METHODS OF TREATING VIRALLY ASSOCIATED CANCERS WITH HISTONE DEACETYLASE INHIBITORS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 62/855,454 filed on May 31, 2019, which is incorporated by reference herein in its entirety.

SUMMARY

[0001a] In one aspect, provided herein is the use of nanatinostat in the manufacture of a first medicament and use of an effective amount of an antiviral agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an Epstein-Barr virus associated lymphoproliferative disorder in an individual, wherein the nanatinostat is to be administered at a total daily dose from 10 milligrams to 20 milligrams per day, wherein the individual is to be treated according to a treatment schedule having a duration of one week, and wherein the individual is to be administered nanatinostat for 4 days of the treatment schedule.

[0001b] In another aspect, provided herein is the use of nanatinostat in the manufacture of a first medicament and use of valganciclovir in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an Epstein-Barr virus associated lymphoproliferative disorder in an individual, wherein the nanatinostat is to be administered at a total daily dose of about 20 mg, wherein the valganciclovir is to be administered at a total daily dose of about 900 mg, wherein the individual is to be treated according to a weekly treatment schedule, and wherein the individual is to be administered nanatinostat for 4 consecutive days of the treatment schedule, and valganciclovir is to be administered every day of the treatment schedule.

[0002] Described herein are certain dosing schedules and amounts that effectively provide efficacy and prevent and manage side effects associated with treatment of histone deacetylase inhibitor (HDACi) treatment. Optionally, these schedules and dosing regimens include treatment with an antiviral agent.

[0003] Described herein, in one example, is a method of treating a cancer in an individual, the method comprising administering to the individual: (a) an effective amount of a histone deacetylase inhibitor (HDACi) as a viral inducing agent, wherein the HDACi is characterized by an elimination half-life of less than 30 hours; and (b) an effective amount of an antiviral drug; wherein the individual is treated according to a treatment schedule, wherein the individual is administered a lower dosage of the HDACi for at least one dose of the treatment schedule. In

certain examples, the individual is not administered the HDACi for at least one day of the treatment schedule. In certain examples, the HDACi is administered orally. In certain examples, the HDACi is selected from the list consisting of: vorinostat, romidepsin, mocetinostat, belinostat, pracinostat, givinostat, panobinostat, CUDC-101, CDX101, chidamide, domatinostat, and nanatinostat. In certain examples, the HDACi inhibits activity of a class I histone deacetylase. In certain examples, the HDACi is characterized by an elimination half-life of less than 24 hours. In certain examples, the HDACi is characterized by an elimination half-life of less than 12 hours. In certain examples, the HDACi is characterized by an elimination half-life of less than 4 hours. In certain examples, the HDACi is nanatinostat. In certain examples, the HDACi is administered at a total daily dose from about 10 milligrams to about 40 milligrams. In certain examples, the HDACi is administered at a total daily dose of about 10 milligrams. In certain examples, the HDACi is administered at a total daily dose of about 15 milligrams. In certain examples, the HDACi is administered at a total daily dose of about 20 milligrams. In certain examples, the HDACi is administered at a total daily dose of about 25 milligrams. In certain examples, the HDACi is administered at a total daily dose of

about 30 milligrams. In certain examples, the HDACi is administered once per day. In certain examples, the HDACi is administered twice per day. In certain examples, the cytotoxic activity of the antiviral agent is activated by a viral kinase. In certain examples, the viral kinase comprises, an Epstein-Barr virus protein kinase, an Epstein-Barr virus thymidine kinase, a human herpes virus thymidine kinase, or a human cytomegalovirus protein. In certain examples, the antiviral agent is selected from the list consisting of aciclovir, ganciclovir, valaciclovir, valganciclovir, and famciclovir. In certain examples, the antiviral agent is valganciclovir. In certain examples, the antiviral agent is administered at a total daily dose of 1800 milligrams. In certain examples, the antiviral agent is administered at a total daily dose of 900 milligrams. In certain examples, the antiviral agent is administered at a total daily dose of 450 milligrams. In certain examples, the antiviral agent is administered every day of the treatment schedule. In certain examples, the antiviral agent is administered orally. In certain examples, the individual is not administered the HDACi for at least two days of the treatment schedule. In certain examples, the individual is not administered the HDACi for at least three days of the treatment schedule. In certain examples, the individual is not administered the HDACi for at least four days of the treatment schedule. In certain examples, the individual is not administered the HDACi for at least five days of the treatment schedule. In certain examples, the treatment schedule has a duration of one week. In certain examples, the treatment schedule is repeated. In certain examples, the HDACi is administered with food or a caloric substance. In certain examples, the cancer is a solid tissue cancer. In certain examples, the solid tissue cancer is salivary gland cancer, nasopharyngeal carcinoma, head and neck cancer, gastric cancer, a colorectal cancer, breast cancer, glioblastoma, prostate cancer, renal cancer, leiomyosarcoma, pancreatic cancer, or lung cancer. In certain examples, the solid tissue cancer is salivary gland cancer, nasopharyngeal carcinoma, head and neck cancer, gastric cancer, a colorectal cancer, or leiomyosarcoma. In certain examples, the cancer is a leukemia or a lymphoma. In certain examples, the leukemia or lymphoma is a B cell leukemia or lymphoma. In certain examples, the leukemia or lymphoma is a T cell leukemia or lymphoma. In certain examples, the leukemia or lymphoma is non-Hodgkin’s lymphoma. In certain examples, the leukemia or lymphoma is Hodgkin’s lymphoma. In certain examples, the leukemia or lymphoma is a cytomegalovirus virus positive leukemia or lymphoma. In certain examples, the leukemia or lymphoma is an Epstein-Barr virus positive leukemia or lymphoma. In certain examples, the individual is afflicted with thrombocytopenia. In

certain examples, the individual has a platelet count of less than 50,000 platelets per microliter. In certain examples, the individual has an elevated creatinine level. In certain examples, the elevated creatinine level exceeds 1.1 mg/dL for a woman or 1.3 mg/dL for a man. In certain examples, the individual is selected for treatment according to the treatment schedule based on the presence of thrombocytopenia. In certain examples, the individual is selected based on a platelet count of less than 50,000 per microliter. In certain examples, the individual is selected for treatment according to the treatment schedule based on the presence of an elevated creatinine level. In certain examples, the elevated creatinine level exceeds 1.1 mg/dL for a woman and 1.3 mg/dL for a man.

[0004] In another example, described herein, is a method of treating an Epstein-Barr associated lymphoma in an individual, the method comprising administering to the individual: (a) an effective amount of nanatinostat; and (b) an effective amount of valganciclovir; wherein the individual is treated according to a treatment schedule, wherein the individual is not administered the nanatinostat for at least three days of the treatment schedule.

[0005] In another example, described herein, is a kit comprising: (a) an HDACi as a viral inducing agent; and (b) an antiviral agent as a cytotoxic anti-cancer agent; wherein the kit comprises a plurality of oral dosage forms, the oral dosage forms comprising the HDACi and the antiviral agent co-packaged into separate oral dosage forms. In another example, described herein, is a kit comprising: (a) an HDACi; and (b) an antiviral agent; wherein the kit comprises a plurality of oral dosage forms, the oral dosage forms comprising the HDACi and the antiviral agent co-formulated into a single oral dosage form, wherein at least one of the plurality of oral dosage forms comprises the antiviral agent and does not comprise the HDACi. In certain examples, the plurality of oral dosage forms are a pill, capsule, tablet, or gel cap. In certain examples, the HDACi is selected from the list consisting of: vorinostat, romidepsin, mocetinostat, belinostat, pracinostat, givinostat, panobinostat, CUDC-101, CDX101, chidamide, and nanatinostat. In certain examples, the HDACi inhibits activity of a class I histone deacetylase. In certain examples, the HDACi is characterized by an elimination half-life of less than 24 hours. In certain examples, the HDACi is characterized by an elimination half-life of less than 12 hours. In certain examples, the HDACi is characterized by an elimination half-life of less than 4 hours. In certain examples, the HDACi is nanatinostat. In certain examples, the cytotoxic activity of the antiviral agent is activated by a viral kinase. In certain examples, the viral kinase comprises, an Epstein-Barr virus protein kinase, an Epstein-Barr virus thymidine kinase, a human herpes virus thymidine kinase, or a human cytomegalovirus protein. In certain

examples, the antiviral agent is selected from the list consisting of aciclovir, ganciclovir, valaciclovir, valganciclovir, and famciclovir. In certain examples, the antiviral agent is valganciclovir. In certain examples, the plurality of oral dosage forms comprise about 900mg of valganciclovir. In certain examples, the plurality of oral dosage forms comprise about 450mg of valganciclovir. In certain examples, the plurality of oral dosage forms comprise about 20mg of nanatinostat. In certain examples, the plurality of oral dosage forms comprise about 15mg of nanatinostat. In certain examples, the plurality of oral dosage forms comprise about 10mg of nanatinostat. In certain examples, the plurality of oral dosage forms comprise seven or a multiple thereof. In certain examples, one of the plurality of oral dosage forms comprises the antiviral agent and does not comprise the HDACi. In certain examples, two of the plurality of oral dosage forms comprises the antiviral agent and a lower dosage amount of the HDACi. In certain examples, two of the plurality of oral dosage forms comprises the antiviral agent and does not comprise the HDACi. In certain examples, three of the plurality of oral dosage forms comprises the antiviral agent and does not comprise the HDACi. In certain examples, four of the plurality of oral dosage forms comprises the antiviral agent and does not comprise the HDACi. In certain examples, five of the plurality of oral dosage forms comprises the antiviral agent and does not comprise the HDACi. In certain examples, the HDACi comprises nanatinostat and the antiviral agent comprise valganciclovir.

INCORPORATION BY REFERENCE

[0006] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0008] FIG. 1 illustrates rapid recovery of platelet counts in patients on nanatinostat dose hold.

CLAIMS

What is claimed is:

1. Use of nanatinostat in the manufacture of a first medicament and use of an effective amount of an antiviral agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an Epstein-Barr virus associated lymphoproliferative disorder in an individual,
wherein the nanatinostat is to be administered at a total daily dose from 10 milligrams to 20 milligrams per day,
wherein the individual is to be treated according to a treatment schedule having a duration of one week, and
wherein the individual is to be administered nanatinostat for 4 days of the treatment schedule.

2. The use of claim 1, wherein the nanatinostat is to be administered at a total daily dose of 10 milligrams.

3. The use of claim 1, wherein the nanatinostat is to be administered at a total daily dose of 20 milligrams.

4. The use of claim 1, wherein the nanatinostat is to be administered once per day.

5. The use of claim 1, wherein the nanatinostat is to be administered twice per day.

6. The use of claim 1, wherein the antiviral agent is valganciclovir.

7. The use of claim 6, wherein the valganciclovir is to be administered at a total daily dose of 1,800 milligrams.

8. The use of claim 6, wherein the valganciclovir is to be administered at a total daily dose of 900 milligrams.

9. The use of claim 6, wherein the valganciclovir is to be administered at a total daily dose of 450 milligrams.

10. The use of claim 1, wherein the antiviral agent is to be administered every day of the treatment schedule.

11. The use of claim 1, wherein the antiviral agent is not to be administered on one or more days of the treatment schedule.

12. The use of claim 1, wherein the antiviral agent is to be administered once a day.

13. The use of claim 1, wherein the antiviral agent is to be administered twice a day.

14. The use of claim 1, wherein the antiviral agent is to be administered orally.

15. The use of claim 1, wherein the nanatinostat is to be administered orally.

16. The use of claim 1, wherein the treatment schedule is to be repeated.

17. The use of claim 1, wherein the Epstein-Barr virus associated lymphoproliferative disorder is an Epstein-Barr virus associated leukemia or a lymphoma.

18. The use of claim 17, wherein the leukemia or lymphoma is a B cell or a T cell leukemia or lymphoma.

19. The use of claim 1, wherein the individual is afflicted with thrombocytopenia.

20. The use of claim 1, wherein the individual has a platelet count of less than 150,000 platelets per microliter.

21. Use of nanatinostat in the manufacture of a first medicament and use of valganciclovir in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an Epstein-Barr virus associated lymphoproliferative disorder in an individual,

wherein the nanatinostat is to be administered at a total daily dose of about 20 mg,

wherein the valganciclovir is to be administered at a total daily dose of about 900 mg,

wherein the individual is to be treated according to a weekly treatment schedule, and

wherein the individual is to be administered nanatinostat for 4 consecutive days of the treatment schedule, and valganciclovir is to be administered every day of the treatment schedule.

22. The use of claim 21, wherein nanatinostat and valganciclovir are to be administered orally.

23. The use of claim 21, wherein nanatinostat and valganciclovir are each to be administered once a day.

24. The use of claim 21, wherein nanatinostat and valganciclovir are each to be administered twice a day.

25. The use of claim 21, wherein the treatment schedule is to be repeated.