COMBINATION THERAPY FOR THE TREATMENT OF GLIOBLASTOMA

Field of the Invention

This invention concerns in general treatment of diseases and pathological conditions with anti-VEGF antibodies. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with glioblastoma using an anti-VEGF antibody, in combination with one or more additional anti-tumor therapeutic agents.

Background of the Invention

Gliomas account for 81% of all malignant brain and CNS tumors. Glioblastoma (glioblastoma multiforme (GBM); World Health Organization (WHO) grade IV astrocytoma), in particular, accounts for 60% to 70% of malignant gliomas and remains the most aggressive subtype of glioma. It occurs mostly in adults (median age at diagnosis: 64 years) and its incidence is estimated to be 3.05/100,000 in the United States. With 1- and 5-year overall survival of 29% and 3%, respectively, the prognosis of glioblastoma remains particularly poor (Central Brain Tumor Registry of the United States (2005) (CBTRUS; http://www.cbtrus.org)).

Although some progress has been made in the treatment of glioblastoma, this disease presents a highly unmet medical need with limited treatment options. In particular, bevacizumab (Avastin®), a monoclonal antibody targeted against the pro-angiogenic vascular endothelial growth factor (VEGF), holds significant therapeutic potential.

Summary ~~of the Invention~~

The present ~~invention~~ disclosure provides methods and kits for treating patients diagnosed with glioblastoma, including patients newly diagnosed with glioblastoma. In a first aspect, the present invention refers to the use of an effective amount of an anti-VEGF antibody, a chemotherapeutic, and a radiotherapy in the manufacture of a medicament for prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody. In another aspect, the present invention refers to a composition comprising an effective amount of an anti-VEGF antibody, a chemotherapeutic, and a radiotherapy for use in a method of prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody. In still another aspect, the present invention refers to a kit for prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody, the kit comprising an anti-VEGF antibody binding essentially to epitope A4.6.1, a chemotherapeutic, and a package insert or label with instructions to treat a patient diagnosed with a glioblastoma wherein said patient received two or fewer prior anti-cancer regimens.

In one ~~aspect~~example, the ~~invention~~ disclosure provides methods of treating a patient diagnosed with a glioblastoma, including administering to the patient a therapy including an effective amount of an anti-VEGF antibody, an effective amount of a chemotherapeutic, and an effective amount of radiotherapy, wherein the treatment prolongs the patient's median overall survival (OS) time as compared to a glioblastoma patient receiving the chemotherapeutic without an anti-VEGF antibody.

In another exampleaspect, the invention disclosure features the use of an effective amount of an anti-VEGF antibody, a chemotherapeutic, and a radiotherapy in the manufacture of a medicament for prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody.

In another aspectexample, the invention disclosure features a composition comprising an effective amount of an anti-VEGF antibody, a chemotherapeutic, and a radiotherapy for use in a method of prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody.

In some embodiments examplesof any one of the above aspects, the patient can have a WHO performance status of ≤2. In some exampleembodiments, the chemotherapeutic can be temozolomide (TMZ). In some exampleembodiments, the effective amount of the TMZ can be 150 mg/m^2, optionally, administered orally. In some exampleembodiments, the effective amount of the TMZ can be 200 mg/m^2, optionally, administered

orally. In some exampleembodiments, the effective amount of the TMZ can be 200 mg/m^2, optionally, administered orally. In some exampleembodiments, the radiotherapy can be administered at 2 Gy. In some embodiments, the anti-VEGF antibody can bind the A4.6.1 epitope. In some exampleembodiments, the anti-VEGF antibody can be bevacizumab. In some exampleembodiments, the anti-VEGF antibody may comprise a variable heavy chain (VH) and a variable light chain (VL), wherein the VH can have an amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAAS GYTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADF KRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWGQGTLVTVSS (SEQ ID NO: 2) and the VL can have an amino acid sequence of DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKPGKAPKVLIYFTSSLHS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTV PWTFGQGTKVEIKR (SEQ ID NO: 1). In some examplesembodiments, the effective amount of the anti-VEGF antibody can be about 10 mg/kg (e.g., 10 mg/kg), optionally administered intravenously every two weeks, and can be, for example, administered initially intravenously over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes. In some examplesembodiments, the effective amount of the anti-VEGF antibody can be about 15 mg/kg (e.g., 15 mg/kg), optionally administered intravenously every two weeks, and can be, for example, administered initially intravenously over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes. In some examplesembodiments, the anti-VEGF antibody can be administered first to the patient at the first cycle, and, optionally, any subsequent administrations of the anti-VEGF antibody can be either prior to or after the chemotherapeutic. In another exampleembodiment, the anti-VEGF antibody can be administered concurrently with the chemotherapeutic, and, optionally, radiotherapy. In some exampleembodiments, administration of steroids to the patient can be discontinued. In some exampleembodiments, the glioblastoma is of a proneural subtype. In some exampleembodiments, the glioblastoma is a newly diagnosed glioblastoma.

In the methods, uses, and compositions described above, the median OS time may be prolonged by about 4.9 months with a hazard ratio (HR) equal to about 0.42, as compared to a glioblastoma patient receiving the chemotherapeutic without the anti-VEGF antibody. In another exampleembodiment, the median OS time may be prolonged by about 4.9 months with a HR from about 0.24 to about 0.72, as compared to a glioblastoma patient receiving the chemotherapeutic without the anti-VEGF antibody. In another exampleembodiment, the median OS time may be prolonged by at least 5 months or greater with a HR from about 0.24 to about 0.72, as compared to a glioblastoma patient receiving the chemotherapeutic without the anti-VEGF antibody. In some exampleembodiments of the methods described above, the patient can be less than 65 years old. In other exampleembodiments of the methods described above, the patient can be equal to or greater than 65 years old.

In another exampleaspect, the ~~invention~~ disclosure provides kits including an anti-VEGF antibody binding essentially to epitope A4.6.1, a chemotherapeutic, and a package insert or label with instructions to treat a patient diagnosed with a glioblastoma, including administering to the patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, wherein the treatment prolongs the patient's median OS time as compared to a glioblastoma patient receiving the chemotherapeutic without the anti-VEGF antibody. In some exampleembodiments ~~of this aspect~~, the patient may have received two or fewer prior anti-cancer regimens. In some exampleembodiments ~~of this aspect~~, the anti-VEGF antibody can be bevacizumab. In some exampleembodiments ~~of this aspect~~, the glioblastoma is of a proneural subtype. In some exampleembodiments ~~of this aspect~~, the glioblastoma is a newly diagnosed glioblastoma.

WHAT IS CLAIMED IS:

1. Use of an effective amount of an anti-VEGF antibody, a chemotherapeutic, and a radiotherapy in the manufacture of a medicament for prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody.

2. The use of claim 1, wherein said patient has a WHO performance status of ≤ 2.

3. The use of claim 1, wherein the chemotherapeutic is temozolomide (TMZ).

4. The use of claim 3, wherein the TMZ is to be administered at 150 mg/m^2.

5. The use of claim 3, wherein the TMZ is to be administered at 200 mg/m^2.

6. The use of claim 1, wherein the radiotherapy is to be administered at 2 Gy.

7. The use of claim 1, wherein said anti-VEGF antibody binds the A4.6.1 epitope.

8. The use of claim 1, wherein said anti-VEGF antibody is bevacizumab.

9. The use of claim 1, wherein said anti-VEGF antibody comprises a variable heavy chain (VH) and a variable light chain (VL), wherein said VH has an amino acid sequence of SEQ ID NO: 2 and said VL has an amino acid sequence of SEQ ID NO: 1.

10. The use of claim 1, wherein said effective amount of said anti-VEGF antibody is 10 mg/kg intravenously every two weeks.

11. The use of claim 1, wherein said effective amount of said anti-VEGF antibody is 15 mg/kg intravenously every three weeks.

12. The use of claim 1, wherein said effective amount of said anti-VEGF antibody is to be administered initially intravenously over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes.

13. The use of claim 1, wherein said anti-VEGF antibody is to be administered first to said patient at the first cycle.

14. The use of claim 10, wherein subsequent administrations of said anti-VEGF antibody are either prior to or after said chemotherapeutic.

15. The use of claim 1, wherein said glioblastoma is of a proneural subtype.

16. The use of claim 1, wherein said glioblastoma is a newly diagnosed glioblastoma.

17. The use of claim 1, wherein said anti-VEGF antibody is to be administered concurrently with said chemotherapeutic.

18. The use of claim 1, wherein said median overall survival time is prolonged by about 4.9 months with a hazard ratio (HR) equal to 0.42, as compared to a glioblastoma patient receiving said chemotherapeutic without the anti-VEGF antibody.

19. The use of claim 1, wherein said median overall survival time is prolonged by about 4.9 months with a hazard ratio (HR) from about 0.24 to about 0.72, as compared to a glioblastoma patient receiving said chemotherapeutic without the anti-VEGF antibody.

20. The use of claim 18 or 19, wherein said patient is less than 65 years old.

21. The use of claim 18 or 19, wherein said patient is equal to or greater than 65 years old.

22. A composition comprising an effective amount of an anti-VEGF antibody, a chemotherapeutic, and a radiotherapy for use in a method of prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody.

23. A kit for prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody, the kit comprising an anti-VEGF antibody binding essentially to epitope A4.6.1, a chemotherapeutic, and a package insert or label with instructions to treat a patient diagnosed with a glioblastoma wherein said patient received two or fewer prior anti-cancer regimens.

24. The kit of claim 23, wherein said anti-VEGF antibody is bevacizumab.

25. The kit of claim 23, wherein said glioblastoma is of a proneural subtype.

26. The kit of claim 23, wherein said glioblastoma is a newly diagnosed glioblastoma.

WHAT IS CLAIMED IS:

1. A method of treating a patient diagnosed with a glioblastoma comprising administering to said patient a therapy comprising an effective amount of an anti-VEGF antibody, an effective amount of a chemotherapeutic, and an effective amount of radiotherapy, wherein said treatment prolongs said patient's median overall survival time as compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody.

2. The method of claim 1, wherein said patient has a WHO performance status of ≤ 2.

3. The method of claim 1, wherein the chemotherapeutic is temozolomide (TMZ).

4. The method of claim 3, wherein the TMZ is administered at 150 mg/m^2.

5. The method of claim 3, wherein the TMZ is administered at 200 mg/m^2.

6. The method of claim 1, wherein the radiotherapy is administered at 2 Gy.

7. The method of claim 1, wherein said anti-VEGF antibody binds the A4.6.1 epitope.

8. The method of claim 1, wherein said anti-VEGF antibody is bevacizumab.

9. The method of claim 1, wherein said anti-VEGF antibody comprises a variable heavy chain (VH) and a variable light chain (VL), wherein said VH has an amino acid sequence of SEQ ID NO: 2 and said VL has an amino acid sequence of SEQ ID NO: 1.

10. The method of claim 1, wherein said effective amount of said anti-VEGF antibody is 10 mg/kg intravenously every two weeks.

11. The method of claim 1, wherein said effective amount of said anti-VEGF antibody is 15 mg/kg intravenously every three weeks.

12. The method of claim 1, wherein said effective amount of said anti-VEGF antibody is administered initially intravenously over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes.

13. The method of claim 1, wherein said anti-VEGF antibody is administered first to said patient at the first cycle.

14. The method of claim 10, wherein subsequent administrations of said anti-VEGF antibody are either prior to or after said chemotherapeutic.

15. The method of claim 1, wherein said glioblastoma is of a proneural subtype.

16. The method of claim 1, wherein said glioblastoma is a newly diagnosed glioblastoma.

17. The method of claim 1, wherein said anti-VEGF antibody is administered concurrently with said chemotherapeutic.

18. The method of claim 1, wherein said median overall survival time is prolonged by about 4.9 months with a hazard ratio (HR) equal to 0.42, as compared to a glioblastoma patient receiving said chemotherapeutic without the anti-VEGF antibody.

19. The method of claim 1, wherein said median overall survival time is prolonged by about 4.9 months with a hazard ratio (HR) from about 0.24 to about 0.72, as compared to a glioblastoma patient receiving said chemotherapeutic without the anti-VEGF antibody.

20. The method of claim 18 or 19, wherein said patient is less than 65 years old.

21. The method of claim 18 or 19, wherein said patient is equal to or greater than 65 years old.

22. Use of an effective amount of an anti-VEGF antibody, a chemotherapeutic, and a radiotherapy in the manufacture of a medicament for prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody.

23. A composition comprising an effective amount of an anti-VEGF antibody, a chemotherapeutic, and a radiotherapy for use in a method of prolonging the median overall survival time of a patient diagnosed with a glioblastoma compared to a glioblastoma patient receiving said chemotherapeutic without an anti-VEGF antibody.

24. A kit comprising an anti-VEGF antibody binding essentially to epitope A4.6.1, a chemotherapeutic, and a package insert or label with instructions to treat a patient diagnosed with a glioblastoma comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, wherein said patient received two or fewer prior anti-cancer regimens, wherein said treatment prolongs said patient's median overall survival time as compared to a glioblastoma patient receiving said chemotherapeutic without the anti-VEGF antibody.

25. The kit of claim 24, wherein said anti-VEGF antibody is bevacizumab.

26. The kit of claim 24, wherein said glioblastoma is of a proneural subtype.

27. The kit of claim 24, wherein said glioblastoma is a newly diagnosed glioblastoma.