Field

[0003] The present disclosure relates in some aspects to adoptive cell therapy involving the administration of doses of cells for treating subjects with disease and conditions such as certain B cell malignancies, and related methods, compositions, uses and articles of manufacture. The cells generally express recombinant receptors such as chimeric antigen receptors (CARs). In some embodiments, the disease or condition is a non-Hodgkin lymphoma (NHL), such as relapsed or refractory NHL or specific NHL subtype; in some embodiments, the subject is of a specific group or subset of NHL subjects, such as heavily pretreated or poor-prognosis subjects.

Background

[0004] Various immunotherapy and/or cell therapy methods are available for treating diseases and conditions. For example, adoptive cell therapies (including those involving the administration of cells expressing chimeric receptors specific for a disease or disorder of interest, such as chimeric antigen receptors (CARs) and/or other recombinant antigen receptors, as well as other adoptive immune cell and adoptive T cell therapies) can be beneficial in the treatment of cancer or other diseases or disorders. Improved approaches are needed. Provided are methods and uses that meet such needs.

Summary

[0005] Provided herein are methods, uses, compositions, formulations and articles of manufacture for treating subjects having or suspected of having a disease or condition, such as a cancer or tumor, optionally a B cell malignancy such as NHL or ALL or CLL or a subtype thereof. The methods and other examples generally relate to administering to the subject T cells, generally engineered T cells, such as those expressing or containing a recombinant receptor such as a chimeric antigen receptor (CAR) or TCR.

[0005a] In one aspect, the present disclosure refers to use of a first composition comprising CD4+ T cells in the manufacture of a medicament for treating a subject having or suspected of having a B cell malignancy ~~with a dose of CD4$^+$ T cells and CD8$^+$ T cells~~, wherein: the medicament is to be administered with a second composition comprising CD8+ T cells to form a dose of T cells comprising the first composition and the second composition; each of the CD4$^+$ T cells and the CD8$^+$ T cells, individually, comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the CAR comprised by the CD4+ T cells and the CD8+ T cells is the same; the dose of the ~~CD4+ T cells~~

~~and CD8+~~ T cells is to be administered as a plurality of separate compositions, the plurality of separate compositions comprising the first composition comprising the $CD4^+$ T cells and the second composition comprising the $CD8^+$ T cells, wherein the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and the dose of ~~the CD4+ T cells and CD8+~~ T cells comprises (i) between 1 x 10^7 and 1~~2~~ x 10^8 total CAR-expressing viable T cells, inclusive; and (ii) a ~~defined~~ ratio of CAR-expressing viable CD4+ cells to CAR-expressing viable CD8+ cells, wherein the ratio is 1:1 ~~that is between 1:3 and 3:1~~.

[0005b] In another aspect, the present disclosure refers to use of a first composition comprising CD8+ T cells in the manufacture of a medicament for treating a subject having or suspected of having a B cell malignancy ~~with a dose of $CD4^+$ T cells and $CD8^+$ T cells~~, wherein: the medicament is to be administered with a second composition comprising CD4+ T cells to form a dose comprising the first composition and the second composition; each of the $CD4^+$ T cells and the $CD8^+$ T cells, individually, comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the CAR comprised by the CD4+ T cells and the CD8+ T cells is the same; the dose of the CD4+ T cells and CD8+ T cells is to be administered as a plurality of separate compositions, the plurality of separate compositions comprising the first composition comprising the $CD8^+$ T cells and the second composition comprising the $CD4^+$ T cells, wherein the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and the dose of the CD4+ T cells and CD8+ T cells comprises (i) between 1 x 10^7 and 1~~2~~ x 10^8 total CAR-expressing viable T cells, inclusive; and (ii) a ~~defined~~ ratio of CAR-expressing viable CD4+ cells to CAR-expressing viable CD8+ cells, wherein the ratio is 1:1 ~~that is between 1:3 and 3:1~~.

[0006] In some examples, the dose of cells or cells administered in connection with any examples of the provided methods, compositions, articles of manufacture and uses, contains $CD4^+$ T cells or a subtype or phenotype thereof (such as engineered or recombinant receptor-expressing $CD4^+$ T cells) and/or $CD8^+$ T cells or a subtype thereof (such as an engineered or recombinant receptor-expressing $CD4^+$ cells). In some examples, the $CD8^+$ cells or subtype or phenotype are present at a particular dose or amount or number; in some examples the $CD4^+$ cells or subtype or phenotype are present at a particular dose or amount or number. In

first dose of the T cells and a consecutive dose of the T cells, wherein one or both of the first dose and the second dose comprises administration of the plurality of compositions of T cells. In certain examples of any of the provided methods, the consecutive dose is administered at a point in time that is at least or more than about 7 days or 14 days after and less than about 28 days after initiation of the administration of the first dose of cells.

[0118] Provided herein is an article of manufacture comprising a cell therapy comprising a dose or composition of genetically engineered cells expressing a chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify: the dose of cells is to be administered to a subject having or identified to have non-Hodgkin lymphoma (NHL), the NHL selected from diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (de novo or transformed from indolent lymphoma), or follicular lymphoma Grade 3B, wherein the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG) status of 0 or 1; and the dose of T cells to be administered comprises between at or about 5 x 10^7 CAR-expressing T cells and 1 x 10^8 CAR-expressing T cells, inclusive. In some examples of any of the provided articles of manufacture, the instructions specify administering the dose of T cells at a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR and/or of $CD4^+$ cells to $CD8^+$ cells, which ratio optionally is approximately 1:1 or is between approximately 1:3 and approximately 3:1.

~~**[0118a]** In another aspect, the present disclosure refers to an article of manufacture comprising one or more dose of a cell therapy, each dose comprising a first composition comprising one of CD4+ T cells or CD8+ T cells and a second composition comprising the other of the CD4+ or CD8+ T cells, wherein the dose comprises CD4+ T cells and CD8+ T cells expressing the same CAR that specifically binds to CD19, and instructions for administering the cell therapy, wherein the instructions specify:~~

~~(i) the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and~~

~~(ii) the dose of cells is to be administered to a subject having or identified to have a non-Hodgkin lymphoma (NHL); the dose of cells to be administered comprises between 1 x 10^7 CAR-expressing T cells and 2 x 10^8 CAR-expressing T cells, inclusive; and the dose of cells is to be administered at a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR and/or of $CD4^+$ cells to $CD8^+$ cells, which ratio optionally is 1:1 or is between 1:3 and 3:1.~~

[0119] Provided herein is an article of manufacture comprising a cell therapy comprising a dose or composition of genetically engineered cells expressing a chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify: the dose of T cells is to be administered at a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR and/or of $CD4^+$ cells to $CD8^+$ cells, which ratio is approximately or is 1:1; and the dose of cells is to be administered to a subject having or identified to have non-Hodgkin lymphoma (NHL), the NHL selected from diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), NOS (de novo or transformed from indolent lymphoma), or follicular lymphoma Grade 3B.

[0120] Provided herein is an article of manufacture comprising a cell therapy comprising a dose or composition of genetically engineered cells expressing a chimeric antigen receptor (CAR), and instructions for administering the cell therapy, wherein the instructions specify: the dose of cells is to be administered to a subject having or identified to have non-Hodgkin

CLAIMS

1. Use of a first composition comprising CD4+ T cells in the manufacture of a medicament for treating a subject having or suspected of having a B cell malignancy ~~with a dose of $CD4^+$ T cells and $CD8^+$ T cells~~, wherein:

the medicament is to be administered with a second composition comprising CD8+ T cells to form a dose of T cells comprising the first composition and the second composition;

each of the $CD4^+$ T cells and the $CD8^+$ T cells, individually, comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the CAR comprised by the CD4+ T cells and the CD8+ T cells is the same;

the dose of the ~~CD4+ T cells and CD8+~~ T cells is to be administered as a plurality of separate compositions, the plurality of separate compositions comprising the first composition comprising the $CD4^+$ T cells and the second composition comprising the $CD8^+$ T cells, wherein the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and

the dose of ~~the CD4+ T cells and CD8+~~ T cells comprises (i) between 1 x 10^7 and 12~~10^8~~ x 10^8 total CAR-expressing viable T cells, inclusive; and (ii) a ~~defined~~ ratio of CAR-expressing viable CD4+ cells to CAR-expressing viable CD8+ cells ~~that is between 1:3 and 3:1~~, wherein the ratio is 1:1.

2. Use of a first composition comprising CD8+ T cells in the manufacture of a medicament for treating a subject having or suspected of having a B cell malignancy ~~with a dose of $CD4^+$ T cells and $CD8^+$ T cells~~, wherein:

the medicament is to be administered with a second composition comprising CD4+ T cells to form a dose comprising the first composition and the second composition;

each of the $CD4^+$ T cells and the $CD8^+$ T cells, individually, comprises a chimeric antigen receptor (CAR) that specifically binds to CD19, wherein the CAR comprised by the CD4+ T cells and the CD8+ T cells is the same;

the dose of the CD4+ T cells and CD8+ T cells is to be administered as a plurality of separate compositions, the plurality of separate compositions comprising the first composition comprising the $CD8^+$ T cells and the second composition comprising the $CD4^+$ T cells, wherein

the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and

the dose of the CD4+ T cells and CD8+ T cells comprises (i) between 1 x 10^7 and 12 ~~2~~ x 10^8 total CAR-expressing viable T cells, inclusive; and (ii) a ~~defined~~ ratio of CAR-expressing viable CD4+ cells to CAR-expressing viable CD8+ cells ~~that is between 1:3 and 3:1~~, wherein the ratio is 1:1.

3. The use of claim 1 or claim 2, wherein

the first composition and the second composition are to be administered between 1 minute and 1 hour apart or between 5 minutes and 30 minutes apart.

4. The use of any of claims 1-3, wherein the first composition and the second composition are to be administered no more than 2 hours, no more than 1 hour, no more than 30 minutes, no more than 15 minutes, no more than 10 minutes or no more than 5 minutes apart.

5. The use of any of claims 1-4, wherein the composition comprising the CD8+ T cells is to be administered prior to the composition comprising the CD4+ T cells.

~~6. The use of any of claims 1-5, wherein the defined ratio is 1:1.~~

6~~7~~. The use of any of claims 1-5~~6~~, wherein the T cells are autologous to the subject.

7~~8~~. The use of any of claims 1-6~~7~~, wherein the subject is or has been identified as having an ECOG status of 0 or 1.

8~~9~~. The use of any of claims 1-7~~8~~, wherein

the dose of T cells ~~comprises between 5 x 10^7 CAR-expressing T cells and~~ 1.0~~5~~ x 10^8 CAR-expressing viable T cells, inclusive.

9~~10~~. The use of any of claims 1-8~~9~~, wherein the B cell malignancy is acute lymphoblastic leukemia (ALL), adult ALL, chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), or Diffuse Large B-Cell Lymphoma (DLBCL).

101. The use of claim 9, wherein the B cell malignancy is a non-Hodgkin lymphoma (NHL).

112. The use of any of claims 1-101, wherein prior to initiation of administration of the dose of T cells, the subject has not been administered an agent or treatment capable of treating, preventing, delaying, reducing or attenuating the development or risk of development of a toxicity following administration of the dose of T cells.

123. The use of any of claims 1-112, wherein:

the medicament is to be administeredadministration of the dose of T cells and any follow up is carried out on an outpatient basis and/or without requiring admission to or an overnight stay at a hospital; and

if the subject exhibits a sustained fever or a fever that is or has not been reduced by more than 1ºC after treatment with an antipyretic, the subject is to be admitted to a hospital or to an overnight stay at a hospital and/or is to be administered an agent or treatment for the treatment, prevention, reduction or attenuation of a neurotoxicity and/or a cytokine release syndrome or risk thereof.

134. The use of any of claims 101-123, wherein the NHL is selected from the group consisting of aggressive NHL, diffuse large B cell lymphoma (DLBCL), NOS (de novo and transformed from indolent), primary mediastinal large B cell lymphoma (PMBCL), mantle cell lymphoma (MCL), and/or follicular lymphoma Grade 3B (FL3B).

145. The use of any of claims 121-134, wherein, at or immediately prior to administration of the dose of cells, the subject has relapsed following remission after treatment with, or become refractory to, one or more prior therapies for the NHL.

156. The use of any of claims 1-145, wherein, at or prior to administration of the dose of T cells:

the subject is or has been identified as having a double/triple hit lymphoma; and/or

the subject is or has been identified as having a chemorefractory lymphoma, or a chemorefractory DLBCL; and/or

the subject has not achieved complete remission (CR) in response to a prior therapy; and/or

the subject has relapsed within 1 year or less than 1 year after receiving an autologous stem cell transplant (ASCT).

167. The use of any of claims 1-156, wherein:

the CAR comprises an scFv specific for CD19, a transmembrane domain, a cytoplasmic signaling domain derived from a costimulatory molecule, a cytoplasmic signaling domain that comprises a CD3zeta signaling domain and a spacer between the transmembrane domain and the scFv.

178. The use of claim 167, wherein the costimulatory molecule is or comprises a 4-1BB.

189. The use of claim 167 or claim 178, wherein the spacer consists of all or a portion of an immunoglobulin hinge and is 15 amino acids or fewer in length.

1920. The use of any of claims 167-189, wherein the spacer consists of 12 amino acids in length.

201. The use of any of claims 167-1920, wherein the spacer consists of the sequence set forth in SEQ ID NO:1.

212. The use of any of claims 1-201, wherein the CAR comprises a CDRL1 sequence of RASQDISKYLN (SEQ ID NO:35), a CDRL2 sequence of SRLHSGV (SEQ ID NO:36), a CDRL3 sequence of GNTLPYTFG (SEQ ID NO:37); a CDRH1 sequence of DYGVS (SEQ ID NO:38), a CDRH2 sequence of VIWGSETTYYNSALKS (SEQ ID NO:39), and a CDRH3 sequence of YAMDYWG (SEQ ID NO:40).

223. The use of any of claims 1-212, wherein the CAR comprises the V_H sequence set forth in SEQ ID NO:41 and the V_L sequence set forth in SEQ ID NO:42.

234. The use of any of claims 1-223, wherein the CAR comprises the sequence set forth in SEQ ID NO:43.

245. The use of any of claims 1-234, wherein~~, prior to administration of the dose of T cells,~~ the subject has been preconditioned with a lymphodepleting therapy comprising the administration of fludarabine and/or cyclophosphamide.

256. The use of any of claims 1-245, wherein the dose of T cells comprises 1 x 10^8 CAR-expressing viable cells.

~~27. An article of manufacture comprising one or more dose of a cell therapy, each dose comprising a first composition comprising one of CD4+ T cells or CD8+ T cells and a second composition comprising the other of the CD4+ or CD8+ T cells, wherein the dose comprises CD4+ T cells and CD8+ T cells expressing the same CAR that specifically binds to CD19, and instructions for administering the cell therapy, wherein the instructions specify:~~

~~(i) the first composition and the second composition are to be administered between 0 and 12 hours apart, between 0 and 6 hours apart or between 0 and 2 hours apart; and~~

~~(ii) the dose of cells is to be administered to a subject having or identified to have a non-Hodgkin lymphoma (NHL); the dose of cells to be administered comprises between 1 x 10^7 CAR-expressing T cells and 2 x 10^8 CAR-expressing T cells, inclusive; and the dose of cells is to be administered at a defined ratio of $CD4^+$ cells expressing the CAR to $CD8^+$ cells expressing the CAR and/or of $CD4^+$ cells to $CD8^+$ cells, which ratio optionally is 1:1 or is between 1:3 and 3:1.~~