

METHOD FOR PREDICTING CLINICAL TOXICITY AND OUTCOME

FIELD OF THE INVENTION

[0001] The present invention relates to cancer therapy. In particular, methods for predicting the sensitivity of a patient with cancer to receptor tyrosine kinase inhibitor therapy.

BACKGROUND OF THE INVENTION

[0002] Cancer therapy includes surgery, chemotherapy, targeted therapy, immunotherapy and radiation therapy. Targeted therapy is directed against cancer-specific molecules and signaling pathways within the tumor. Accordingly, drugs used in targeted therapy include drugs that inhibit angiogenesis and drugs that induce apoptosis. An example of a class of drugs used in targeted therapy is tyrosine kinase inhibitors (TKIs).

[0003] However, tumor response and individual survival vary among patients and therefore the therapeutic benefits of TKIs are not universal but individualized. In addition, despite its effectiveness in prolonging survival, life quality-compromising and potentially lethal toxicities are common. These include diarrhea, hand-foot syndrome, mucositis, hypertension, leucopenia, neutropenia and thrombocytopenia. Toxicities lead to dose interruption, dose reduction and prevent patients from benefitting fully from the drug. Toxicity presentation and severity, like survival, are also not universal but vary greatly among patients.

[0004] Therefore, there is a need to provide a method for determining the sensitivity of a patient with cancer to TKI therapy and a need to provide a method of identifying the most appropriate TKI therapy regimen for a patient. There is also a need for a kit to be used in such methods.

identity of at least one SNP genotype selected from the group consisting of rs1933437, rs1045642, rs1128503, rs2032582 and rs2231142 and any combination thereof, wherein said sensitivity is selected from one or more of neutropenia, diarrhea, tumor response, early toxicity-necessitated treatment termination, overall survival and progression-free survival.

[0020] In one embodiment, the cancer may be selected from the group consisting of renal cancer, neuroendocrine cancer, breast cancer, prostate cancer, cervical cancer, ovarian cancer, gastric cancer, colorectal cancer, pancreatic cancer, liver cancer, brain cancer, lung cancer, hematological malignancies, melanoma and sarcomas.

[0021] In another embodiment, the renal cancer is metastatic renal cell carcinoma (mRCC). In some embodiments the patient may suffer from mRCC. Alternatively, the patient suffers from mRCC and undergoes receptor tyrosine kinase inhibitor treatment.

[0022] In some embodiments, the biological sample is obtained from the group consisting of frozen tissue, tissue biopsies, circulating cells, bodily fluids and cheek swab.

[0023] The biological sample may be non-neoplastic or neoplastic.

[0024] In one embodiment the bodily fluids may be selected from the group consisting of blood, saliva, ascites, effusions and urine.

[0025] The receptor tyrosine kinase inhibitor may be a multikinase inhibitor for receptor tyrosine kinase including but not limited to sunitinib, pazopanib, axitinib, sorafenib, regorafenib, tivantinib or combinations thereof.

[0026] In some embodiments the patient is a mammal or a human. The human may be an ethnic Asian, or an ethnic Caucasian, or an ethnic African.

[0027] In another embodiment, for determining the risk of diarrhea during receptor tyrosine kinase inhibitor treatment, the method may further comprise: (a) screening for at least one SNP genotype selected from the group consisting of rs1128503 and rs1045642, and (b) determining the risk of diarrhea based on the screening result

CLAIMS

1. A method for determining the risk of early toxicity-necessitated treatment termination in a patient with cancer during receptor tyrosine kinase inhibitor therapy, comprising:
 - a) isolating a nucleic acid sample from a biological sample obtained from the said patient;
 - b) screening for the SNP genotype of rs1128503, and
 - c) determining the risk of early toxicity-necessitated treatment termination based on the genotyping result obtained in step (b).
2. The method according to claim 1, wherein the cancer is renal cancer, neuroendocrine cancer, breast cancer, prostate cancer, cervical cancer, ovarian cancer, gastric cancer, colorectal cancer, pancreatic cancer, liver cancer, brain cancer, lung cancer, hematological malignancies, melanoma and sarcomas.
3. The method according to claim 2, wherein the renal cancer is metastatic renal cell carcinoma (mRCC).
4. The method according to claim 2, wherein the patient suffers from mRCC or wherein the patient suffers from mRCC and undergoes receptor tyrosine kinase inhibitor treatment.
5. The method according to claim 1, wherein the biological sample is obtained from the group consisting of frozen tissue, tissue biopsies, circulating cells, bodily fluids and cheek swab.
6. The method according to claim 5, wherein the biological sample is non-neoplastic.
7. The method according to claim 5, wherein the biological sample is neoplastic.
8. The method according to claim 5, wherein the bodily fluids are selected from the group consisting of blood, saliva, ascites, effusions and urine.

9. The method according to claim 1, wherein the receptor tyrosine kinase inhibitor is a multikinase inhibitor for receptor tyrosine kinase including but not limited to sunitinib, pazopanib, axitinib, sorafenib, regorafenib, tivantinib or combinations thereof.
10. The method according to claim 1, wherein the patient is a mammal or a human.
11. The method according claim 10, wherein the human is an ethnic Asian, or an ethnic Caucasian, or an ethnic African.
12. The method according to claim 1, wherein in step (c), the risk of early toxicity-necessitated treatment termination during receptor tyrosine kinase inhibitor treatment is higher for a CC or CT genotype than a TT genotype.
13. Use of the method according to claim 1 to identify the most appropriate receptor tyrosine kinase inhibitor therapy regimen for a patient with renal cancer.