

a consecutive dose is designed to minimize risk of toxicity and/or host immune response to the cells by the subject, thereby improving persistence and efficacy.

Background

[0004] Various methods are available for adoptive cell therapy using engineered cells expressing recombinant receptors, such as chimeric antigen receptor (CARs). Improved methods are needed, for example, to reduce the risk of toxicity and/or to increase efficacy, for example, by increasing exposure of the subject to the administered cells, for example, by improving expansion and/or persistence of the administered cells. Provided are methods, compositions, and articles of manufacture that meet such needs.

Summary

[0004a] In one aspect, the present disclosure refers to use of a composition comprising T cells expressing a chimeric antigen receptor (CAR) for manufacture of a medicament to be administered as a consecutive dose of CAR-expressing cells for treatment of a tumor or a cancer in a subject previously treated with a first dose of CAR-expressing cells, wherein:

the composition comprising the consecutive dose is to be used 14 to 28 days after the initiation of administration of the first dose of CAR-expressing cells; and

the composition comprising the consecutive dose is formulated for administration of an increased number of CAR-expressing cells as compared to the first dose and in an amount sufficient for reduction in burden of a disease or condition in the subject having been previously treated with the first dose of CAR-expressing cells.

[0004b] In another aspect, the present disclosure refers to use of T cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament to be administered as a first dose of CAR-expressing cells and a consecutive dose of CAR-expressing cells for treating a tumor or a cancer in a subject, wherein: the first dose comprises no more than 1×10^6 of the CAR-expressing cells per kilogram body weight of the subject, no more than 1×10^8 of the CAR-expressing cells, and/or no more than 1×10^8 of the CAR-expressing cells cells/m² of the subject; and

the consecutive dose of CAR-expressing cells is to be administered at a time point that is at least or more than 14 days after and less than 28 days after initiation of

CLAIMS

1. Use of a composition comprising T cells expressing a chimeric antigen receptor (CAR) for manufacture of a medicament to be administered as a consecutive dose of CAR-expressing cells for treatment of a tumor or a cancer in a subject previously treated with a first dose of CAR-expressing cells, wherein:

the composition comprising the consecutive dose is to be used 14 to 28 days after the initiation of administration of the first dose of CAR-expressing cells; and

the composition comprising the consecutive dose is formulated for administration of an increased number of CAR-expressing cells as compared to the first dose and in an amount sufficient for reduction in burden of a disease or condition in the subject having been previously treated with the first dose of CAR-expressing cells.

2. The use of claim 1, wherein the first dose of CAR-expressing cells reduced tumor burden in the subject prior to use of the consecutive dose and/or the subject does not exhibit morphologic disease prior to use of the consecutive dose and/or the subject does not exhibit greater than 5% blast cells in the bone marrow prior to use of the consecutive dose.

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

the first dose of CAR-expressing cells comprises no more than 1×10^6 of the CAR-expressing cells per kilogram body weight of the subject, no more than 1×10^8 of the CAR-expressing cells, and/or no more than 1×10^8 of the CAR-expressing cells cells/m² of the subject; or

the first dose of CAR-expressing cells comprises between 1×10^6 and 1×10^8 CAR-expressing cells, inclusive; or no more than 2×10^6 CAR-expressing cells, no more than 5×10^6 CAR-expressing cells, no more than 1×10^7 CAR-expressing cells, no more than 5×10^7 CAR-expressing cells, or no more than 1×10^8 CAR-expressing cells.

4. Use of T cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament to be administered as a first dose of CAR-expressing cells and a consecutive dose of CAR-expressing cells for treating a tumor or a cancer in a subject, wherein: the first dose comprises no more than 1×10^6 of the CAR-expressing cells per kilogram body weight of the

subject, no more than 1×10^8 of the CAR-expressing cells, and/or no more than 1×10^8 of the CAR-expressing cells/m² of the subject; and

the consecutive dose of CAR-expressing cells is to be administered at a time point that is at least or more than 14 days after and less than 28 days after initiation of administration of the first dose of cells, and wherein the consecutive dose of CAR-expressing cells comprises an increased number of CAR-expressing cells as compared to the first dose.

5. The use of any of claims 1-4, wherein the composition comprising cells of the consecutive dose is formulated for administration in an amount that (i) does not induce severe cytokine release syndrome (CRS) in the subject or does not induce CRS in the subject; (ii) does not induce grade 3 or higher neurotoxicity in the subject; (iii) based on clinical data, does not induce severe CRS in a majority of subjects so-treated; and/or (iv) based on clinical data, does not induce grade 3 or higher neurotoxicity in a majority of subjects so-treated.

6. The use of any of claims 1-5, wherein the increased number is at least 2-fold, 5-fold, or 10-fold greater than the number in the first dose.

7. The use of any of claims 1-6, wherein the composition is to be used in a subject in which:

(i) the serum level in the subject of a factor indicative of cytokine release syndrome (CRS) is less than 10 times, less than 25 times, and/or less than 50 times that in the subject immediately prior to administration of the first dose of CAR-expressing cells;

(ii) the subject does not exhibit grade 3 or higher neurotoxicity;

(iii) a CRS-related outcome or symptom of neurotoxicity in the subject following said administration of said first dose of CAR-expressing cells has reached a peak level and begun to decline following administration of the first dose of CAR-expressing cells, and/or

(iv) the subject does not exhibit a detectable humoral or cell-mediated immune response against the CAR expressed by the cells of said first dose of cells.

8. The use of any of claims 1-7, wherein the consecutive dose is formulated for administration of a number of cells that is:

between 2×10^6 cells per kilogram (cells/kg) body weight and 6×10^6 cells/kg, between 2.5×10^6 cells/kg and 5.0×10^6 cells/kg, or between 3.0×10^6 cells/kg and 4.0×10^6 cells/kg, each inclusive;

between 1.5×10^8 cells and 4.5×10^8 cells, between 1.5×10^8 cells and 3.5×10^8 cells or between 2×10^8 cells and 3×10^8 cells, each inclusive; or

between 1.5×10^8 cells/m² and 4.5×10^8 cells/m², between 1.5×10^8 cells/m² and 3.5×10^8 cells/m² or between 2×10^8 cells/m² and 3×10^8 cells/m², each inclusive.

9. The use of any of claims 4-8, wherein: the composition comprising the first and/or consecutive dose is formulated for administration in one or more unit dose, each unit dose comprising between 5×10^7 of the cells and 5×10^8 cells, between 5×10^7 of the cells and 2.5×10^8 cells or between 2.5×10^8 cells and 4×10^8 cells; or

the composition comprising cells of the first and/or consecutive dose is formulated in a unit dose comprising no more than 5×10^7 cell, no more than 1×10^8 cells, no more than 2×10^8 of the cells, no more than 2.5×10^8 of the cells, no more than 3.0×10^8 of the cells or no more than 4×10^8 of the cells;

the composition comprising the consecutive dose is formulated for administration in one or more unit dose, each unit dose comprising at least 1×10^6 CAR-expressing cells, at least 2×10^6 CAR-expressing cells; at least 3×10^6 CAR-expressing cells, at least 5×10^6 CAR-expressing cells, at least 1×10^7 CAR-expressing cells, at least 1×10^8 CAR-expressing cells or at least 1×10^9 CAR-expressing cells;

the composition comprising the first dose is formulated for administration in one or more unit dose, each unit dose comprising between 1×10^6 and 1×10^8 CAR-expressing cells, inclusive; or the number of cells administered in the first dose is no more than 2×10^6 CAR-expressing cells, no more than 5×10^6 CAR-expressing cells, no more than 1×10^7 CAR-expressing cells, no more than 5×10^7 CAR-expressing cells, or no more than 1×10^8 CAR-expressing cells.

10. The use of any of claims 4-9, wherein the composition comprising the first and/or consecutive dose of cells is formulated for administration of a single unit dose.

11. The use of any of claims 4-9, wherein the composition comprising the first and/or consecutive dose of cells is formulated for administration of two or more unit doses.

12. The use of any of claims 1-11, wherein the tumor or cancer is leukemia or lymphoma.
13. The use of claim 12, wherein the composition is to be used in treating acute lymphoblastic leukemia.
14. The use of any of claims 1-13, wherein the composition is to be used in treating non-Hodgkin lymphoma (NHL).
15. The use of any of claims 1-14, wherein the antigen bound by the CAR expressed by the cells in the first dose and the antigen bound by the CAR expressed by the cells in the consecutive dose is the same antigen and/or the CAR expressed by the cells in the first dose and the CAR expressed by the cells in the consecutive dose contain the same antigen-binding domain.
16. The use of any of claims 1-15, wherein the CAR expressed by the cells in the consecutive dose contains at least one immunoreactive epitope present in the CAR expressed by the cells in the first dose.
17. The use of any of claims 1-16, wherein the CAR expressed by the cells in the consecutive dose is identical to the CAR expressed by the cells in the first dose.
18. The use of any of claims 1-17, wherein the CAR expressed by the cells in the consecutive dose specifically binds to an antigen expressed by a cell or tissue of the disease or condition or associated with the disease or condition.
19. The use of any of claims 1-18, wherein the subject has been previously treated with a chemotherapeutic agent prior to administration of the first dose and/or prior to the administration of the consecutive dose.

20. The use of claim 19, wherein the chemotherapeutic agent comprises conditioning chemotherapy, which reduces burden of the disease or condition in the subject.

21. The use of claim 19 or claim 20, wherein the chemotherapeutic agent comprises an agent selected from the group consisting of cyclophosphamide and fludarabine.

22. The use of any of claims 19-21, wherein the chemotherapeutic agent comprises a combination of cyclophosphamide and fludarabine.

23. The use of any of claims 1-22, wherein the T cells are CD4⁺ and/or CD8⁺ T cells.

24. The use of any of claims 1-23, wherein the cells of the first and/or consecutive dose are autologous to the subject to whom they are to be administered.

25. The use of any of claims 1-24, wherein the consecutive dose of CAR-expressing cells is to be administered at a time point that is between 15 and 27 days after initiation of administration of the first dose of cells.

26. The use of any of claims 1-24, wherein the consecutive dose of CAR-expressing cells is to be administered at a time point that is between 17 and 21 days after initiation of administration of the first dose of cells.