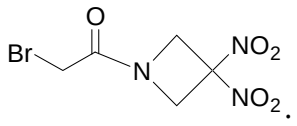
[0004] Treatment options for cancer patients often include surgery, radiotherapy, chemotherapy, hormone therapy, or a combination thereof. The compound ABDNAZ described in, for example, U.S. Patent Nos. 7,507,842; 8,299,053; and 8,927,527 has been studied in multiple clinical trials for use in treating cancer. ABDNAZ is typically formulated as a mixture with water, dimethylacetamide, and a poly(ethylene glycol) for intravenous infusion to the patient suffering from cancer. In clinical trials, patients receiving the aforementioned mixture of ABDNAZ by intravenous infusion have complained of significant pain at the site of infusion due to the ABDNAZ mixture. The significant pain at the site of infusion due to the ABDNAZ mixture has required medical personnel to reduce the rate at which the ABDNAZ mixture is administered to the patient, sometimes requiring infusion times up to eight hours. The long infusion times and slow rate of administration has, in some instances, limited the amount of ABDNAZ that can be administered to a patient when the ABDNAZ is used in combination with radiation therapy to be performed the same day as administration of ABDNAZ.

[0005] The present invention provides a new formulation containing ABDNAZ that can be rapidly administered to the patient without causing any significant pain at the site of infusion and has other advantages as described herein below.

SUMMARY

[0006] The present disclosure provides compositions and methods for intravenous administration of 2-bromo-1-(3,3-dinitroazetidin-1-yl)ethanone (ABDNAZ), including formulations containing autologous whole blood and ABDNAZ that can be rapidly administered to a patient by intravenous infusion. The compositions and methods provide the further advantage that rapid administration of the formulation does not result in any significant pain at the site of intravenous infusion due to the administration. The compound ABDNAZ has the following chemical structure:



[0007] The ABDNAZ formulations contain whole blood (preferably autologous whole blood), ABDNAZ, and an anticoagulant. The formulations and methods are particularly useful for

administering ABDNAZ to a patient suffering from cancer. The ABDNAZ formulations can be administered intravenously to the patient at a rate of, for example, at least 5 mL/hour, 10 mL/hour, 30 mL/hour, or higher rates. The rapid rate of administration reduces the time required to administer a therapeutically effective amount of ABDNAZ for treating cancer, and has particular advantages when large doses of ADBDNAZ need to be administered to the patient during the same day as the patient receives radiation therapy. The methods can be further characterized according to the magnitude of pain experienced by the patient at the site of administering the ABDNAZ formulation, wherein the magnitude of any pain experienced by the patient is small. The present disclosure having been generally described is explained in more detail in the aspects and embodiments below and in the detailed description.

[0007a] In one aspect of the present disclosure, there is provided a use of an ABDNAZ formulation comprising whole blood, ABDNAZ, and an anticoagulant, in the manufacture of a medicament for treating cancer.

[0007b] In another aspect of the present disclosure, there is provided a use of an ABDNAZ formulation comprising whole blood, ABDNAZ, and an anticoagulant, in the manufacture of a medicament for rapid intravenous administration to a patient while minimizing injection site pain experienced by the patient, wherein the ABDNAZ formulation is to be intravenously administered to the patient at a rate of at least 10 mL/hour, and wherein any pain experienced by the patient at the site of intravenous administration of the ABDNAZ formulation due to intravenous administration of the ABDNAZ formulation is no greater than Grade 2, or no greater than Grade 1.

[0007c] In a further aspect of the present disclosure, there is provided an intravenous formulation containing ABDNAZ for intravenous administration to a patient, comprising:

a. whole blood in an amount of at least 60% v/v of the formulation;

b. a polyethylene glycol at a concentration of from about 0.4 μL/mL to about 30 μL/mL in the formulation;

c. N,N-dimethylacetamide at a concentration of from about 0.2 μL/mL to about 15 μL/mL in the formulation;

d. ABDNAZ at a concentration of at least 10 μg/mL in the formulation;

e. water; and

f. an anticoagulant.

[0008] The present disclosure provides a method for intravenous administration of an ABDNAZ formulation to a patient suffering from cancer in order to treat the cancer. The method comprises intravenously administering to the patient in need thereof a therapeutically effective amount of an ABDNAZ formulation described herein (such as a formulation comprising whole blood, ABDNAZ, and an anticoagulant) in order to treat the cancer. The ABDNAZ formulation may be administered at a rate of, for example, at least 5 mL/hour or at least 10 mL/hour. The method provides the advantage of being able to rapidly administer ABDNAZ without causing undue pain at the site of administering the ABDNAZ formulation, and any such pain may be characterized according to, for example, the feature that any such pain is no greater than Grade 1 pain.

[0009] The present disclosure also provides a method for rapid intravenous administration of an ABDNAZ formulation to a patient while minimizing injection site pain experienced by the patient, wherein the method comprises intravenously administering to the patient at a rate of, for example, at least 10 mL/hour, an ABDNAZ formulation described herein (such as a formulation comprising whole blood, ABDNAZ, and an anticoagulant), wherein any pain experienced by the patient at the site of intravenous administration of the ABDNAZ formulation due to intravenous administration of the ABDNAZ formulation is no greater than Grade 2. The ABDNAZ formulation may be further characterized according to the concentration of ABDNAZ in the

formulation, such as where the formulation contains ABDNAZ at a concentration of, for example, at least 10 μg/mL, at least 20 μg/mL, at least 50 μg/mL, at least 100 μg/mL, or at least 150 μg/mL.

[0010] The present disclosure further provides an intravenous formulation containing ABDNAZ for intravenous administration to a patient, wherein the formulation comprises: (a) whole blood in an amount of at least 60% v/v of the formulation; (b) a polyethylene glycol at a concentration of from about 0.4 μL/mL to about 30 μL/mL in the formulation; (c) N,N-dimethylacetamide at a concentration of from about 0.2 μL/mL to about 15 μL/mL in the formulation; (d) ABDNAZ at a concentration of at least 10 μg/mL in the formulation; (e) water; and (f) an anticoagulant. The intravenous formulations are suited for use in the methods described herein, and provide the advantage of being able to be rapidly administered to the patient by intravenous infusion without causing any significant pain at the site of administration.

[0011] The present disclosure also provides a kit for intravenous administration of an ABDNAZ formulation to a patient suffering from cancer in order to treat the cancer. The kit comprises: (i) a formulation comprising ABDNAZ, and (ii) instructions for intravenous administration of an ABDNAZ formulation to a patient suffering from cancer in order to treat the cancer according to procedures described herein. One benefit of the kit is that it provides an ABDNAZ formulation capable of being rapidly administered to the patient by intravenous infusion without causing any significant pain at the site of administration.

[0012] The present disclosure further provides a kit for rapid intravenous administration of an ABDNAZ formulation to a patient while minimizing injection site pain experienced by the patient. The kit comprises: (i) a formulation comprising ABDNAZ, and (ii) instructions for rapid intravenous administration of an ABDNAZ formulation to a patient while minimizing injection site pain experienced by the patient according to procedures described herein.

DETAILED DESCRIPTION

[0013] The invention provides compositions and methods for intravenous administration of 2-bromo-1-(3,3-dinitroazetidin-1-yl)ethanone (ABDNAZ), including formulations containing autologous whole blood and ABDNAZ that can be rapidly administered to a patient by intravenous

What is claimed is:

1. Use of an ABDNAZ formulation comprising whole blood, ABDNAZ, and an anticoagulant, in the manufacture of a medicament for treating cancer.

2. The use of claim 1, wherein the whole blood is autologous whole blood.

3. The use of claim 1 or 2, wherein the ABDNAZ formulation is to be intravenously administered to the patient at a rate of at least 5 mL/hour.

4. The use of any one of claims 1-3, wherein the cancer is a solid tumor, brain cancer, bladder cancer, breast cancer, cervical cancer, cholangiocarcinoma, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, renal cancer, stomach cancer, testicular cancer, or uterine cancer, leukemia, lymphoma,B-cell lymphoma, or non-Hodgkin lymphoma.

5. The use of any one of claims 1-4, wherein any pain experienced by the patient at the site of intravenous administration of the ABDNAZ formulation due to intravenous administration of the ABDNAZ formulation is no greater than Grade 2, or no greater than Grade 1.

6. Use of an ABDNAZ formulation comprising whole blood, ABDNAZ, and an anticoagulant, in the manufacture of a medicament for rapid intravenous administration to a patient while minimizing injection site pain experienced by the patient, wherein the ABDNAZ formulation is to be intravenously administered to the patient at a rate of at least 10 mL/hour, and wherein any pain experienced by the patient at the site of intravenous administration of the ABDNAZ formulation due to intravenous administration of the ABDNAZ formulation is no greater than Grade 2, or no greater than Grade 1.

7. The use of claim 6, wherein the patient is suffering from cancer, preferably wherein the cancer is a solid tumor, brain cancer, bladder cancer, breast cancer, cervical cancer, cholangiocarcinoma, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, renal cancer, stomach cancer, testicular cancer, uterine cancer, leukemia, lymphoma,B-cell lymphoma, or non-Hodgkin lymphoma.

8. The use of any one of claims 1-7, wherein the ABDNAZ formulation contains ABDNAZ at a concentration of:

   (i) at least 10 μg/mL;

   (ii) at least 20 μg/mL;

   (iii) at least 50 μg/mL;

   (iv) at least 100 μg/mL;

   (v) at least 150 μg/mL;

   (vi) in the range of about 10 μg/mL to about 1 mg/mL;

   (vii) in the range of about 10 μg/mL to about 0.5 mg/mL;

   (viii) in the range of about 10 μg/mL to about 250 μg/mL; or

   (ix) in the range of about 20 μg/mL to about 200 μg/mL.

9. The use of any one of claims 1-8 , wherein:

   (i) the ABDNAZ formulation consists essentially of whole blood, ABDNAZ, and an anticoagulant;

   (ii) the ABDNAZ formulation consists of whole blood, ABDNAZ, an anticoagulant, and optionally one or more of water, a polyethylene glycol, and N,N-dimethylacetamide;

   (iii) the ABDNAZ formulation consists of whole blood, ABDNAZ, an anticoagulant, and optionally one or more of water, a polyethylene glycol having a number average molecular weight in the range of about 200 g/mol to about 600 g/mol, and N,N-dimethylacetamide;

   (iv) the ABDNAZ formulation consists of whole blood, ABDNAZ, an anticoagulant, water, a polyethylene glycol having a number average molecular weight in the range of about 200 g/mol to about 600 g/mol, and N,N-dimethylacetamide;

(v) the ABDNAZ formulation consists of whole blood, ABDNAZ, an anticoagulant, and optionally one or more of water, a polyethylene glycol having a number average molecular weight of about 400 g/mol, and N,N-dimethylacetamide; or

(vi) the ABDNAZ formulation consists of whole blood, ABDNAZ, an anticoagulant, water, a polyethylene glycol having a number average molecular weight of about 400 g/mol, and N,N-dimethylacetamide.

10. The use of any one of claims 1-9, wherein:

(i) the anticoagulant comprises one or more of heparin and a citrate salt;

(ii) the anticoagulant is a solution comprising an alkali metal citrate salt, dextrose, and water; or

(iii) the anticoagulant is present in the ABDNAZ formulation in an amount ranging from about 0.1% wt/wt to about 15% w/w.

11. The use of any one of claims 1-10, wherein the whole blood constitutes:

(i) at least 30% wt/wt of the ABDNAZ formulation;

(ii) at least 60% wt/wt of the ABDNAZ formulation;

(iii) at least 75% wt/wt of the ABDNAZ formulation;

(iv) at least 90% wt/wt of the ABDNAZ formulation;

(v) from about 60% wt/wt to about 99% wt/wt of the ABDNAZ formulation;

(vi) from about 70% wt/wt to about 95% wt/wt of the ABDNAZ formulation; or

(vii) from about 75% wt/wt to about 90% wt/wt of the ABDNAZ formulation.

12. The use of any one of claims 1-11, wherein:

(i) there is from about 90 mL to about 110 mL of whole blood in the ABDNAZ formulation;

(ii) there is from about 95 mL to about 105 mL of whole blood in the ABDNAZ formulation;

(iii) there is about 100 mL of whole blood in the ABDNAZ formulation;

(iv) there is about 10 mL to about 20 mL of whole blood in the ABDNAZ formulation; or

(v) there is about 10 mL of whole blood in the ABDNAZ formulation.

13. The use of any one of claims 1-12, wherein the ABDNAZ formulation has a volume in the range of:

(i) about 50 mL to about 200 mL;

(ii) about 75 mL to about 150 mL;

(iii) about 90 mL to about 140 mL;

(iv) about 100 mL to about 140 mL;

(v) about 100 mL to about 120 mL; or

(vi) about 10 mL to about 20 mL.

14. The use of any one of claims 1-13, wherein the ABDNAZ formulation is to be intravenously administered, and wherein the intravenous administration of the ABDNAZ formulation commences within:

(i) about 1 hour after formation of the ABDNAZ formulation;

(ii) about 30 minutes after formation of the ABDNAZ formulation;

(iii) about 20 minutes after formation of the ABDNAZ formulation;

(iv) about 6 hours after formation of the ABDNAZ formulation; or

(v) about 4 hours after formation of the ABDNAZ formulation.

15. The use of any one of claims 1-14, wherein an aliquot of whole blood is to be obtained from the patient, and then using said aliquot to prepare the ABDNAZ formulation for administration to the patient.

16. The use of any one of claims 1-15, wherein the ABDNAZ formulation is to be intravenously administered, and wherein the intravenous administration is central intravenous administration, or peripheral intravenous administration.

17. The use of any one of claims 1-16, wherein the patient is an adult human, a pediatric human, does not suffer from anemia or have reduced blood volume, or has at least 95% of the amount of their average daily blood volume.

18. An intravenous formulation containing ABDNAZ for intravenous administration to a patient, comprising:
    a. whole blood in an amount of at least 60% v/v of the formulation;
    b. a polyethylene glycol at a concentration of from about 0.4 μL/mL to about 30 μL/mL in the formulation;
    c. N,N-dimethylacetamide at a concentration of from about 0.2 μL/mL to about 15 μL/mL in the formulation;
    d. ABDNAZ at a concentration of at least 10 μg/mL in the formulation;
    e. water; and
    f. an anticoagulant.

19. The intravenous formulation of claim 18, wherein the polyethylene glycol is a polyethylene glycol having a number average molecular weight in the range of about 200 g/mol to about 600 g/mol, or having a number average molecular weight of about 400 g/mol.

20. The intravenous formulation of claim 18 or 19, wherein the anticoagulant comprises one or more of heparin and a citrate salt, or is a solution comprising an alkali metal citrate salt, dextrose, and water.

21. The intravenous formulation of any one of claims 18-20, wherein the ABDNAZ formulation contains ABDNAZ at a concentration:

    (i) of at least 20 μg/mL;

    (ii) of at least 50 μg/mL;

(iii) of at least 100 μg/mL;

(iv) of at least 150 μg/mL;

(v) in the range of about 10 μg/mL to about 1 mg/mL;

(vi) in the range of about 10 μg/mL to about 0.5 mg/mL;

(vii) in the range of about 10 μg/mL to about 250 μg/mL; or

(viii) in the range of about 20 μg/mL to about 200 μg/mL.

22. The intravenous formulation of any one of claims 18-21, wherein the whole blood constitutes:

(i) at least 60% wt/wt of the formulation;

(ii) at least 75% wt/wt of the formulation;

(iii) at least 90% wt/wt of the formulation;

(iv) from about 60% wt/wt to about 99% wt/wt of the formulation;

(v) from about 70% wt/wt to about 95% wt/wt of the formulation; or

(vi) from about 75% wt/wt to about 90% wt/wt of the formulation.

23. The intravenous formulation of any one of claims 18-22, wherein there is:

(i) from about 90 mL to about 110 mL of whole blood in the formulation;

(ii) from about 95 mL to about 105 mL of whole blood in the formulation;

(iii) about 100 mL of whole blood in the formulation; or

(iv) about 10 mL to about 20 mL of whole blood in the formulation.

24. The intravenous formulation of any one of claims 18-23, wherein the formulation is in the form of a unit dose having a volume in the range of:

(i) about 50 mL to about 200 mL;

(ii) about 75 mL to about 150 mL;

(iii) about 90 mL to about 140 mL;

(iv) about 100 mL to about 140 mL;

(v) about 100 mL to about 120 mL; or

(vi) about 10 mL to about 30 mL.

25. The intravenous formulation of any one of claims 18-24, wherein the polyethylene glycol is present at a concentration of from about 0.4 μL/mL to about 4 μL/mL in the formulation, or wherein the N,N-dimethylacetamide at a concentration of from about 0.2 μL/mL to about 2 μL/mL in the formulation.

26. The intravenous formulation of any one of claims 18-25, wherein the formulation is characterized by the feature that any pain experienced by the patient at the site of intravenous administration due to intravenous administration of the formulation to the patient at a rate in the range of 10 mL/hour to 50 mL/hour is no greater than Grade 2, or no greater than Grade 1.