ACTIVATED LYMPHOCYTIC CELLS AND METHODS OF USING THE SAME TO TREAT CANCER AND INFECTIOUS CONDITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/861,487, filed June 14, 2019, which is hereby incorporated by reference in its entirety.

FIELD

[0002] Provided herein are methods for treating a patient with human immunodeficiency virus (HIV), cancer, a viral infection, or a bacterial infection, comprising administering cellular compositions comprising activated lymphocytic cells, such as natural kill (NK) cells. Related compositions, kits, and methods for modulating the immune system using such activated cells are also provided.

BACKGROUND

[0003] Natural killer (NK) cells are innate lymphocytes important for mediating anti-viral and anti-cancer immunity through cytokine and chemokine secretion, and through the release of cytotoxic granules (Vivier *et al*. Science 331(6013):44-49 (2011); Caligiuri, Blood 112(3):461-469 (2008); Roda *et al*., Cancer Res. 66(1):517-526 (2006)). Thus, NK cells are part of the body's defense system and act as an army to protect from invaders like viruses and infections. Similarly, NK cells are important immune effector cells for fighting cancer.

[0004] Early clinical trials using autologous NK cells failed to demonstrate significant clinical benefit. Since NK cells in cancer patients are highly dysfunctional and reduced in number, methods and compositions for restoring or increasing cytolytic NK cell numbers and increasing their anti-tumor, anti-viral, and/or anti-bacterial activity are greatly needed.

SUMMARY

[0005] In one aspect, the present disclosure provides a use of a lymphocytic cellular composition comprising activated natural killer (NK) cells in the manufacture of a medicament for treating a patient with HIV, cancer, a viral infection, or a bacterial infection, wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient’s immune system for a period of 5-7 cells.

[0005a] In another aspect, the present disclosure provides a use of a lymphocytic cellular composition comprising activated natural killer (NK) cells in the manufacture of a medicament for inhibiting HIV replication in a patient, wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

[0005b] In another aspect, the present disclosure provides a use of a lymphocytic cellular composition comprising activated natural killer (NK) cells in the manufacture of a medicament for inhibiting tumor growth in a patient, wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

[0005c] In another aspect, the present disclosure provides a use of a lymphocytic cellular composition comprising activated natural killer (NK) cells in the manufacture of a medicament for treating a patient having a viral or bacterial infection, wherein said treatment comprises inhibiting a viral or bacterial replication or reproduction in the patient; and wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

[0005d] In some examples, methods of treating a patient with HIV, cancer, a viral infection, or a bacterial infection, the method comprising administering an effective amount of a lymphocytic cellular composition comprising activated NK cells to the patient are provided.

[0006] In some examples, methods for increasing immune response in a patient in need thereof, comprising administering an effective amount of a lymphocytic cellular composition comprising activated NK cells to the patient are provided.

[0007] In some examples, methods of inhibiting HIV replication in a patient, the method comprising administering to the subject with HIV an effective amount of a lymphocytic cellular composition comprising activated natural killer (NK) cells to the patient are provided.

[0008] In some examples, methods of inhibiting tumor growth in a patient, the method comprising administering to the patient with the tumor an effective amount of a lymphocytic cellular composition comprising activated natural killer (NK) cells to the patient are provided.

[0009] In some examples, methods of inhibiting a viral or bacterial replication or reproduction in a subject having a viral or bacterial infection, the method comprising administering to the subject with the viral or bacterial infection an effective amount of a lymphocytic cellular composition comprising activated natural killer (NK) cells to the patient are provided.

[0010] In some examples, methods of activating NK cells, the method comprising contacting a cellular composition comprising the NK cells *in vitro* with at least one cytokine and optionally soluble fibroblast growth factor receptor 1(sFGFR1) are provided.

[0011] In some examples, a cytokine and optionally soluble fibroblast growth factor receptor 1(sFGFR1) activated lymphocytic cellular composition comprising activated natural killer (NK) cells is provided. In some examples, the composition is a pharmaceutical composition.

[0012] In a further aspect, the present disclosure provides a cytokine and soluble fibroblast growth factor receptor 1(sFGFR1) activated lymphocytic cellular composition comprising activated natural killer (NK) cells for use in treating a patient with HIV, cancer, a viral infection, or a bacterial infection, wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells. In some examples, a cytokine and optionally soluble fibroblast growth factor receptor 1(sFGFR1) activated lymphocytic cellular composition comprising activated natural killer (NK) cells for treating a patient with HIV, cancer, a viral infection, or a bacterial infection is provided. In some examples, the composition is a pharmaceutical composition.

[0013] In a further aspect, the present disclosure provides a use of a cytokine and soluble fibroblast growth factor receptor 1(sFGFR1) activated lymphocytic cellular composition comprising activated natural killer (NK) cells in the preparation of a medicament for treating a patient with HIV, cancer, a viral infection, or a bacterial infection, wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells. In some examples, a cytokine and optionally soluble fibroblast growth factor receptor 1(sFGFR1) activated lymphocytic cellular composition comprising activated natural killer (NK) cells for the preparation of a medicament for treating a patient with HIV, cancer, a viral infection, or a bacterial infection are provided. In some examples, the composition is a pharmaceutical composition.

[0014] In certain examples, the cellular compositions further comprise activated Gamma delta T cells (GDT cells). In some examples, the cellular compositions further comprise invariant natural killer T cells (iNKT cells). In some examples, the cellular compositions further comprise CD3 T cells.

[0015] In some examples, prior to administration to the patient, the lymphocytic cellular composition is activated by mixing/incubating/contacting the cells with at least one cytokine and optionally soluble fibroblast growth factor receptor 1(sFGFR1).

[0016] In some examples, the cytokine is selected from the group consisting of IL-2, IL-15, IL-21, Flt3-L, stem cell factor (SCF), IL-7, IL-12, and IL18, and any combination thereof.

[0017] In some examples, the cytokine is incubated/mixed/contacted with the cellular composition for between about 6-24 hours.

WHAT IS CLAIMED IS:

1. Use of a lymphocytic cellular composition comprising activated natural killer (NK) cells in the manufacture of a medicament for treating a patient with HIV, cancer, a viral infection, or a bacterial infection,

wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

2. Use of a lymphocytic cellular composition comprising activated natural killer (NK) cells in the manufacture of a medicament for inhibiting HIV replication in a patient,

wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

3. Use of a lymphocytic cellular composition comprising activated natural killer (NK) cells in the manufacture of a medicament for inhibiting tumor growth in a patient,

wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

4. Use of a lymphocytic cellular composition comprising activated natural killer (NK) cells in the manufacture of a medicament for treating a patient having a viral or bacterial infection,

wherein said treatment comprises inhibiting a viral or bacterial replication or reproduction in the patient; and

wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to

administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

5. The use of any one of claims 1-4, wherein the cellular composition further comprises activated gamma delta T cells (GDT cells).

6. The use of any one of claims 1-4, wherein the cellular composition further comprises invariant natural killer T cells (iNKT cells).

7. The use of any one of claims 1-4, wherein the cellular composition further comprises $CD3^+$ T cells.

8. The use of any of claims 1-7, wherein prior to administration to the patient, the lymphocytic cellular composition is activated by mixing/incubating/contacting the cells with at least one cytokine and optionally soluble fibroblast growth factor receptor 1 (sFGFR1).

9. The use of claim 8, wherein the cytokine is selected from the group consisting of IL-2, IL-15, IL-21, Flt3-L, stem cell factor (SCF), IL-7, IL-12, and IL18, and any combination thereof.

10. The use of claim 9, wherein the cytokine is incubated/mixed/contacted with the cellular composition for between 6-24 hours.

11. The use of claim 9, wherein the amount of cytokine incubated with the cellular composition is between 100-1000IU/ml.

12. The use of any of claims 1-11, wherein the NK cells are killed by the patient's immune system within 4-15 days after administration.

13. The use of claim 12, wherein the lympho-suppressive or chemotherapeutic agent comprises any one of 6TG, 6-MMP, one or more purine analogues selected from the group consisting of clofarabine, fludarabine, and cytarabine, or any combination thereof.

14. The use of claim 13, wherein the dose of the lympho-suppressive or chemotherapeutic agent ranges from 5mg/m^2 to 50mg/m^2.

15. The use of claim 12, wherein the chemotherapeutic or immunosuppressive agent comprises any cyclophosphamide, rituximab, a steroid, or any combination thereof.

16. The use of claim 15, wherein the steroid is a glucocorticoid steroid.

17. The use of claim 16, wherein the steroid is prednisone.

18. The use of claim 15, wherein the dose of the chemotherapeutic agent or immunosuppressive agent ranges from 20 mg/m2 to 1000 mg/m2.

19. The use of claim 12, further comprising that the patient is to be administered interferon-alpha (IFN-α), or a biological equivalent thereof, at a dosage of from 1 x 10^6 IU/m^2/d to 10 x 10^6 IU/m^2/d, two days and/or 1 day prior to administration of the lymphocytic cellular composition.

20. The use of any of claims 1-19, further comprising that the patient is to be administered IL-2 on the day of administration of the lymphocytic cellular composition and on the first day following administration of the lymphocytic cellular composition, and optionally continuing for between 3-14 additional days following administration of the lymphocytic cellular composition, in a dosage of 3-6 x 10^6 IU/m^2 per dose.

21. The use of any of claims 1-21, further comprising that the patient is to be administered a COX-2 inhibitor or a nonsteroidal anti-inflammatory drug (NSAID), or a combination thereof, on the day of administration of the lymphocytic cellular composition, and continuing for between at least 14 and 60 days following administration of the lymphocytic cellular composition.

22. The use of claim 21, wherein the COX-2 inhibitor is celecoxib or Rofecoxib, and the nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin, indomethacin, ibuprofen, naproxen, piroxicam, and nabumetone.

23. The use of any of claims 1-22, wherein the activated NK cells are allogeneic to the patient.

24. The use of any of claims 1-23, wherein the NK cells are not HLA-matched with the patient.

25. The use of any of claims 1-24, wherein the dosage of activated cells ranges from 3-50 x 10^6.

26. The use of any of claims 1-25, wherein the viral infection is selected from the group consisting of viral infections caused by retroviruses (*e.g.*, human T-cell lymphotrophic virus (HTLV) types I and II and human immunodeficiency virus (HIV)), herpes viruses (*e.g.*, herpes simplex virus (HSV) types I and II, Epstein-Ban virus and cytomegalovirus), arenaviruses (*e.g.*, lassa fever virus), paramyxoviruses (*e.g.*, morbillivirus virus, human respiratory syncytial virus, and pneumovirus), adenoviruses, bunyaviruses (*e.g.*, hantavirus), coronaviruses, filoviruses (*e.g.*, Ebola virus), flaviviruses (*e.g.*, hepatitis C virus (HCV), yellow fever virus, and Japanese encephalitis virus), hepadnaviruses (*e.g.*, hepatitis B viruses (HBV)), orthomyoviruses (*e.g.*, Sendai virus and influenza viruses A, B and C), papovaviruses (*e.g.*, papillomaviruses), picornaviruses (*e.g.*, rhinoviruses, enteroviruses and hepatitis A viruses), poxviruses, reoviruses (*e.g.*, rotaviruses), togaviruses (*e.g.*, rubella virus), and rhabdoviruses (*e.g.*, rabies virus), and any combination thereof.

27. The use of any of claims 1-25, wherein the cancer is a hematological or hematogenous cancer selected from the group consisting of acute leukemia, acute myelocytic leukemia, acute myelogenous leukemia, myeloblastic leukemia, promyelocytic leukemia, myelomonocytic leukemia, monocytic leukemia, erythro leukemia, chronic leukemia, chronic myelocytic (or granulocytic) leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (indolent and high grade forms), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia and myelodysplasia, and any combination thereof.

28. The use of any of claims 1-25, wherein the cancer is a solid tumor selected from the group consisting of fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, and other sarcomas, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, lymphoid malignancy, pancreatic cancer, breast cancer, lung cancers, ovarian cancer, prostate cancer, hepatocellular carcinoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, pheochromocytomas sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, Wilms' tumor, cervical cancer, testicular tumor, seminoma, bladder carcinoma, melanoma, and CNS tumors (such as a glioma (such as brainstem glioma and mixed gliomas), glioblastoma (also known as glioblastoma multiforme) astrocytoma, CNS lymphoma, germinoma, medulloblastoma, Schwannoma craniopharyogioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, neuroblastoma, retinoblastoma and brain metastases.

29. The use of any of claims 1-25, wherein the bacterial infection is caused by one of the pathogenic bacterial species Bacteroides, Clostridium, Streptococcus, Staphylococcus, Pseudomonas, Haemophilus, Legionella, Mycobacterium, Escherichia, Salmonella, Shigella, or Listeria.

30. The use of any of claims 1-25, wherein graft versus host disease (GVHD) is decreased or eliminated, while graft versus tumor (GVT) or graft versus virus (GVV) is increased in the patient.

31. The use of claims 1-19, wherein administration of IL-2 is counter-indicated and not to be administered following administration of the lymphocytic cellular composition comprising activated NK cells, when the patient has lymphocytic or lymphoblastic leukemia or lymphoma.

32. The use of any of claims 1-25, wherein at a time-frame of from 4-14 days following administration of the lymphocytic cellular composition comprising activated NK cells, the patient is to be further administered an immune check-point inhibitor, including any one or combination of two check point inhibitors, including an inhibitor of PD-1 or PD-L1 (B7-H1), such as an anti-

PD-1 antibody, including nivolumab (Nivolumab from Bristol-Myers Squibb), pembrolizumab/lambrolizumab, also known as MK-3475 (Keytruda from Merck), pidilizumab (Curetech), AMP-224 (Amplimmune), or an anti-PD-L1 antibody, including MPDL3280A (Roche), MDX-1105 (Bristol Myer Squibb), MEDI-4736 (AstraZeneca) and MSB-0010718 C (Merck), an antagonist of CTLA-4, such as an anti-CTLA-4 antibody including anti-CTLA4 antibody Yervoy™(ipilimumab, Bristol-Myers Squibb), tremelimumab (Pfizer), Ticilimumab (AstraZeneca) or AMGP-224 (Glaxo Smith Kline), or a tumor specific antibody trastuzumab (Herceptin) for breast cancer, rituximab (Rituxan) for lymphoma, or cetuximab (Erbitux).

33. The use of any of claims 1-21, wherein the treatment or increasing the immune response is repeated periodically for time frames of from once every month, to once every two months, to once every 3 months, to once every 4 months, to once every 5 months, to once every 6 months, or once every 7 months, or once every 8 months, or once every 9 months, or once every 10 months, or once every 11 months, or once annually as a maintenance treatment for as long as the patient exhibits improvement, or stable/non-progressing disease.

34. The use of any of claims 1-25, further comprising that the patient is to be administered one or two antihistamine drugs, on the same day, but at least 2-6 hours prior to administration of the lymphocytic cellular composition comprising activated NK cells to the patient.

35. A cytokine and soluble fibroblast growth factor receptor 1(sFGFR1) activated lymphocytic cellular composition comprising activated natural killer (NK) cells for use in treating a patient with HIV, cancer, a viral infection, or a bacterial infection,

wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

36. Use of a cytokine and soluble fibroblast growth factor receptor 1(sFGFR1) activated lymphocytic cellular composition comprising activated natural killer (NK) cells in the

preparation of a medicament for treating a patient with HIV, cancer, a viral infection, or a bacterial infection,

wherein the patient is pre-conditioned with at least one lympho-suppressive agent, chemotherapeutic agent, or immunosuppressive agent for between 3-5 days prior to administration of the lymphocytic cellular composition so as to temporarily suppress the patient's immune system for a period of 5-7 cells.

37. The use according to claim 35 or 36, wherein the NK cells are killed by the patient's immune system within 4-15 days after administration.