THERAPEUTIC, DIAGNOSTIC AND PROGNOSTIC METHODS FOR CANCER OF THE BLADDER

FIELD OF THE INVENTION

The present invention is directed to methods for treating, diagnosing, and providing prognoses for cancer, e.g., bladder cancer.

BACKGROUND

Cancer remains one of the most deadly threats to human health. In the United States, cancer affects nearly 1.3 million new patients each year, and is the second leading cause of death after heart disease, accounting for approximately 1 in 4 deaths. Solid tumors are responsible for most of those deaths. Malignant tumors metastasize and grow rapidly in an uncontrolled manner, making timely detection and treatment extremely difficult.

Bladder cancer is the fifth-most common malignancy worldwide, with close to 400,000 newly diagnosed cases and approximately 150,000 associated deaths reported per year. Approximately 75-80% of bladder cancer patients present with non-muscle-invasive bladder cancer (NMIBC) at the time of initial diagnosis. Although confined to the lamina propria and typically not life-threatening, approximately 50-80% of NMIBCs recur, often requiring costly clinical intervention. NMIBCs can progress in about 20-30% of instances to the more serious muscle-invasive bladder cancer (MIBC). MIBCs (T2 and T3) constitute only ~10-15% of new cases, but they confer a higher risk for developing metastatic bladder cancer (pT4). Metastatic bladder cancer is associated with a dismal 5-year survival likelihood and represents a major unmet medical need with few effective therapies to date.

Therefore, there remains a need for effective means for treating, diagnosing, and providing prognoses for cancer, for example, bladder cancer.

SUMMARY

The present disclosure is directed to methods for treating, diagnosing, and providing prognoses for cancer, e.g., bladder cancer.

Disclosed is a method of treating a patient suffering from a bladder cancer, the method comprising administering to the patient a therapeutically effective amount of an anti-cancer therapy, wherein the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample obtained from the patient has been determined to be increased relative to a reference level of the at least one gene. In one aspect, there is provided a use of an anti-cancer therapy in the manufacture of a medicament for treating a patient suffering from a non-muscle invasive bladder cancer (NMIBC), wherein the expression level of at least two of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient has been determined to be increased relative to a reference level of the at least two genes.

Disclosed is a method for diagnosing a bladder cancer in a patient, the method comprising the steps of: (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and (b) comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient having a bladder cancer. In some embodiments, the method further comprises (c) informing the patient that they have a bladder cancer. In some embodiments, the method further comprises (d) selecting an anti-cancer therapy for treatment of said patient when an increase in the level

of expression of the at least one gene in the patient sample relative to the reference level is detected. In some embodiments, the method further comprises (e) administering a therapeutically effective amount of an anti-cancer therapy to the patient.

In another aspect, there is provided a method for the prognosis of a patient suffering from an NMIBC, the method comprising: (a) determining the expression level of at least two of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; (b) comparing the expression level of the at least two genes to a reference level of the at least two genes; and (c) determining a prognosis for the patient, wherein a poor prognosis is indicated by an expression level of the at least two genes in the patient sample that is increased relative to the reference level. In some embodiments, the prognosis is a prognosis of survival. In some embodiments, the method is carried out prior to administering an anti-cancer therapy to the patient. In some embodiments, the method further comprises (d) identifying the patient as likely to benefit from administration of an anti-cancer therapy when the patient is determined to have a poor prognosis of survival. In some embodiments, the method further comprises (e) administering a therapeutically effective amount of an anti-cancer therapy to the patient, if the patient is determined to have a poor prognosis of survival. In some embodiments, the survival is disease-free survival or overall survival.

Disclosed is a method of determining whether a patient having a bladder cancer is likely to respond to treatment with an anti-cancer therapy, the method comprising: (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and (b) comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment comprising an anti-cancer therapy. In some embodiments, the method further comprises (c) administering a therapeutically effective amount of an anti-cancer therapy to the patient.

Disclosed is a method of optimizing therapeutic efficacy of an anti-cancer therapy for a patient having a bladder cancer, the method comprising: (a) determining the expression level of at least one of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient; and (b) comparing the expression level of the at least one gene to a reference level of the at least one gene, wherein an increase in the expression level of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment comprising an anti-cancer therapy. In some embodiments, the method further comprises (c) administering a therapeutically effective amount of an anti-cancer therapy to the patient.

Disclosed is a method of treating a patient suffering from a bladder cancer, the method comprising administering to the patient a therapeutically effective amount of an anti-cancer therapy other than Bacillus Calmette-Guérin (BCG) vaccine, wherein the expression level of *TP53* in a sample obtained from the patient has been determined to be increased relative to a reference level of *TP53*. Disclosed is use of an anti-cancer therapy other than Bacillus Calmette-Guérin (BCG) vaccine in the manufacture of a medicament for treating a patient suffering from a bladder cancer, wherein the expression level of *TP53* in a sample that has been obtained from the patient has been determined to be increased relative to a reference level of *TP53*.

In some embodiments of any one of the above aspects, the anti-cancer therapy comprises an FGFR3 antagonist, a TP53 antagonist, and/or an EGFR antagonist. In some embodiments, the anti-cancer therapy comprises an FGFR3 antagonist and an EGFR antagonist. In some embodiments, the

CLAIMS

1. Use of an anti-cancer therapy in the manufacture of a medicament for treating a patient suffering from a non-muscle invasive bladder cancer (NMIBC), wherein the expression level of at least two of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient has been determined to be increased relative to a reference level of the at least two genes.

2. The use of claim 1, wherein the anti-cancer therapy comprises an FGFR3 antagonist, a TP53 antagonist, and/or an EGFR antagonist.

3. The use of claim 2, wherein the anti-cancer therapy comprises an FGFR3 antagonist and an EGFR antagonist.

4. The use of claim 2 or 3, wherein the FGFR3 antagonist, EGFR antagonist, or TP53 antagonist is an antibody or a functional fragment thereof.

5. The use of claim 4, wherein the FGFR3 antagonist is an anti-FGFR3 antibody, or a functional fragment thereof.

6. The use of claim 4, wherein the EGFR antagonist is an anti-EGFR antibody, or a functional fragment thereof.

7. The use of claim 4, wherein the TP53 antagonist is an anti-TP53 antibody, or a functional fragment thereof.

8. The use of claim 2 or 3, wherein the FGFR3 antagonist, TP53 antagonist, or EGFR antagonist is a small molecule antagonist.

9. The use of claim 8, wherein the FGFR3 antagonist or EGFR antagonist is a tyrosine kinase inhibitor.

10. The use of claim 9, wherein the EGFR antagonist is erlotinib (TARCEVA™).

11. The use of any one of claims 1-10, wherein the anti-cancer therapy further comprises (i) an agent selected from the group consisting of an anti-neoplastic agent, a chemotherapeutic agent, a growth-inhibitory agent, and a cytotoxic agent, (ii) radiotherapy, or (iii) a combination thereof.

12. The use of any one of claims 1-11, wherein the expression level of the at least two genes in the sample that has been obtained from the patient has been determined by measuring mRNA.

13. The use of claim 12, wherein the expression level of the at least two genes in the sample that has been obtained from the patient has been determined by a polymerase chain reaction (PCR) assay.

14. The use of claim 13, wherein the PCR assay is a quantitative PCR assay.

15. The use any one of claims 1-11, wherein the expression level of the at least two genes in the sample that has been obtained from the patient has been determined by measuring protein.

16. The use of claim 15, wherein the expression level of the at least two genes in the sample that has been obtained from the patient has been determined by an immunohistochemical (IHC) method.

17. The use of any one of claims 1-16, wherein the sample that has been obtained from the patient is a tumor sample.

18. The use of claim 17, wherein the tumor sample is a formalin-fixed paraffin-embedded (FFPE) tumor sample.

19. The use of any one of claims 1-18, wherein the expression level of all three of the genes has been determined.

20. The use of any one of claims 1-19, wherein the expression level of FGFR3 has been determined to be increased at least 2-fold relative to a reference level.

21. The use of claim 20, wherein the expression level of FGFR3 has been determined to be increased at least 4-fold relative to a reference level.

22. The use of any one of claims 1-21, wherein the expression level of EGFR has been determined to be increased at least 4-fold relative to a reference level.

23. The use of claim 22, wherein the expression level of EGFR has been determined to be increased at least 8-fold relative to a reference level.

24. The use of any one of claims 1-23, wherein the expression level of at least one additional gene selected from the group consisting of: DUSB3, FRS2, TSC1, ERBB3, CDKN1A, CCND1, TP63, MMP2, ZEB2, PIK3CB, PIK3R1, MDM2, SNAI2, AXL, ZEB1, BCL2B, TSC2, RB1, FGFR32, PIK3IP1, MTOR, PIK3CA, PTEN, AKT1, BCL2A, FRS3, ERBB2, FGFR31, FGF1, SNAI1, FGFR34, FGF9, and FGF2, in a sample that has been obtained from the patient has been determined to be changed relative to a reference level of the at least one additional gene.

25. The use of any one of claims 1-24, wherein the NMIBC is a recurrent NMIBC.

26. A method for the prognosis of a patient suffering from an NMIBC, the method comprising:

(a) determining the expression level of at least two of the following genes: *FGFR3*, *TP53*, and *EGFR*, in a sample that has been obtained from the patient;

(b) comparing the expression level of the at least two genes to a reference level of the at least two genes; and

(c) determining a prognosis for the patient, wherein a poor prognosis is indicated by an expression level of the at least two genes in the patient sample that is increased relative to the reference level.

27. The method of claim 26, wherein the prognosis is a prognosis of survival.

28. The method of claim 26 or 27, wherein the method is carried out prior to administration of an anti-cancer therapy comprising an FGFR3 antagonist and/or an EGFR antagonist to the patient.

29. The method any one of claims 26-28, further comprising (d) identifying the patient as likely to benefit from administration of an anti-cancer therapy when the patient is determined to have a poor prognosis of survival, wherein the anti-cancer therapy comprises an FGFR3 antagonist and/or an EGFR antagonist.

30. The method of any one of claims 26-29, wherein if the patient is determined to have a poor prognosis of survival, the patient is to be administered an anti-cancer therapy comprising an FGFR3 antagonist and/or an EGFR antagonist.

31. The method of any one of claims 26-30, wherein the survival is disease-free survival or overall survival.

32. The method of any one of claims 28-31, wherein the anti-cancer therapy comprises an FGFR3 antagonist, a TP53 antagonist, and/or an EGFR antagonist.

33. The method of claim 32, wherein the anti-cancer therapy comprises an FGFR3 antagonist and an EGFR antagonist.

34. The method of claim 32 or 33, wherein the FGFR3 antagonist, EGFR antagonist, or TP53 antagonist is an antibody or a functional fragment thereof.

35. The method of claim 34, wherein the FGFR3 antagonist is an anti-FGFR3 antibody, or a functional fragment thereof.

36. The method of claim 34, wherein the EGFR antagonist is an anti-EGFR antibody, or a functional fragment thereof.

37. The method of claim 34, wherein the TP53 antagonist is an anti-TP53 antibody, or a functional fragment thereof.

38. The method of claim 32 or 33, wherein the FGFR3 antagonist, TP53 antagonist, or EGFR antagonist is a small molecule antagonist.

39. The method of claim 38, wherein the FGFR3 antagonist or EGFR antagonist is a tyrosine kinase inhibitor.

40. The method of claim 39, wherein the EGFR antagonist is erlotinib (TARCEVA™).

41. The method of any one of claims 32-40, wherein the anti-cancer therapy further comprises (i) an agent selected from the group consisting of an anti-neoplastic agent, a chemotherapeutic agent, a growth-inhibitory agent, and a cytotoxic agent, (ii) radiotherapy, or (iii) a combination thereof.

42. The method of any one of claims 26-41, wherein the expression level of the at least two genes in the sample that has been obtained from the patient is determined by measuring mRNA.

43. The method of claim 42, wherein the expression level of the at least two genes in the sample that has been obtained from the patient is determined by a PCR assay.

44. The method of claim 43, wherein the PCR assay is a quantitative PCR assay.

45. The method any one of claims 26-41, wherein the expression level of the at least two genes in the sample that has been obtained from the patient is determined by measuring protein.

46. The method of claim 45, wherein the expression level of the at least two genes in the sample that has been obtained from the patient is determined by an IHC method.

47. The method of any one of claims 26-46, wherein the sample that has been obtained from the patient is a tumor sample.

48. The method of claim 47, wherein the tumor sample is an FFPE tumor sample.

49. The method of any one of claims 26-48, further comprising determining the expression level of all three of the genes.

50. The method of any one of claims 26-49, wherein the expression level of *FGFR3* has been determined to be increased at least 2-fold relative to a reference level.

51. The method of claim 50, wherein the expression level of *FGFR3* has been determined to be increased at least 4-fold relative to a reference level.

52. The method of any one of claims 26-51, wherein the expression level of *EGFR* has been determined to be increased at least 4-fold relative to a reference level.

53. The method of claim 52, wherein the expression level of *EGFR* has been determined to be increased at least 8-fold relative to a reference level.

54. The method of any one of claims 26-53, further comprising determining the expression level of at least one additional gene selected from the group consisting of: *DUSB3*, *FRS2*, *TSC1*, *ERBB3*, *CDKN1A*, *CCND1*, *TP63*, *MMP2*, *ZEB2*, *PIK3CB*, *PIK3R1*, *MDM2*, *SNAI2*, *AXL*, *ZEB1*, *BCL2B*, *TSC2*, *RB1*, *FGFR32*, *PIK3IP1*, *MTOR*, *PIK3CA*, *PTEN*, *AKT1*, *BCL2A*, *FRS3*, *ERBB2*, *FGFR31*, *FGF1*, *SNAI1*, *FGFR34*, *FGF9*, and *FGF2*, in a sample that has been obtained from the patient, wherein the expression level of the at least one additional gene is changed relative to a reference level of the at least one additional gene.

55. The method of any one of claims 26-54, wherein the NMIBC is a recurrent NMIBC.