Nivolumab probably does not increase ORR (RR 0.34, 95% CI 0.18 to 0.63; 309 participants; moderate-certainty evidence), but may not increase less serious AEs (RR 1.03, 95% CI 0.96 to 1.10; 347 participants; low-certainty evidence).

Nivolumab plus bevacizumab 10 mg/kg versus nivolumab plus bevacizumab 3 mg/kg in people with recurrent GBM (1 trial, 90 participants)

Nivolumab plus bevacizumab 10 mg/kg may not increase OS (HR 1.39, 95% CI 0.86 to 2.25; 9.90% more, 95% CI 5.20 fewer to 18.80 more; 90 participants; low-certainty evidence). The evidence for PFS (HR 1.23, 95% CI 0.78 to 1.93; 5.80% more, 95% CI 8.20 fewer to 14.20 more; 90 participants) and SAE (RR 1.19, 95% CI 0.79 to 1.79; 90 participants) is very uncertain. Nivolumab may not increase less serious AEs (RR 1.02, 95% CI 0.96 to 1.09; low-certainty evidence; 90 participants).

Pembrolizumab plus bevacizumab versus pembrolizumab in people with recurrent GBM (1 trial, 80 participants)

The evidence for OS (HR 1.03, 95% CI 0.65 to 1.63; 0.30% more, 95% CI 7.60 fewer to 2.90 more; 80 participants), PFS (HR 0.97, 95% CI 0.61 to 1.54: 0.40% fewer, 95% CI 9.20 fewer to 2.80 more; 80 participants), SAE (RR 1.32, 95% CI 0.75 to 2.42; 80 participants), and ORR (RR 12.76, 95% CI 0.77 to 210.27; 80 participants) is very uncertain. Pembrolizumab plus bevacizumab may not increase less serious AEs (RR 1.04, 95% CI 0.96 to 1.13; 80 participants; low-certainty evidence).

Neoadjuvant (before surgical resection) and adjuvant (after surgical resection) pembrolizumab versus adjuvant-only pembrolizumab in people with recurrent GBM (1 trial, 35 participants)

The evidence for OS (HR 0.39, 95% CI 0.17 to 0.92; 25.20% fewer, 95% CI 37.10 fewer to 2.10 fewer; 35 participants), PFS (HR 0.43, 95% CI 0.20 to 0.91; 30.10% fewer, 95% CI 52.20 fewer to 3.60 fewer; 35 participants), and SAE (RR 1.00, 95% CI 0.31 to 3.28; 32 participants) is very uncertain.

Nivolumab plus radiotherapy versus temozolomide plus radiotherapy in people with newly diagnosed unmethylated GBM (1 trial, 560 participants)

Nivolumab plus radiotherapy probably does not increase OS (HR 1.31, 95% CI 1.09 to 1.58 months; 8.30% more, 95% CI 2.80 more to 12.90 more; 560 participants) and PFS (HR 1.38, 95% CI 1.15 to 1.65 months; 7.50% more, 95% CI 3.60 more to 10.30 more; 560 participants; moderate-certainty evidence). The evidence for SAE is very uncertain (RR 0.87, 95% CI 0.65 to 1.18; 553 participants). It may not increase ORR (RR 1.08, 95% CI 0.43 to 2.69; 560 participants; low-certainty evidence) and probably does not increase less serious AEs (RR 1.00, 95% CI 0.96 to 1.04; 560 participants; moderate-certainty evidence). The evidence for time to deterioration of QoL is very uncertain (HR 0.76, 95% CI 0.59 to 0.99; 560 participants).

Nivolumab plus temozolomide plus radiotherapy versus placebo plus temozolomide plus radiotherapy in people with newly diagnosed methylated GBM (1 trial, 716 participants)

Nivolumab plus temozolomide plus radiotherapy probably does not increase OS (HR 1.10, 95% CI 0.92 to 1.32; 3.50 more, 95% CI 3.80 fewer to 9.60 more; 716 participants) and PFS (HR 1.10, 95% CI 0.92 to 1.32; 3.00 more, 95% CI 3.50 fewer to 7.90 more; 716 participants), and probably increases SAE (RR 2.91, 95% CI 2.05 to 4.12; 709 participants; moderate-certainty evidence). It does not increase less serious AEs (RR 1.02, 95% CI 1.00 to 1.04; 709 participants; high-certainty evidence).

Adjuvant nivolumab plus temozolomide versus temozolomide in older people with GBM (1 trial, 103 participants)

Nivolumab plus temozolomide probably does not increase OS (HR 0.85, 95% CI 0.54 to 1.33; 3.10 fewer, 95% CI 15.80 fewer to 3.60 more; 103 participants; moderate-certainty evidence) and PFS (HR 0.77, 95% CI 0.49 to 1.19; 5.40 fewer, 95% CI 19.10 fewer to 2.40 more; 103 participants; moderate-certainty evidence). The evidence for SAE is very uncertain (RR 1.58, 95% CI 0.88 to 2.81; 103 participants). The evidence for QoL is very uncertain (results only reported graphically; 103 participants).

Authors' conclusions

In recurrent GBM, nivolumab alone probably has no benefit. Anti-PD1 plus bevacizumab may also be ineffective based on low- to very low-certainty evidence. Neoadjuvant plus adjuvant pembrolizumab may improve OS and PFS, but this was based on only one small trial and very low-certainty evidence. In newly diagnosed GBM, nivolumab plus radiotherapy in unmethylated and plus radiotherapy plus temozolomide in methylated GBM probably has no benefit. In older participants, adjuvant nivolumab probably offers no benefit.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of different immunotherapy drugs for treating glioblastoma (a cancerous brain tumour)?

Key messages

• A form of immunotherapy known as immune checkpoint inhibitors (ICIs), which uses the body's immune system to fight disease, has shown encouraging results in the treatment of some cancers.

• Seven studies looked at the ICI anti-programmed cell death 1 (anti-PD-1) for the treatment of adults with glioblastoma. Six of them showed no benefit. One small trial showed an improvement in overall survival and progression-free survival, but the evidence is very uncertain.

• More high-quality studies looking at different combinations of ICIs are needed.

What is glioblastoma?

Glioblastoma (GBM) is the most common cancerous brain tumour in adults. People diagnosed with GBM can have a variety of symptoms, including headache, changes in behaviour and personality, seizures or other symptoms similar to a stroke. This can occur over a longer or shorter period of time. Overall survival (the length of time from the date of diagnosis or the start of treatment to death) is around 16 months.

Treatment is based on removing as much of the tumour as possible by surgery, followed by chemotherapy and radiotherapy; however, these are not very effective, thus there is a need for alternative treatments. New treatments using immunotherapy (immune checkpoint inhibitors (ICIs), or immune checkpoint blockers (ICBs)) have shown promising results for treating some cancers, with good response rates, leading to improved survival. ICIs stop unwanted inflammation and damage to normal tissues, acting as a 'brake' to halt the body's immune response. Recent studies of tumour tissue from people with GBM showed that they have receptors that interact with ICIs. We need to know if ICIs can treat GBM and improve patient survival.

What did we want to find out?

We wanted to find out if two types of ICIs (anti-programmed cell death 1 (anti-PD-1) and anti-programmed cell death ligand 1 (anti-PD-L1)) are effective and safe in adults with GBM.

We need to distinguish people with GBM who will respond to a particular type of treatment from those that will not. The identification of markers that predict response to anti-PD-1/anti-PD-L1 will help to determine who will benefit the most from this treatment.

What did we do?

We searched for studies that looked at the effects of ICIs (such as nivolumab and pembrolizumab) in adults with GBM. We compared and summarised the results of these studies and rated our confidence in the evidence based on factors such as study methods and sizes.

What did we find?

We found seven studies dating from 2019 to 2023. The studies looked at anti-PD-1 treatment in a total of 1953 people with newly diagnosed (3 studies) and recurrent (4 studies) GBM. Each trial looked at a different comparison, preventing the combining of data. The studies looked at the following seven comparisons.

• Nivolumab versus bevacizumab

• Nivolumab plus high-dose bevacizumab versus nivolumab plus low-dose bevacizumab

• Pembrolizumab plus bevacizumab versus pembrolizumab

• Pembrolizumab used before and after surgery to remove the tumour versus pembrolizumab used only after surgery

• Nivolumab plus radiotherapy versus temozolomide plus radiotherapy

• Nivolumab plus temozolomide plus radiotherapy versus temozolomide plus radiotherapy

• Nivolumab plus temozolomide versus temozolomide in older people

Results from six trials showed no benefit for overall survival. One trial suggested that pembrolizumab used before and after surgery to remove the tumour may improve overall survival when compared with pembrolizumab used only after surgery, but the evidence is very uncertain.

Results from six trials showed no benefit for progression-free survival (the length of time a person is on treatment before the cancer starts to regrow). One trial suggested that pembrolizumab used before and after surgery to remove the tumour may improve progression-free survival when compared with pembrolizumab used only after surgery, but the evidence is very uncertain.

What are the limitations of the evidence?

We are only very low to moderately confident in the evidence because study methods were sometimes unclear and therefore could have been inadequate, and in six studies, the people evaluating the outcomes knew which treatments participants had received, which could have influenced the results. High-quality studies are needed to increase our confidence in the findings.

How up-to-date is this evidence?

The evidence is current to 8 March 2024.