Autologous Hematopoietic Stem Cell Transplantation in Lymphoma: An Observational Study on 1038 Patients From Fondazione Italiana Linfomi. Biol Blood Marrow Transplant, 2018. 24(9): p. 1814-182.

[0006] There is a pressing need in the art for new and improved therapies the treatment and prevention of severe toxicities related to the use of chemotherapeutic agents, including high dose therapy (HDT). The present invention addresses this need.

SUMMARY ~~OF THE INVENTION~~

[0007] The present invention is based, in part, on certain discoveries made in the course of performing Phase 1 clinical trials to assess the safety of administering engineered endothelial cells to human subjects with various hematologic malignancies undergoing high dose chemo therapy and hematopoietic stem cell transplantation. In performing these clinical studies, it was found that, not only were there no apparent negative side effects or safety issues associated with the endothelial cell administration, but also that administration of the endothelial cells mitigated numerous non-hematologic and hematologic severe regimen related toxicities (SSRTs) in the treated patients. It was also found that different doses of endothelial cells resulted in different effects – with some side effects being mitigated at both low and high doses and other side effects being preferentially mitigated at higher doses. For example, it was found that the occurrence of severe oro-gastrointestinal toxicities was eliminated and the occurrence of febrile neutropenia was reduced by around 75% following administration of endothelial cells to patients having lymphoma without CNS involvement. These and other discoveries are described in more detail in the Examples section of this patent disclosure.

[0008] Building on these discoveries, the present invention provides various new methods and compositions for the mitigation of side effects of chemotherapy, including high dose therapy (HDT), including, but not limited to, HDT administered to patients in conjunction with hematopoietic stem cell transplantation.

[0009] Accordingly, the present invention provides methods for mitigating the side effects of chemotherapy in subjects in need thereof, such methods comprising administering an effective

amount of a therapeutic composition comprising endothelial cells to subjects that have been treated with chemotherapy, thereby mitigating one or more of the side effects of the chemotherapy in the subject. The present invention also provides therapeutic compositions comprising endothelial cells, for example for use in such methods. The present invention also provides endothelial cells for use in the preparation of a therapeutic composition (or medicament) for example use in such methods.

[0009a] In one aspect, disclosed herein is a use of a therapeutic composition comprising an effective amount of E4ORF1+ HUVECs in the manufacture of a medicament for mitigating a non-hematologic severe regimen-related toxicity (SRRT) in a human subject in need thereof, wherein the medicament is to be administered intravenously to an adult human subject with Hodgkin's lymphoma or non-Hodgkin's lymphoma, wherein: (a) the effective amount is from about $10x10^6$ cells per kg bodyweight to about $30x10^6$ cells per kg bodyweight, (b) the subject has previously received high-dose therapy (HDT) and an autologous hematopoietic stem cell transplant (AHCT), (c) the medicament is to be administered to the subject on the same day that the subject receives the AHCT, and (d) the non-hematologic SRRT is selected from the group consisting of an oral / gastrointestinal SSRT and febrile neutropenia, thereby mitigating the SSRT in the subject.

[0009b] In another aspect, disclosed herein is a use of a therapeutic composition comprising an effective amount of endothelial cells (ECs) in the manufacture of a medicament for mitigating a non-hematologic severe regimen-related toxicity (SRRT) in a human subject in need thereof, wherein the medicament is to be administered to a human subject who has undergone, is undergoing, or will undergo chemotherapy, wherein the use results in mitigation of a SRRT in the subject.

[0009c] In another aspect, disclosed herein is a use of a therapeutic composition comprising an effective amount of endothelial cells (ECs) in the manufacture of a medicament for mitigating a chemotherapy side effect in a human subject in need thereof, wherein the medicament is to be administered to a human subject who has undergone, is undergoing, or will undergo chemotherapy, wherein the use results in mitigation of the chemotherapy side effect in the subject.

[0010] In some embodiments the endothelial cells are umbilical vein endothelial cells (UVECs). In some embodiments the endothelial cells are human umbilical vein endothelial cells (HUVECs). In some embodiments the endothelial cells are engineered to express a recombinant protein. In some embodiments the endothelial cells are engineered to express the adenovirus E4ORF1 protein – i.e., they are E4ORF1+ endothelial cells. In some embodiments the endothelial cells are E4ORF1+ HUVECS.

[0011] In some embodiments the subjects to whom the endothelial cells are administered are adults. In some embodiments the subjects to whom the endothelial cells are administered are ≥ 18 years old. In some embodiments the subjects to whom the endothelial cells are administered are ≥ 20 years old. In some embodiments the subjects to whom the endothelial cells are administered are ≥ 30 years old. In some embodiments the subjects to whom the endothelial cells are administered are ≥ 40 years old. In some embodiments the subjects to whom the endothelial cells are administered are ≥ 50 years old. In some embodiments the subjects to whom the endothelial cells are administered are ≥ 60 years old.

[0012] In some embodiments the subjects to whom the endothelial cells are administered have a disease or disorder that can be treated using a chemotherapeutic regimen that results in severe regimen-related toxicity (SRRT). In some embodiments the subjects to whom the endothelial cells are administered have a disease or disorder that can be treated using high dose therapy (HDT). In some embodiments the subjects to whom the endothelial cells are administered have a disease or disorder that can be treated using a combination of chemotherapy (e.g., high dose therapy (HDT)) and a hematopoietic stem cell transplant.