

multiforme, Stevens Johnson Syndrome, toxic epidermal necrosis or drug eruption with eosinophilia and systemic symptoms.

The present invention provides methods for reducing the incidence or treatment of cutaneous adverse drug reactions caused by epidermal growth factor receptor inhibitors.

The present invention also provides a method for assessing the risk of developing cutaneous adverse drug reaction caused by epidermal growth factor receptor inhibitors and treating said cutaneous adverse drug reaction, comprising the following steps: (a) detecting the presence of at least one allele selected from the following alleles in a sample of a subject: HLA-B*5101 or HLA-B*5102, (b) the presence of at least one of the following alleles in the sample: HLA-B*5101 or HLA-B*5102, indicates the subject has an increased risk of developing cutaneous adverse drug reactions induced by epidermal growth factor receptor inhibitor; and (c) administration of a drug to treat the cutaneous adverse drug reaction.

In a specific embodiment, the method of treating the cutaneous adverse drug reactions is administering a drug including (but not limited to) liquid, steroid, immunoglobulin, cyclosporine, anti-TNF- α agent or plasma exchange.

The present invention also relates to a method for assessing the risk of developing cutaneous adverse drug reactions induced by epidermal growth factor receptor inhibitors and reducing the incidence of said cutaneous adverse drug reactions, comprising the following steps: (a) detecting the presence of at least one allele selected from the following alleles in a sample of a patient: HLA-B*5101 or HLA-B*5102, (b) the presence of at least one of the following alleles in the sample: HLA-B*5101 or HLA-B*5102, indicates that the patient has an increased risk of developing a cutaneous adverse drug reaction; and (c) the patient is not given the epidermal growth factor receptor inhibitors.

The present invention further provides a method for treating a disease that can be treated by epidermal growth factor receptor inhibitor, comprising the following steps: (a) detecting the presence of at least one allele selected from the following alleles in a sample of a patient : HLA-B*5101 or HLA-B*5102, (b) the presence of at least one of

the following alleles in the sample: HLA-B*5101 or HLA-B*5102, indicates that the patient has an increased risk of developing a cutaneous adverse drug reaction; and (c) avoid using the epidermal growth factor receptor inhibitor to treat this disease to reduce the risk of cutaneous adverse drug reactions.

The terms "invention" and "present invention" as used in the present invention are intended to broadly refer to the application the claims. The statements containing these terms are to be understood as not limiting the scope of the application or the scope of the claims. The working examples of the invention are defined by the application and not by the content of the present invention. This summary is a high-level overview of various aspects of the invention and is a description of some concepts that are further described in the section below. This Summary is not intended to identify key or essential features of the claimed application, and is not intended to be used solely to determine the scope of the claimed application. The objectives of the application should be understood by reference to any or all of the figures and the appropriate parts of each claim.

Working Example

In the following working example, 11 patients with epidermal growth factor receptor inhibitor induced CADR_s (including MPE, EM, SJS/TEN, and DRESS), were enrolled for HLA typing by nucleic acid sequencing-based typing and the HLA typing results were compared with that of 2038 normal healthy controls. The results show that HLA-B*5101 allele, HLA-B*5102 allele or a combination of HLA-B*5101 allele and HLA-B*5102 allele were associated with CADR_s induced by epidermal growth factor receptor inhibitors (see Table 1)-.

With respect to HLA-B*5101 allele, 5 out of 11 patients (45.45%) with epidermal growth factor receptor inhibitor induced CADR_s carried this genotype, whereas only 170 out of 2038 (8.34%) normal healthy subjects in the control group carried this genotype. This shows that HLA-B*5101 is associated with epidermal growth factor receptor inhibitor induced CADR_s (CADR_s vs. healthy control group: $P=1.30 \times 10^{-3}$, odds ratio or OR = 9.16 (2.77-30.32), sensitivity: 45.45%, specificity: 91.66%).

With respect to the HLA-B*5102 allele, 4 out of 11 (8.3436.36%) with epidermal growth factor receptor inhibitor induced CADR_s carried this genotype, whereas only 64 out of 2038 (3.14%) normal healthy people in the control group had this genotype. This shows that HLA-B*5102 is associated with epidermal growth factor receptor inhibitor induced CADR_s (CADR_s vs. healthy control group: $P=3.07 \times 10^{-4}$, odds ratio or OR = 17.63 (5.03-61.73), sensitivity: 36.36%, specificity: 96.86%).

Further analysis of the HLA-B*5101 allele and HLA-B*5102 allele combination shows such combination significantly increases the correlation with and sensitivity in predicting the risk of developing epidermal growth factor receptor inhibitor induced CADR_s (CADR_s vs. healthy control group: $P=1.80 \times 10^{-7}$, odds ratio or OR=34.69 (7.45-161.54), sensitivity: 81.81%, specificity: 88.52%).

Based on the above results, the presence of HLA-B*~~4501~~5101 allele and/or HLA-B*5102 allele can be used to assess the risk of developing CADR_s caused by epidermal growth factor receptor inhibitors.

Table 1. Analysis and comparison of HLA-B*5101 and/or HLA-B*5102 genotypes of 11 patients with CADR_s caused by epidermal growth factor receptor inhibitors and 2038 normal healthy controls.

HLA Allele	CADR _s N (%)	Healthy Control N (%)	OR (95% CI)	P Value	Sensitivity (%)	Specificity (%)
HLA-B*51:01	5/11 (45.45%)	170/2038 (8.34%)	9.16 (2.77-30.32)	1.30×10^{-3}	45.45%	91.66%
HLA-B*51:02	4/11 (36.36%)	64/2038 (3.14%)	17.63 (5.03-61.73)	3.07×10^{-4}	36.36%	96.86%
HLA-B*51:01 / B*5102	9/11 (81.81%)	234/2038 (11.48%)	34.69 (7.45-	1.80×10^{-7}	81.81%	88.52%

Claims

1. A method for assessing the risk of developing a cutaneous adverse drug reaction in a patient, comprising the step of detecting the presence of the allele selected from the following:

(a) HLA-B*5101; or

(b) HLA-B*5102; or

(c) HLA-B*5101 and HLA-B*5102,

wherein the presence of at least one HLA allele is detected in the DNA, RNA, proteins, cells or serum sample prepared from the peripheral blood of the patient indicates the patient has a higher risk of developing the cutaneous adverse drug reaction induced by a epidermal growth factor receptor inhibitor compared to a patient without the corresponding HLA allele.

2. The method of claim 1, wherein the cutaneous adverse drug reaction comprises at least one adverse reaction selected from the following: maculopapular eruption (MPE), erythema multiforme (EM), Stevens Johnson Syndrome, (SJS), toxic epidermal necrolysis (TEN), or drug rash with eosinophilia and systemic symptoms (DRESS).

~~3. The method according to claim 1, wherein the HLA-B*5101 allele or HLA-B*5102 allele is detected in the DNA, RNA, proteins, cells or serum sample prepared from the peripheral blood of the patient.~~

~~43. The method of claim 1, wherein the epidermal growth factor receptor inhibitor is an anti-epidermal growth factor receptor monoclonal antibody (mAb) or an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI).~~

4. The method of claim 1, wherein said HLA allele is HLA-B*5101 allele.

5. The method of claim 1, wherein said HLA allele is HLA-B*5102 allele.

6. The method of claim 1, wherein said HLA allele is the combination of HLA-B*5101 allele and HLA-B*5102 allele.

7. The method of claim 3, wherein said anti-epidermal growth factor receptor monoclonal antibody is Cetuximab, Zalutumumab, Nimotuzumab, Matuzumab or Panitumumab.

8. The method of claim 3, wherein said EGFR-TKI is Erlotinib, Gefitinib, Lapatinib, Afatinib, Brigatinib.

~~5. A detection kit for assessing the risk of cutaneous adverse drug reaction caused by an epidermal growth factor receptor inhibitor in a patient, the kit comprises a reagent for detecting the presence of at least one of the following allele in a test sample of a patient:~~

~~(a) HLA-B*5101; or~~

~~(b) HLA-B*5102.~~

~~6. The detection kit of claim 5, wherein said kit comprises an oligonucleotide that specifically hybridizes to the nucleic acids of the HLA allele.~~

~~7. The use of a reagent for detecting HLA-B*5101 allele or HLA-B*5102 allele in the manufacture of a detection kit to evaluate the risk of developing cutaneous adverse drug reaction induced by an epidermal growth factor receptor inhibitor.~~

~~8. The use according to claim 7, wherein the cutaneous adverse drug reaction comprises at least one adverse reaction selected from the following: maculopapular eruption (MPE), erythema multiforme (EM), Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS).~~

~~9. The use according to claim 7, wherein said kit comprises an oligonucleotide that specifically hybridizes to the nucleic acids of the HLA allele.~~

~~10. The use according to claim 7, wherein the epidermal growth factor receptor inhibitor is an epidermal growth factor receptor monoclonal antibody or an epidermal growth factor receptor tyrosine kinase inhibitor.~~