Review Article
Published: 17 Apr, 2018

Journal of Clinical Pathology Forecast

The Rising Applications of Pharmacogenomics based Personalized Medication Fingerprints in Malignancies

*Chen JQ[1], Wang F[1], Chen X[1], Zhang Y[1] and Liu HX[2]**

[1]Pathology & Laboratory Medicine Division, Hebei Yanda Lu Daopei Hospital, Langfang, China

[2]Translational Medicine Research Center, Beijing Lu Daopei Institute of Hematology, Beijing, China

Abstract

Because of the majority of tumor therapeutic drugs with more adverse reaction, narrow treatment window, and significant individual differences, the correct and rational application of anti-tumor drugs will help to reduce mortality, relapse rate and incidence of adverse drug reactions of patients with malignancies. With the progress of Pharmacogenomics research, the genetic polymorphism of drugs in the human genome that influence drug treatment is increasingly being discovered. In recent years, individualized treatment under the guidance of genetic pharmacogenomics has been increasingly attention. Especially in the treatment of some severe diseases, it is often necessary to detect the genetic polymorphisms associated with multiple drug treatments. The promotion and application of the new generation of gene sequencing technology has greatly facilitated the simultaneous detection and analysis of polygenes and genomics. In this review, the concept of personalized medication fingerprints was proposed to emphasize in the diagnosis and treatment of severe disease to highlight the practical value of pre-empting multiple pharmacogenomic polymorphism sites with panel testing or based on omics analysis.

Keywords: Personalized medication fingerprints; Pharmacogenomics; Gene Polymorphism; Malignancies

OPEN ACCESS

*Correspondence:
Liu HX, Pathology & Laboratory Medicine Division, Hebei Yanda Lu Daopei Hospital, Translational Medicine Research Center, Beijing Lu Daopei Institute of Hematology,710B Huabin Bulding No. 8 of Yongan Dongli Road, Chaoyang Dsitrict, Beijing, China.
Tel: 13693165205
Fax: 10-80841219
E-mail: starliu@pku.edu.cn

Received Date: 07 Mar 2018
Accepted Date: 11 Apr 2018
Published Date: 17 Apr 2018

Citation: Chen JQ, Wang F, Chen X, Zhang Y, Liu HX. The Rising Applications of Pharmacogenomics based Personalized Medication Fingerprints in Malignancies. J Clin Pathol Forecast. 2018; 1(1): 1002.

ISSN 2690-4187

Copyright © 2018 Liu HX. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

With the completion of the Human Genome Project, the research and application of medicine have gradually entered the post-genomic era [1]. As one of the clinical applications of the post-genomic era, the pharmacogenomics aims to bring real-world "personalized medicine" to the right patient at the right time, using the right medication instead of "one size fits all "mode of administration [2]. The basis of its realization is based on relevant genotypes, therapeutic drug monitoring and other laboratory testing indicators to determine the patient's individual mode of administration, to reduce the poor efficacy and adverse reactions caused by empirical drug delivery.

In 1959, Vogel proposed the concept of Pharmacogenetics, and then some scholars proposed the concept of Pharmacogenomics. Some scholars think the pharmacogenomics should be defined as based on direct or indirect index to evaluate the individual due to genetic composition caused by the different reactions to drugs to guide the choice of drugs and dose adjustments, in order to realize the individualized treatment [3]. In most severe diseases, such as hematologic malignancies, it has the characteristics of many types of drugs, adverse drug reactions, narrow therapeutic windows and large individual differences. With the in-depth study of pharmacogenomics and the popularization of gene detection clinical application, there are more and more gene polymorphisms that are closely related to the common clinical treatment of drugs, and gradually become the routine examination of clinical medication. Full understanding the relevant pharmacogenomics will help guide more rational drug use and thus reduce the mortality, relapse rate and adverse effects of unreasonable drug use the incidence of reaction.

Genetic Pharmacogenomics of Chemotherapy Drugs Commonly Used in Cancer Treatment

Although the methods and therapeutic agents in the treatment of tumor development is rapid, including targeted drugs and immune therapy, new treatments are being developed, but the traditional chemotherapy drugs is still one of the main means of clinical cancer treatment. Because they do not have the target effect, so they are more susceptible to drug resistance and toxicity, which has become the biggest problem in the clinical practice of these drugs, often directly led to the

failure of treatment of patients, some serious side effects even lead the patient to die

Platinum

Platinum compounds are a class of drugs containing heavy metal complexes, which are widely used in the clinical application of antitumor drugs. They are used to treat a variety of solid tumors, including lung cancer, head and neck tumor, colorectal cancer, ovarian cancer, etc. [4]. Currently, the commonly used platinum compounds include cisplatin, carboplatin and oxaliplatin. The main mechanism of platinum-type drugs is to produce cross linking with DNA, to form the DNA adduction between the chain and the chain, thus causing irreversible damage to the DNA of tumor cells, and the proliferation of transplanted tumor cells. At present, it is known to predict the genes and mutations associated with the sensitivity of platinum class chemotherapy including ERCC1 rs11615, ERCC2rs13181, XRCC1rs25487 and GSTP1 rs1695. Therefore, the individualized treatment of platinum group can be adjusted according to the expression level and site mutation of the above genes [5,6]. Patients with ERCC1 mRNA or high protein expression, ERCC1 rs11615 allele T carriers, ERCC2 rs13181 allele G carriers, XRCC1 rs25487 allele G carriers and GSTP1 rs1695 allele A carriers are relatively insensitive to platinum-based chemotherapy and should be given priority in the selection of other chemotherapy regimens.

Methotrexate (MTX)

MTX is a commonly used chemotherapy drug in patients with acute lymphoblastic leukemia, but some patients when the conventional dose can be serious bone marrow suppression, liver damage and other adverse reactions. The gene polymorphisms of multiple transporters and enzymes have been reported to affect the metabolism of methotrexate[7]. The mutations in c.677C>T and c.1298A > C loci of human methylenetetrahydrofolate-folate reductase (MTHFR) are considered to be associated with the toxic side effects of MTX. MTHFR c.677C > T genotype significantly increased the risk of gastrointestinal toxicity and leukocyte and thrombocytopenia in patients treated by MTX [8]. *P- glycoproteins* expressed on tumor cells can pump MTX out cells, resulting in lower drug concentration and tumor cell resistance. Among them, ABCB1 c.2677G > T/A, c.1236C > T and c.3435C > T were studied more[9]. Ma et al. [10] studied 178 cases of acute leukemia, to explore the influence of ABCB1 gene polymorphism on high-dose methotrexate. Pongstaporn et al. [11] also supported ABCB1c.3435C > T and c.1236C > T polymorphism to predict the efficacy and toxicity of high-doses of methotrexate.

Tacrolimus (FK506)

Tacrolimus (FK506) is a calcineurin inhibitors, a commonly used drug to prevent graft versus host disease (GVHD) after hematopoietic stem cell transplantation. Itis mainly metabolized by CYP3A5, and the change of CYP3A5 enzyme activity was significantly correlated with the pharmacokinetics of FK506. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend that the initial dose of FK506 should be adjusted based on the CYP3A5 genotype, and the blood concentration should be monitored to avoid serious adverse reactions [12]. There are also reports that the risk of leukemia, colorectal cancer and other diseases of CYP3A5*3 genotypes carriers is significantly increased, possibly related to the reduction of metabolic capacity of environmental toxicants [13]. CYP3A4 gene polymorphism also significantly affected the PK and blood concentration of FK506. It is reported that the concentration of FK506 in CYP3A4*1/*1 carriers in southern Chinese population is higher than that of CYP3A4*1/*1G and CYP3A4*1G/*1G carriers [14].

Thiopurines

TPMT is one of the most important enzymes in the metabolism of thiopurines (such as azathioprine, mercaptopurine and thioguanine). TPMT activity is associated with gene diversity, and TPMT enzyme activity reduces genotype of leukemia patients with moderate or severe bone marrow suppression [15]. The most common is TPMT*3C in Chinese population, carrying rate of about 2% ~ 3%[16]. CPIC recommends TPMT genotype detection for patients using thiopurines to avoid serious adverse reactions. The initial dose of heterozygous poor metabolized patients should be adjusted to 30% ~ 70% of the conventional dose, and the patients with pure and poor metabolism should adjust the dose to 10% [15].

Genetic Pharmacogenomics of Tumor Targeted Therapy

Tumor molecular targeted drugs prevent the growth of cancer cells by targeting specific molecular targets that are necessary for cancer and tumor growth. Tumor molecular targeted therapy can effectively improve the life quality and effectiveness of patients because of its highly selective killing of tumor cells without killing or only rarely damaging normal cells [17]. The action targets of target drugs are the proteins related to membrane receptor signaling pathway, mainly including four types: Human epidermal growth factor receptor (EGFR) pathway, vascular endothelial growth factor (VEGF) pathway, Hepatocyte growth factor receptor (HGFR) pathway and Insulin Like Growth Factor Receptor (IGFR) pathway. Among them, EGFR pathway of research was the most mature, and the most targeted drugs for this signal transduction design [18].

Human epidermal growth factor receptor (EGFR)

The small molecule EGFR tyrosine kinase inhibitors (gefitinib, icotinib, afatinib, erlotinib, etc.) and monoclonal antibodies (cetuximab, panitumumab, etc.) are the main drugs for EGFR targeted therapy at present [19]. When the patients carried EGFR deletions of exon 19 (del E746-A750), exon 21 (L858R) and exon 18 (G719X) mutation, they can benefit from TKI, such as gefitinib, icotinib and erlotinib [20]. A few NSCLC patients (1%~3%) had T790M mutation in EGFR exon 20 before TKI therapy, but more than 50% of patients showed T790M mutation positive after TKI therapy, resulting in secondary drug resistance of TKI [21]. About 10% of EGFR wild-type NSCLC patients were effective for TKI.

The anti-EGFR monoclonal antibody can specifically bind to the EGF receptor on the cell surface through the antigen-antibody reaction, thereby inhibiting the tyrosine kinase (TK) binding to the EGF receptor, blocking the intracellular signal transduction pathway, and finally inhibiting the cancer cells proliferation, induce apoptosis of cancer cells. The most common mutation associated with EGFR monoclonal antibody resistance is the activation mutation of EGFR downstream signaling molecule KRAS/BRAF. Numerous studies have shown that the efficacy of cetuximab is closely related to the polymorphism of KRAS gene. In patients with mutations in codon 12 and / or codon 13 or any mutation in the other codon of exon 2 of KRAS, monoclonal antibodies against EGFR (such as cetuximab, panitumumab, etc.) were ineffective, it is recommended not to use such drugs [22,23,24].

Human epidermal growth factor receptor 2 (HER2)

HER2 targeted therapy drugs currently have two main types:

Monoclonal antibodies (trastuzumab, pertuzumab, T-DM1) as well as HER2 small molecule TKI (lapatinib, sunitinib) [25]. When the HER2 gene was overexpressed or amplified, the patients could benefit from anti-her2 targeted drug therapy using trastuzumab and lapatinib. When HER2 gene expression or amplification is negative, it is not recommended to use trastuzumab and TKI, such as lapatinib [26,27].

Other targeted agents

BRAF, one of the most important human proto-oncogene, is important subtypes of the Raf family in the MARK signal transduction pathways, through the serine threonine protein kinase in the filamentous protein kinase pathway. The most common BRAF mutation occurs at the nucleotide 1799 of exon 15, T >A (T1799A), leading to glutamic acid replace by valine (V600E) [28]. Currently, there are two broad categories of targeted drugs acting on BRAF: one is BRAF V600E inhibitors, such as Vemurafenib, a targeted agent for melanoma [29]. The other is a broad-spectrum inhibitors of RAF kinase, which also inhibit the RAF's subtypes and other kinases, including KIT, VEGFR, such as Sorafenib [30].

Imatinib targeted at v-abl, PDGFR and c-kit, mainly for chronic myelogenous leukemia (CML) acute phase, accelerated or alpha-interferon treatment after failure of chronic patients; and patients with malignant gastrointestinal stromal tumors (GIST) that cannot be resected or metastasized[31]. As well as eculizumab (human anti-C5 monoclonal antibody, Soliris) for the treatment of rare diseases such as paroxysmal nocturnal hemoglobin uria (PNH) and atypical hemolytic uremic syndrome (aHUS). By inhibiting the auto-immune complement reaction in the cascade, thereby inhibiting the autoimmune damage caused by the patient [32].

Personalized Medication Fingerprints

Since the diagnosis and treatment process of patients with severe disease need to use multiple drugs and long-term medication, genomics information may involve polymorphic sites provide multiple drug medication guides. It is also possible to frequently encounter situations where intervention is needed as soon as possible (such as fungal infection), which requires immediate or best immediate access to the relevant genetic polymorphisms of the drug. On the other hand, the genetic polymorphism of these drugs is mostly the source of the germ line, and the information remains unchanged for lifetime (excluding organ transplant patients), which can be measured and read over and over again. From the perspective of experimental technology, NGS provides technical and cost advantages when analyzing multiple gene mutation sites comprehensively. Especially in the omics analysis era of rapid cost reduction (WES, WGS), the most sites of pharmacogenomics can be used as part of this analysis [33,34].

Based on clinical needs and technological advances, we propose the concept of personalized medication fingerprints, which is used to represent multiple combinations of genetic polymorphisms associated with multiple drug treatments in the patient's genome. When the polymorphic locus of the analysis is much enough, the polymorphisms of each patient will be different and remain unchanged for a lifetime, with the properties similar to those of fingerprints. In order to save the overall testing cost and be used as a reference for the first time when new drugs are needed clinically. We recommend especially for drug use in complicated cases of severe patients, children and the elderly, should be draw the personalized medication fingerprints as soon as possible after the first visit based on a panel test or omics analysis. This will improve the clinical rapid and accurate response ability and reduce the overall detection cost, to achieve better medical economics effect.

The Prospect of Pharmacogenomics in the Personalized Treatment of Tumors

The treatment of tumors has made significant progress in the past few decades, which is partly due to the research and application of pharmacogenomics. Personalized treatment regimens and treatment model should be based on the in-depth study of the dynamics of drug metabolism and pharmacodynamics, combined with genetic testing to help us better improve the effect of treatment and avoid adverse reaction. Moreover, with the increasing improvement of genetic testing, the decreasing of detection cost, it has not only been aimed at the sick people, but also should be more available to the healthy group.

Based on the existing detection techniques and analytical methods, we obtained the combination of drug genetic polymorphisms for each individual draws our own personalized medication fingerprints of our own. According to each person's special combination, clinicians provide for safer and more effective Medication guidance can also help increase the effectiveness of the first dose of prescription and reduce medical costs and reduce the financial burden on patients. With the progress of pharmacogenomics research and the popularization of the application, it will provide more reference for clinical precision medicine.

The personalized medication fingerprints are based on multi-gene panel detection or omics analysis and summarizes the genetic polymorphisms associated with drug therapy to provide each individual with a unique analysis report on pharmacogenomics, which will benefit us for life.

References

1. TA Manolio, RL Chisholm, B Ozenberger, DM Roden, MS Williams, R Wilson, et al. Ginsburg. Implementing genomic medicine in the clinic: the future is here. Genet Med. 2013; 15: 258-267.
2. O Iqbal. Pharmacogenomics in anticoagulant drug development. Pharmacogenomics. 2002; 3: 823-828.
3. JJ Swen, TW Huizinga, H Gelderblom, EG de Vries, WJ Assendelft, J Kirchheiner, et al. Translating pharmacogenomics: challenges on the road to the clinic. PLoS Med. 2007; 4: e209.
4. X Wang, Z Guo. Targeting and delivery of platinum-based anticancer drugs. Chem Soc Rev. 2013; 42: 202-224.
5. AV Khrunin, A Moisseev, V Gorbunova, S Limborska. Genetic polymorphisms and the efficacy and toxicity of cisplatin-based chemotherapy in ovarian cancer patients. Pharmacogenomics J. 2010; 10: 54-61.
6. JY Yin, X Li, HH Zhou, ZQ Liu. Pharmacogenomics of platinum-based chemotherapy sensitivity in NSCLC: toward precision medicine. Pharmacogenomics. 2016; 17: 1365-1378.
7. J Swierkot, R Slezak, P Karpinski, J Pawlowska, L Noga, J Szechinski, et al. Associations between single-nucleotide polymorphisms of RFC-1, GGH, MTHFR , TYMS, and TCII genes and the efficacy and toxicity of methotrexate treatment in patients with rheumatoid arthritis. Pol Arch Med Wewn. 2015; 125: 152-161.
8. DS Eissa, TM Ahmed. C677T and A1298C polymorphisms of the methylenetetrahydrofolate reductase gene: effect on methotrexate-related

toxicity in adult acute lymphoblastic leukaemia. Blood Coagul Fibrinolysis. 2013; 24: 181-188.

9. H He, J Yin, X Li, Y Zhang, X Xu, M Zhai, et al. Association of ABCB1 polymorphisms with prognostic outcomes of anthracycline and cytarabine in Chinese patients with acute myeloid leukemia. Eur J Clin Pharmacol. 2015; 71: 293-302.

10. CX Ma, YH Sun, HY Wang. ABCB1 polymorphisms correlate with susceptibility to adult acute leukemia and response to high-dose methotrexate. Tumour Biol. 2015; 36: 7599-7606.

11. W Pongstaporn, S Pakakasama, P Chaksangchaichote, T Pongtheerat, S Hongeng, S Permitr. MDR1 C3435T and C1236T polymorphisms: association with high-risk childhood acute lymphoblastic leukemia. Asian Pac J Cancer Prev. 2015; 16: 2839-2843.

12. KA Birdwell, B Decker, JM Barbarino, JF Peterson, CM Stein, W Sadee, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015; 98: 19-24.

13. BS Wang, Z Liu, WX Xu, SL Sun. CYP3A5*3 polymorphism and cancer risk: a meta-analysis and meta-regression. Tumour Biol. 2013; 34: 2357-2366.

14. CJ Li, L Li, L Lin, HX Jiang, ZY Zhong, WM Li, et al. Impact of the CYP3A5, CYP3A4, COMT, IL-10 and POR genetic polymorphisms on tacrolimus metabolism in Chinese renal transplant recipients. PLoS One. 2014; 9: e86206.

15. MV Relling, EE Gardner, WJ Sandborn, K Schmiegelow, CH Pui, SW Yee, et al. Clinical Pharmacogenetics Implementation. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013; 93: 324-325.

16. D Chen, Z Yang, H Xia, JF Huang, Y Zhang, TN Jiang, et al. Enhanced specificity of TPMT*2 genotyping using unidirectional wild-type and mutant allele-specific scorpion primers in a single tube. PLoS One. 2014; 9: e91824.

17. AM Tsimberidou, AM Eggermont, RL Schilsky. Precision cancer medicine: the future is now, only better. Am Soc Clin Oncol Educ Book. 2014; 61-69.

18. C Rodriguez-Antona, M Taron. Pharmacogenomic biomarkers for personalized cancer treatment. J Intern Med. 2015; 277: 201-217.

19. D Sanoudou, G Mountzios, DA Arvanitis, D Pectasides. Array-based pharmacogenomics of molecular-targeted therapies in oncology. Pharmacogenomics J. 2012; 12: 185-196.

20. D Kazandjian, GM Blumenthal, W Yuan, K He, P Keegan, R Pazdur. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer. Clin Cancer Res. 2016; 22: 1307-1312.

21. CH Yun, KE Mengwasser, AV Toms, MS Woo, H Greulich, KK Wong, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci U S A. 2008; 105: 2070-2075.

22. F Pietrantonio, F Petrelli, A Coinu, M Di Bartolomeo, K Borgonovo, C Maggi, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J Cancer. 2015; 51: 587-594.

23. MJ Sorich, MD Wiese, A Rowland, G Kichenadasse, RA McKinnon, CS Karapetis. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol. 2015; 26: 13-21.

24. C Therkildsen, TK Bergmann, T Henrichsen-Schnack, S Ladelund, M Nilbert. The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis. Acta Oncol. 2014; 53: 852-864.

25. Z Du, CM Lovly. Mechanisms of receptor tyrosine kinase activation in cancer. Mol Cancer. 2018; 17: 58.

26. SD Richman, K Southward, P Chambers, D Cross, J Barrett, G Hemmings, et al. HER2 overexpression and amplification as a potential therapeutic target in colorectal cancer: analysis of 3256 patients enrolled in the QUASAR, FOCUS and PICCOLO colorectal cancer trials. J Pathol. 2016; 238: 562-570.

27. Parikh, C Atreya, WM Korn, AP Venook. Prolonged Response to HER2-Directed Therapy in a Patient With HER2-Amplified, Rapidly Progressive Metastatic Colorectal Cancer. J Natl Compr Canc Netw. 2017; 15: 3-8.

28. PJ Roberts, CJ Der. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene. 2007; 26: 3291-3310.

29. PB Chapman, A Hauschild, C Robert, JB Haanen, P Ascierto, J Larkin, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011; 364: 2507-2516.

30. J Hasskarl. Sorafenib: targeting multiple tyrosine kinases in cancer. Recent Results Cancer Res. 2014; 201: 145-164.

31. N Iqbal, N Iqbal. Imatinib: a breakthrough of targeted therapy in cancer. Chemother Res Pract. 2014; 2014: 357027.

32. J Nishimura, Y Kanakura. [The C5 gene polymorphism in patients with PNH]. Rinsho Ketsueki. 2015; 56: 103-110.

33. B Rabbani, H Nakaoka, S Akhondzadeh, M Tekin, N Mahdieh. Next generation sequencing: implications in personalized medicine and pharmacogenomics. Mol Biosyst. 2016; 12: 1818-1830.

34. SM Caspar, N Dubacher, AM Kopps, J Meienberg, C Henggeler, G Matyas. Clinical sequencing: From raw data to diagnosis with lifetime value. Clin Genet. 2018; 93: 508-519.