Background

[0004] Various therapies are available for treating disease, such as cancer. For example, photoimmunotherapy (PIT) is a method that uses a photosensitizer conjugated to an antibody or other targeting molecule to target a cell surface protein in order to permit the targeted killing of specific cells. In some cases, PIT can selectively target disease cells, such as tumor cells, and thereby selectively kill such cells without damaging healthy cells. Improved strategies are needed to improve photoimmunotherapy methods, for example, to increase the efficacy of treatment. Provided are compositions and methods that meet such needs.

Summary

[0005] Provided in some examples is a method of treating a disease or condition in a subject containing using photoimmunotherapy (PIT). In some examples, the method includes administering to the subject having a disease or condition a conjugate containing a phthalocyanine dye linked to a targeting molecule, such as an antibody or an antigen-binding fragment thereof, that binds to a protein on the surface of a cell present in the microenvironment of a lesion associated with the disease or condition. In some examples, the conjugate is administered to effect a systemic exposure that is no more than 75% of the total therapeutically effective systemic exposure of the antibody or antigen-binding fragment that is not so conjugated for treating the same disease or condition as described at the label approved for commercialization by the regulatory agencies (*e.g.* FDA, EMA, PDMA). In some examples, after administering the conjugate, the lesion is irradiated at a wavelength of 500 to 900 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length thereby treating the tumor in the subject. In some examples, the wavelength for irradiation is 600 nm to 850 nm, such as 660 nm to 740 nm.

[0005a] In one aspect, the present disclosure refers to use of a pharmaceutical composition comprising a conjugate, the conjugate comprising a phthalocyanine dye linked to a targeting molecule that binds to a protein on the surface of a cell present in the microenvironment of a lesion associated with a cancer in a subject, for preparation of a medicament formulated for intravenous administration in a dosing schedule for treating the lesion, wherein the dosing schedule comprises:

a) that the conjugate is to be intravenously administered to the subject having the lesion in an amount that is between 160 mg/m^2 and 2000 mg/m^2; and

b) after administration of the conjugate, the lesion is to be irradiated at a wavelength of 600 nm to 850 nm at a dose from 25 J cm^{-2} to 400 J cm^{-2} or from 25 J/cm fiber length to 500 J/cm fiber length.

[0005b] In another aspect, the present disclosure refers to use of a pharmaceutical composition comprising a conjugate comprising a phthalocyanine dye linked to cetuximab for preparation of a medicament formulated for intravenous administration in a dosing schedule for treating a tumor in a subject having a head or neck cancer, wherein the dosing schedule comprises:

a) that the conjugate is to be intravenously administered to the subject having the tumor in an amount that is between 160 mg/m^2 and 2000 mg/m^2; and

b) after administration of the conjugate, the tumor is to be irradiated at a wavelength of 690 ± 50 nm at a dose of at least or at 50 J cm^{-2} or 100 J/cm of fiber length.

[0006] In some examples, the conjugate is administered in a dosing schedule in which: the administration of the conjugate is performed only one time as a single injection or infusion; or the dosing schedule does not include a subsequent dose of the conjugate; or the dosing schedule does not include a subsequent dose of the targeting molecule, *e.g.*, a macromolecule, that is not so conjugated.

[0007] In some examples, the conjugate is administered systemically. In some examples, the conjugate is administered intravenously.

CLAIMS

1. Use of a pharmaceutical composition comprising a conjugate, the conjugate comprising a phthalocyanine dye linked to a targeting molecule that binds to a protein on the surface of a cell present in the microenvironment of a lesion associated with a cancer in a subject, for preparation of a medicament formulated for intravenous administration in a dosing schedule for treating the lesion, wherein the dosing schedule comprises:

a) that the conjugate is to be intravenously administered to the subject having the lesion in an amount that is between 160 mg/m^2 and 2000 mg/m^2; and

b) after administration of the conjugate, the lesion is to be irradiated at a wavelength of 600 nm to 850 nm at a dose from 25 J cm^{-2} to 400 J cm^{-2} or from 25 J/cm fiber length to 500 J/cm fiber length.

2. The use of claim 1, wherein the targeting molecule is an antibody or an antigen-binding antibody fragment.

3. The use of claim 1 or 2, wherein the protein on the surface of the cell is selected from among ACTHR, endothelial cell Anxa-1, aminopeptidase N, IL-6R, alpha-4-integrin, alpha-5-beta-3 integrin, alpha-5-beta-5 integrin, alpha-fetoprotein (AFP), ANPA, ANPB, APA, APN, APP, 1AR, 2AR, AT1, B1, B2, BAGE1, BAGE2, B-cell receptor BB1, BB2, BB4, calcitonin receptor, cancer antigen 125 (CA 125), CCK1, CCK2, CD5, CD10, CD11a, CD13, CD14, CD19, CD20, CD22, CD25, CD30, CD33, CD38, CD45, CD52, CD56, CD68, CD90, CD133, CD7, CD15, CD34, CD44, CD206, CD271, CEA (Carcinoembryonic Antigen), CGRP, chemokine receptors, cell-surface annexin-1, cell-surface plectin-1, Cripto-1, CRLR, CXCR2, CXCR4, DCC, DLL3, E2 glycoprotein, EGFR, EGFRvIII, EMR1, Endosialin, EP2, EP4, EpCAM, EphA2, ET receptors, Fibronectin, Fibronectin ED-B, FGFR, frizzled receptors, GAGE1, GAGE2, GAGE3, GAGE4, GAGE5, GAGE6, GLP-1 receptor, G-protein coupled receptors of the Family A (Rhodopsin-like), G-protein coupled receptors of the Family B (Secretin receptor-like), G-protein coupled receptors of the Family C (Metabotropic Glutamate Receptor-like), GD2, GP100, GP120, Glypican-3, hemagglutinin, Heparin sulfates, HER1, HER2, HER3, HER4, HMFG, HPV 16/18 and E6/E7 antigens, hTERT, IL11-R, IL-13R, ITGAM, Kalikrien-9, Lewis Y, LH receptor, LHRH-R, LPA1, MAC-1, MAGE 1, MAGE 2,

MAGE 3, MAGE 4, MART1, MC1R, Mesothelin, MUC1, MUC16, Neu (cell-surface Nucleolin), Neprilysin, Neuropilin-1, Neuropilin-2, NG2, NK1, NK2, NK3, NMB-R, Notch-1, NY-ESO-1, OT-R, mutant p53, p97 melanoma antigen, NTR2, NTR3, p32 (p32/gC1q-R/HABP1), p75, PAC1, PAR1, Patched (PTCH), PDGFR, PDFG receptors, PDT, Protease-cleaved collagen IV, proteinase 3, prohibitin, protein tyrosine kinase 7, PSA, PSMA, purinergic P2X family, P2X1-5, mutant Ras, RAMP1, RAMP2, RAMP3 patched, RET receptor, plexins, smoothened, sst1, sst2A, sst2B, sst3, sst4, sst5, substance P, TEMs, T-cell CD3 Receptor, TAG72, TGFBR1, TGFBR2, Tie-1, Tie-2, Trk-A, Trk-B, Trk-C, TR1, TRPA, TRPC, TRPV, TRPM, TRPML, TRPP, TRPV1-6, TRPA1, TRPC1-7, TRPM1-8, TRPP1-5, TRPML1-3, TSH receptor, VEGF receptors, VEGFR1, Flt-1, VEGFR2, FLK-1/KDR, VEGF-3, FLT-4, voltage-gated ion channels, VPAC1, VPAC2, Wilms tumor 1, Y1, Y2, Y4, and Y5.

4. The use of claim 2 or 3, wherein the antibody or the antigen-binding antibody fragment is selected from among cetuximab, panitumumab, zalutumumab, nimotuzumab, Tositumomab (Bexxar ®), Rituximab (Rituxan, Mabthera), Ibritumomab tiuxetan (Zevalin), Daclizumab (Zenapax), Gemtuzumab (Mylotarg), Alemtuzumab, CEA-scan Fab fragment, OC125 monoclonal antibody, ab75705, B72.3, Bevacizumab (Avastin ®), Basiliximab, nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP321, BMS-986016, LAG525, urelumab, PF-05082566, TRX518, MK-4166, dacetuzumab, lucatumumab, SEA-CD40, CP-870, CP-893, MED16469, MEDI6383, MEDI4736, MOXR0916, AMP-224, PDR001, MSB0010718C, rHIgM12B7, Ulocuplumab, BKT140, Varlilumab (CDX-1127), ARGX-110, MGA271, lirilumab (BMS-986015, IPH2101), IPH2201, AGX-115, Emactuzumab, CC-90002 and MNRP1685A or is an antigen-binding antibody fragment thereof.

5. The use of any one of claims 2-4, wherein the antibody or antigen-binding antibody fragment is cetuximab.

6. The use of any one of claims 1-5, wherein the cancer is a head or neck cancer.

7. The use of any one of claims 1-6, wherein the irradiation is to be carried out at a wavelength of 690 ± 50 nm or at a wavelength of 690 ± 20 nm.

8. Use of a pharmaceutical composition comprising a conjugate comprising a phthalocyanine dye linked to cetuximab for preparation of a medicament formulated for intravenous administration in a dosing schedule for treating a tumor in a subject having a head or neck cancer, wherein the dosing schedule comprises:

a) that the conjugate is to be intravenously administered to the subject having the tumor in an amount that is between 160 mg/m^2 and 2000 mg/m^2; and

b) after administration of the conjugate, the tumor is to be irradiated at a wavelength of 690 ± 50 nm at a dose of at least or at 50 J cm^{-2} or 100 J/cm of fiber length.

9. The use of any one of claims 1-8, wherein the conjugate is to be administered in an amount that is 640 mg/m^2.

10. The use of any one of claims 1-8, wherein the conjugate is to be administered in an amount that is 320 mg/m^2.

11. The use of any one of claims 1-10, wherein the irradiation is to be carried out between 30 minutes and 96 hours after administration of the conjugate.

12. The use of any one of claims 1-11, wherein the irradiation is to be carried out 24 hours ± 4 hours after administration of the conjugate.

13. The use of any one of claims 1-12, wherein the phthalocyanine dye is IR700.

14. The use of any one of claims 1-13, wherein the irradiation is to be carried out at a wavelength of 690 ± 20 nm.

15. The use of any one of claims 1-7 and 9-14, wherein the irradiation is to be carried out at a dose of 50 J cm^{-2} or 100 J/cm of fiber length.

16. The use of any one of claims 1-15, wherein the dosing schedule is to be repeated, whereby steps (a) and (b) are to be repeated.

17. The use of claim 16, wherein the dosing schedule is to be repeated if a residual lesion remains at a time that is more than or about 2 weeks, 3 weeks, 4 weeks, 2 months, 6 months or 1 year after initiation of the prior administration of the conjugate.

18. The use of claim 16 or 17, wherein the dosing schedule is to be repeated if a residual lesion remains at or about 4 weeks after initiation of the prior administration of the conjugate.

19. The use of any one of claims 1-18, wherein the lesion or the tumor is a superficial tumor.

20. The use of claim 19, wherein the irradiation step comprises illumination of the superficial tumor with a microlens-tipped fiber for surface illumination.

21. The use of any one of claims 1-18, wherein the lesion or the tumor a subcutaneous tumor.

22. The use of claim 21, wherein the irradiation step is to be carried out using cylindrical diffusing fibers.

23. The use of claim 22, wherein the cylindrical diffusing fibers comprise a diffuser length of 0.5 cm to 10 cm and spaced 1.8 ± 0.2 cm apart.

24. The use of any one of claims 1-23, wherein, in the dosing schedule, the conjugate is to be administered in a single injection or a single infusion.

25. The use of any one of claims 1-24, wherein the dosing schedule further comprises administration of an additional therapeutic agent or anti-cancer treatment.