[0009] Pilot investigations into the *ex vivo* cytotoxicity of CPX-351 against fresh leukemia blasts from a variety of leukemia conditions yielded IC_{50} values as low as 50 nM cytarabine:10 nM daunorubicin under incubation conditions where drug release from the liposomes in the medium was non-detectable (Tyner, J., *et al.*, *Blood* (2010) 116:Abstract 2886). This confirmed that the direct anti-leukemic activity of intact CPX-351 liposomes documented previously with leukemia cell lines was relevant for blasts freshly obtained from patients. This also allows the dissection of how genotypic/phenotypic cellular features influence the sensitivity of blasts to CPX-351 independent of PK contributions.

[0010] Consequently, in contrast to the performance of nanoparticulate compositions generally, examination of *ex vivo* CPX-351 cytotoxicity against and/or CPX-351 uptake by fresh patient samples provides a way to predict anti-neoplastic activity of CPX-351 in individual patients and population types.

[0011] The conventional, standard-of-care treatment for leukemia has been the same for over 40 years and employs anthracycline plus cytarabine sequentially in their free forms as "7 + 3" therapy. Though this treatment is "standard," there are side effects and/or poor prognosis in some patients. CPX-351 may offer a positive alternative in such patients. Thus, there is a need to stratify patients with blood cancers such that they can receive CPX-351 as an appropriate therapy. As CPX-351 and/or conventional treatment regimens may not be effective for each and every individual, there is a need to identify diagnostic tests, agents and/or markers that can facilitate selection of an appropriate treatment regimen for a subject with bloodborne cancers.

Summary

[0011a] In one aspect, the present disclosure refers to the use of a combination of a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio, and an inhibitor of FLT-3 in the manufacture of a medicament for treating a hematologic cancer in a hematologic cancer-bearing subject, wherein an effective amount of said combination of the liposome formulation and an inhibitor of FLT-3 is to be administered to the subject.

[0011b] In one aspect, the present disclosure refers to the use of a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio in the manufacture of a medicament for treating a hematologic cancer in a subject, wherein said use includes: (a) determining the presence or absence of a mutation in the Fms-like tyrosine receptor kinase 3 (FLT-3) gene in said subject and an effective amount of the liposome formulation is to be administered to a subject who exhibits a mutation in said FLT-3 gene; and/or (b) determining the presence or absence of a mutation in the nucleophosmin 1 (NPM-1) gene in said subject and an effective amount of the liposome formulation is to be administered to a subject who exhibits a mutation in said NPM-1 gene; and/or (c) determining the presence or absence of a mutation in the CCAAT enhancer binding protein alpha (CEBPα) gene in said subject and an effective amount of the liposome formulation is to be administered to a subject who exhibits a mutation in said CEBPα gene; and/or (d) determining the genotype of said subject as favorable risk,

intermediate-I, intermediate-II or adverse risk and a therapeutically effective amount of the liposome formulation is to be administered to a subject whose genotype is adverse risk or intermediate-II.

[0011c] In one aspect, the present disclosure refers to an *in vitro* method to determine the susceptibility of a hematologic cancer-bearing human subject to treatment with a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio, which method comprises assaying a biological sample of said subject to determine: a) the presence or absence of a mutation in the Fms-like tyrosine receptor kinase 3 (FLT-3) gene in said subject; and/or b) the presence or absence of a mutation in the nucleophosmin 1 (NPM-1) gene in said subject; and/or c) the presence or absence of a mutation in the CCAAT enhancer binding protein alpha (CEBPα) gene in said subject; and/or d) the genotype of said subject as favorable risk, intermediate-I, intermediate-II or adverse risk.

[0011d] In one aspect, the present disclosure refers to the use of a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio in the manufacture of a medicament for treating a hematologic cancer in a hematologic cancer-bearing subject, wherein the liposome formulation is to be administered in combination with an inhibitor of FLT-3.

[0011e] In one aspect, the present disclosure refers to use of an inhibitor of FLT-3 in the manufacture of a medicament for treating a hematologic cancer in a hematologic cancer-bearing subject, wherein the inhibitor of FLT-3 is to be administered in combination with a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio.

Disclosure of the Invention

[0012] The invention, in one aspect, is based on the *ex vivo* assessment of CPX-351 cytotoxicity and/or uptake against a wide range of blast types freshly harvested from hematologic malignancy patients, including cells from major hematologic cancer groups such as AML and CLL as well as different disease sub-types. The results are correlated with patient outcomes following *in vivo* treatments.

[0013] The hematologic cancer includes acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myeloproliferative neoplasms (MPNs) and lymphomas.

[0014] Thus, in this aspect, the invention is directed to a method to predict the probability that administering CPX-351 to a human subject will be effective in treating a hematologic cancer in and subject which method comprises

Claims

1. Use of a combination of a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio, and an inhibitor of FLT-3 in the manufacture of a medicament for treating a hematologic cancer in a hematologic cancer-bearing subject,

wherein an effective amount of said combination of the liposome formulation and an inhibitor of FLT-3 is to be administered to the subject.

2. The use of claim 1, wherein said subject has a mutation in the Fms-like tyrosine receptor kinase 3 (FLT-3) gene.

3. The use of claim 2, wherein the mutation is an activating mutation in the FLT-3 gene.

4. The use of claim 1, wherein the liposome formulation and FLT-3 inhibitor are to be administered simultaneously or wherein the liposome formulation is to be administered prior to treatment with FLT-3 inhibitor or wherein the liposome formulation and FLT-3 inhibitor are to be administered in the same composition.

5. The use of claim 1, wherein the hematologic cancer is selected from the group consisting of acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myeloproliferative neoplasms (MPNs) and lymphomas.

6. The use of any of claims 1-5, wherein the FLT-3 inhibitor is quizartinib, midostaurin, tandutinib, sorafenib, sunitinib, lestaurtinib, crenolanib, gilteritinib, AST-487, dovitinib or linifanib.

7. Use of a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio in the manufacture of a medicament for treating a hematologic cancer in a subject, wherein said use includes:

(a) determining the presence or absence of a mutation in the Fms-like tyrosine receptor kinase 3 (FLT-3) gene in said subject and an effective amount of the liposome formulation is to be administered to a subject who exhibits a mutation in said FLT-3 gene; and/or

(b) determining the presence or absence of a mutation in the nucleophosmin 1 (NPM-1) gene in said subject and an effective amount of the liposome formulation is to be administered to a subject who exhibits a mutation in said NPM-1 gene; and/or

(c) determining the presence or absence of a mutation in the CCAAT enhancer binding protein alpha (CEBPα) gene in said subject and an effective amount of the liposome formulation is to be administered to a subject who exhibits a mutation in said CEBPα gene; and/or

(d) determining the genotype of said subject as favorable risk, intermediate-I, intermediate-II or adverse risk and a therapeutically effective amount of the liposome formulation is to be administered to a subject whose genotype is adverse risk or intermediate-II.

8. An *in vitro* method to determine the susceptibility of a hematologic cancer-bearing human subject to treatment with a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio, which method comprises assaying a biological sample of said subject to determine:

a) the presence or absence of a mutation in the Fms-like tyrosine receptor kinase 3 (FLT-3) gene in said subject; and/or

b) the presence or absence of a mutation in the nucleophosmin 1 (NPM-1) gene in said subject; and/or

c) the presence or absence of a mutation in the CCAAT enhancer binding protein alpha (CEBPα) gene in said subject; and/or

d) the genotype of said subject as favorable risk, intermediate-I, intermediate-II or adverse risk.

9. The method of claim 8, wherein the hematologic cancer is selected from the group consisting of acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myeloproliferative neoplasms (MPNs) and lymphomas.

10. The method of claim 8, wherein the mutation of (a) is an FLT-3 activating mutation.

11. The method of claim 10, wherein the mutation is an FLT-3-ITD or FLT-3-TKD mutation.

12. The method of any of claims 8-11 wherein the biological sample comprises blood, serum, plasma, saliva or blast cells.

13. Use of a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio in the manufacture of a medicament for treating a hematologic cancer in a hematologic cancer-bearing subject, wherein the liposome formulation is to be administered in combination with an inhibitor of FLT-3.

14. Use of an inhibitor of FLT-3 in the manufacture of a medicament for treating a hematologic cancer in a hematologic cancer-bearing subject, wherein the inhibitor of FLT-3 is to be administered in combination with a liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio.

15. The use of claim 13 or 14, wherein said subject has a mutation in the Fms-like tyrosine receptor kinase 3 (FLT-3) gene.

16. The use of claim 15, wherein the mutation is an activating mutation in the FLT-3 gene.

17. The use of claim 13 or 14, wherein the liposome formulation and FLT-3 inhibitor are to be administered simultaneously or wherein the liposome formulation is to be administered prior to treatment with FLT-3 inhibitor or wherein the liposome formulation and FLT-3 inhibitor are to be administered in the same composition.

18. The use of claim 13 or 14, wherein the hematologic cancer is selected from the group consisting of acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myeloproliferative neoplasms (MPNs) and lymphomas.

19. The use of any one of claims 13-18, wherein the FLT-3 inhibitor is quizartinib, midostaurin, tandutinib, sorafenib, sunitinib, lestaurtinib, crenolanib, gilteritinib, AST-487, dovitinib or linifanib.