Review Article
Published: 16 Apr, 2018

Journal of Clinical Pathology Forecast

Ongoing Development of Tumor Mutaome Analysis and Targeted Cocktail Therapy

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Abstract

In the past few years, research in the genetic pathogenic mechanisms of tumors has led to remarkable advances in our understanding of the tumor biology. The study of gene mutations changes the diagnosis, classification and prognostic evaluation of tumors, and directly promotes the rapid development of molecular targeted therapy, and significantly improves the clinical therapeutic effect of many kinds of tumors. This paper introduces the research and clinical application of these fields in recent years, and puts forward the concepts of "mutaome" and "targeted cocktail therapy" combined with clinical experience.

Keywords: Mutaome; Targeted cocktail therapy; Targeted therapy; Gene mutation; Tyrosine kinase inhibitor

Abbreviations

CML: Chronic Myelogenous Leukemia; FDA: Food And Drug Administration; NGS: Next Generation Sequencing; AML: Acute Myeloid Leukemia; NSCLC: Non-Small-Cell Lung Carcinoma; GIST: Gastrointestinal Stromal Tumor; TKI: Tyrosine Kinase Inhibitor; SM: Systemic Mastocytosis; APL: Acute Promyelocytic Leukemia; ATRA: All Trans Retinoic Acid

Introduction

In recent years, the increased understanding of the genetic pathogenesis of tumor, facilitated by next-generation sequencing, has spurred the development of new compounds in the treatment of tumor, particularly the creation of small molecules that target the disease on a molecular level. The first truly small molecular targeted therapies approved for clinical use was imatinib against the BCR-ABL1 fusion protein. A characteristic Philadelphia chromosome (Ph chromosome) was reported in 1960 in Chronic Myelogenous Leukemia (CML) [1], and its corresponding BCR-ABL1 fusion gene was identified in 1985 [2], and the clinical application of imatinib was approved by the US Food and Drug Administration (FDA) in 2001, which has experienced more than 40 years. Nowadays, the rate of discovery of new mutations in tumor genes and the development of targeted drugs have increased dramatically [3].

The Research of Tumor Gene Mutation and the Appearance of Mutaome Concept

The current view is that all malignancies are the result of genetic variation, so theoretically every tumor must have genetic mutations markers. There are many types of gene mutations in tumors, such as fusion gene, gene deletion/ amplification, single base mutation, abnormal expression of proto-oncogene, abnormal splicing of mRNA, and dysregulation of epigenetic modification and abnormal regulation of micro RNA.

Research progression of tumor gene mutation

With the widely application of next generation sequencing (NGS) technology in clinic and the progress of molecular mechanisms research in tumor, more and more molecular markers have been identified and used in clinical diagnosis and treatment decisions [4-7]. Understanding tumors at the gene level plays an important role in assist of the diagnosis and classification, evaluation of the efficacy and prognosis, selection of appropriate treatment options and even targeted drugs. Hundreds of common fusion genes and single gene mutations have been identified in leukemia [8]. Dozens of leukemia gene abnormalities have been used directly in the 2016 revision of WHO classification of myeloid neoplasms and acute leukemia for diagnostic naming [9].

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Received Date: 05 Mar 2018
Accepted Date: 11 Apr 2018
Published Date: 16 Apr 2018

Citation: ZhangY, Wang F, Zhang Y, Chen X, Liu HX. Ongoing Development of Tumor Mutaome Analysis and Targeted Cocktail Therapy. J Clin Pathol Forecast. 2018; 1(1): 1001.

ISSN 2690-4187

It has been clear that most tumors carry multiple gene mutations simultaneously, tumor cells exist both clonal heterogeneity and dynamic evolution and new gene mutations will occur in the course of treatment [10]. Secondary mutations are the source of increased drug resistance and invasiveness of tumors [11]. At the 2010 American Society of Hematology (ASH) annual meeting our team reported on the dynamic changes of gene mutations in patients with CML who have developed resistance to imatinib. Understanding the patterns of changes in these mutations can help to better avoid or even reverse drug resistance mutations [12].

Clinical application of tumor mutation detection

Multiple gene mutations often exist simultaneously in tumors, and different gene mutations can have single or multiple clinical significance in clonal judgment, diagnostic classification, prognosis evaluation, and individualized treatment [13].

An article published in The New England Journal of Medicine (NEJM) journal provides a good example, which detected 18 gene in 398 patients with acute myeloid leukemia (AML) [14] and the main findings were as follows:1) 97.3% of patients could detect at least one somatic alteration; 2) In addition to the previously known FLT3-ITD, newly found mutations in ASXL1 and PHF6 are also considered indicators of poor prognosis; 3) The favorable effect of NPM1 mutations was restricted to patients with co-occurring NPM1 and IDH1 or IDH2 mutations, while patients with co-occurring NPM1 and FLT3-ITD mutation still have a poor prognosis; 4) mutational profiling could be used to guide the targeted therapy and the choice of chemotherapy. In a commentary published in the same issue, it was pointed out that it is no longer enough to detect only a few gene mutations, and detection of more gene mutations and even a whole-genome mutation analysis will become the trend of clinical application [15]. Furthermore, based on the currently updated version of the European Leukaemia Net (ELN) and National Comprehensive Cancer Network (NCCN) risk stratification by genetics, the majority of AML patients can be classified into different risk categories [16,17].

In 2012, our center carried out several panels to detect gene mutation in hematological malignancies, and conducted a mutaome analysis of hematological malignancy based on 58 genes detected by NGS in 2015, which has achieved commendable clinical application results. For example, patients with co-occurring NPM1 and IDH2 mutations could be well controlled by chemotherapy and immunotherapy. Most patients with FLT3-ITD mutations are refractory to conventional chemotherapy but with targeted drugs such as sunitinib and sorafenib can quickly control their condition and fight for the timing of hematopoietic stem cell transplantation. Targeted drugs, while expensive, can save on expensive symptomatic and supportive care, such as blood transfusions and antibiotics, which are exacerbated by illness and in fact save on overall treatment costs.

The concept and significance of tumor mutaome

Based on the current research progress and practical experience, we propose the concept of "mutaome" to refer to the combination of all driver mutations in tumor cells carried by a specific patient at a specific time. Emphasizing the concept of mutaome can help us to understand individual differences of patients, and the mutation combinations of each patient may be different from other patients. The combination of these mutations will also change as the disease changes. It is these different combinations and processes of mutations that determine the different clinical characteristics and treatment outcome of each patient.

Advances in Targeted Therapy for Cancer and the Bright Future of Targeted Cocktail Therapy

Relative to radiotherapy and chemotherapy and other traditional tumor therapy, targeted therapy has the advantages of high specificity, low toxicity, good tolerance etc. The first targeted drug approved for clinical use was rituximab, an antibody class used to treat CD20-positive B cell lymphoma. The most successful paradigm for targeted therapy is imatinib, the first small molecule compound designed artificially for the conformation of oncoproteins, and has achieved great success in clinical treatment. And the most important significance is to provide a brand-new model of drug development, from which small molecule drugs can be designed for clinical treatment.

Progress in research and application of tumor targeted therapy

Dozens of targeted drugs have been approved for clinical treatment, existing drugs are continually added with new indications, and various new agents, such as tyrosine kinase inhibitors, immune checkpoint inhibitors, monoclonal or bispecific T-cell engager antibodies, metabolic and pro-apoptotic agents are currently investigated within clinical trials. Targeted drugs have achieved revolutionary results in the treatment of leukemia, renal cell cancer, non-small-cell lung carcinoma (NSCLC), melanoma, and gastrointestinal stromal tumor (GIST) and other tumors.

For example, the efficiency of traditional chemotherapy for NSCLC was 20% to 35%, and the survival was 10-12 months. However, several phase III studies have demonstrated the superiority of gefitinib, erlotinib (first generation of tyrosine kinase inhibitors (TKIs)) or afatinib (second generation) to chemotherapy in progression-free survival and response rates [18,19]. The efficacy of imatinib in the treatment of CML is even more encouraging, with many patients taking long-term maintenance of the same quality of life as normal people. Imatinib also binds to the kinase domain of KIT protein and platelet derived growth factor receptor (PDGFR) protein. Therefore, imatinib also has a good curative effect on AML, GIST and other tumors with KIT mutation [20], and was approved by the FDA in 2003 for the treatment of GIST. Furthermore, low-dose imatinib leads to rapid induction of major molecular responses and achievement of complete molecular remission in FIP1L1-PDGFRA-positive chronic eosinophilic leukemia [21]. On April 28, 2017, midostaurin was approved by FDA for the treatment of adult patients with newly diagnosed AML who are FLT3 mutation positive. This is the first drug to receive regulatory approval for AML in the United States since the year 2000. FDA also approved midostaurin for the treatment of adults with aggressive systemic mastocytosis (SM), SM with associated hematological neoplasm, or mast cell leukemia. Very recently, two new compounds, CPX-351, a liposomal formulation of cytarabine and daunorubicin that allows more effective delivery to the malignant cells, and enasidenib, an IDH2 inhibitor, received FDA approval for the treatment of AML as outlined below [3].

Dilemma in tumor targeted therapy

At present, the vast majority of targeted therapies are single-targeted drugs, and some of the effects are not as significant as we expected. For example, TKI can prolong the life and improve the quality of life of NSCLC patients, but the effect is still limited. AML patients with FLT3-ITD mutation are refractory to sustained remission

through targeted therapy and may still require hematopoietic stem cell transplantation [22]. The single FLT3-ITD mutation was not enough to cause the occurrence of AML, suggesting that more important gene mutations exist in FLT3-ITD mutated AML, which may be an important reason for the limited effect of FLT3-ITD targeted therapy.

Nearly all targeted drugs have the problem of drug-resistant mutation in the treatment of various tumors. One of the reasons is the widespread genomic instability of tumors, which is the molecular basis of resistant mutation. In addition, tumors are the result of an interaction of multiple mutations that are another major cause of difficult cure for a single target. In CML, one strategy to combat drug resistance is the development of second and third generation TKIs, including dasatinib, nilotinib, bosutinib, and ponatinib [23]. The second and third generation TKIs still have the problem of resistant mutation, especially the second generation TKIs are ineffective on T315I mutation.

Although defining the topology and key features of the molecular landscape are fundamental to development of novel targeted treatment approaches and provide opportunities for better individualization of therapy, confirmation of the genetic complexity presents a huge challenge to successful translation into routine clinical practice. Therefore, there is a high need for dedicated genetic diagnostic standards to avoid wrong, ineffective and expensive targeted treatment approaches [3].

The progressive accessibility and superiority of targeted cocktail therapy

Now that it is clear that tumors are the result of the combined effects of multiple genetic mutations, it is understandable that it is difficult to achieve complete success with a single targeted therapy. Acute Promyelocytic Leukemia (APL) provides a paradigm of multi-target combination therapy. Almost all APL patients carry PML-RARA fusion gene, which is the main molecular mechanism of APL. The early mortality of APL treated by chemotherapy alone was up to 30%, and the complete remission rate was only 60%-80%. The use of all trans retinoic acid (ATRA) and arsenic has increased the complete remission rate of APL to 90-100%, thus APL has changed from the most dangerous leukemia to the most curable leukemia [24]. In our center, the 5-year disease-free survival rate has reached 100% by a combination of ATRA, tetra-arsenic and low-dose chemotherapy and the goal of complete cure has been achieved [25,26]. Although not artificially designed small molecule compound, studies have demonstrated that ATRA and arsenic are indeed have their molecular targeting mechanism: ATRA works by binding to the RARA ligand domain of PML-RARA protein and arsenic works by binding to the PML ligand domain. Either ATRA or PML alone has the problem of drug resistance in the ligand domain [27,28], but when the two drugs are combined, tumor cells that are resistant to one drug can be controlled and eliminated by the other drug in case of appearance. As a result, unprecedented results have been achieved [29].

More and more targeted drugs targeting different therapeutic targets have now been approved for clinical use, and more in the research and clinical trials stage [30]. Hence there will be more and more patients have the opportunity to simultaneously select a variety of targeted drugs for combination therapy [31]. Therefore, we believe that the bright future of tumor targeted therapy is "targeted cocktail therapy", which refers to the combination of multiple different target drugs. In the early treatment of some rapidly progressing tumors (such as AML) may also include the combination of conventional chemotherapy drugs to quickly control the disease. For example, recently FDA approved midostaurin for the treatment of AML who are FLT3+, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. The highest response rates are often achieved when new molecularly targeted therapies are combined with standard chemotherapy. The clinical practice of "targeted cocktail therapy" will also soon be extended to the clinical treatment of many other types of tumors, whose therapeutic effect is reasonable to be expected as good as APL.

Conclusions

The research of tumor molecular landscape provides the basis for the development of targeted drugs. It is also necessary to detect gene mutations in the clinical application and efficacy monitoring of targeted drugs. In the past decade, considerable progress has been made in both research and application, and many patients have benefited. Most targeted drugs have the advantages of oral preparation, convenience, safety and compliance. Personalized selection of one or more targeted drugs based on the gene mutation will be the mainstream of tumor therapy in the future.

The era of "precision medicine", marked by in-depth research of tumor mutaome and precise targeted therapy, has come and brought about a tremendous breakthrough in ideology and concepts [32]. Most tumor patients can maintain good quality of life and ability to work through long-term oral administration. And the cure rate of the tumor, which provides a possibility of transforming the malignant tumor into a chronic and controllable disease.

References

1. Nowell PC, Hungerford DA. Chromosome studies on normal and leukemic human leukocytes. [J]. J Natl Cancer Inst.1960; 25: 85-109.
2. Shtivelman E, Lifshitz B, Gale RP, et al. Alternative splicing of RNAs transcribed from the human abl gene and from the bcr-abl fused gene. [J]. Cell. 1986; 47: 277-284.
3. Kayser S, Levis MJ. Advances in targeted therapy for acute myeloid leukaemia. [J]. Br J Haematol. 2018; 180: 484-500.
4. Zhang Y, Wang F, Chen X, et al. Mutaome profile of 10 common mutated genes in refractory and relapsed acute myeloid leukemia. [J]. Journal of Leukemia & Lymphoma. 2015; 24: 261-264.
5. Wang F, Zhang Y, Chen X, et al. Mutaome analysis including 10 common mutated genes in newly diagnosed acute myeloid leukemia patients [J]. Journal of Leukemia & Lymphoma. 2015; 24: 161-164.
6. Liu M, Zhang Y, Wang F, et al. Mutaome analysis of common mutated genes in patients with myelodysplastic syndromes. Journal of Clinical and Pathological Research. 2017; 37: 2332-2338.
7. Zhang Y, Liu M, Liu HX. Gene mutations and its clinical significance in myelodysplastic syndrome [J]. Journal of Clinical and Pathological Research. 2017; 37: 2237-2242.
8. Taylor J, Xiao W, Abdel-Wahab O. Diagnosis and classification of hematologic malignancies on the basis of genetics. [J]. Blood. 2017; 27; 130: 410-423.
9. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organizationclassification of myeloid neoplasms and acute leukemia. [J]. Blood. 2016; 127: 2391-2405.
10. Walter MJ, Shen D, Ding L, et al. Clonal architecture of secondary acute myeloid leukemia. [J]. N Engl J Med. 2012; 366: 1090-1098.
11. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. [J]. Nature. 2009; 458: 719-724.

12. Liu H, Zhu P, Tong C, et al. Clonal Evolution of BCR-ABL1 Kinase Domain Mutation In Tyrosine Kinase Inhibitor Treatment Patient. [J]. Blood. 2010; 116: 597.

13. Grimwade D, Ivey A, Huntly BJ, et al. Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. [J]. Blood. 2016; 127: 29-41.

14. Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. [J]. N Engl J Med. 2012; 366: 1079-1089.

15. Godley LA. Profiles in leukemia. [J]. N Engl J Med. 2012; 366: 1152-1153.

16. Döhner H, Estey E, Grimwade D, et al. Diagnosis and Management of AML in Adults: 2017 ELN Recommendations from an International Expert Panel [J]. Blood. 2017; 129: 424-447.

17. O'Donnell MR, Tallman MS, Abboud CN, et al. Acute Myeloid Leukemia, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. [J]. J Natl Compr Canc Netw. 2017; 15: 926-957.

18. Kobayashi K, Hagiwara K. Epidermal growth factor receptor (EGFR) mutation and personalized therapy in advanced nonsmall cell lung cancer (NSCLC). [J]. Target Oncol. 2013; 8: 27-33.

19. Hsu WH, Yang JC, Mok TS, et al. Overview of current systemic management of EGFR-mutant NSCLC. [J]. Ann Oncol. 2018; 1; i3-i9.

20. Patel S. Long-term efficacy of imatinib for treatment of metastatic GIST. [J]. Cancer Chemother Pharmacol. 2013; 72: 277-286.

21. Jovanovic JV, Score J, Waghorn K, et al. Low-dose imatinib mesylate leads to rapid induction of major molecular responses and achievement of complete molecular remission in FIP1L1-PDGFRA-positive chronic eosinophilic leukemia. [J]. Blood. 2007; 109: 4635-4640.

22. Lin PH, Lin CC, Yang HI, et al. Prognostic impact of allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia patients with internal tandem duplication of FLT3. [J]. Leuk Res. 2013; 37: 287-292.

23. Jain P, Kantarjian H, Cortes J. Chronic Myeloid Leukemia: Overview of New Agents and Comparative Analysis. [J]. Curr Treat Options Oncol. 2013; 14: 127-143.

24. Rego EM, Kim HT, Ruiz-Arguelles GJ, et al. Improving acute promyelocytic leukemia (APL) outcome in developing countries through networking, results of the International Consortium on APL. [J]. Blood. 2013; 121: 1935-1943.

25. Lu DP, Qiu JY, Jiang B, et al. Tetra-arsenic tetra-sulfide for the treatment of acute promyelocytic leukemia: a pilot report. [J]. Blood. 2002; 99: 3136-3143.

26. Wu S, Lu D, Zhao Y, et al. Arsenic Containing Triple-Agent Therapy for Acute Promyelocytic Leukemia-Comparison of Tetra-Arsenic Tetra-Sulfide vs. Arsenic Trioxide in the Long-Term Follow-up at a Single Hospital [Z]. Orlando: 2010; 116: 1081.

27. Zhou DC, Kim SH, Ding W, et al. Frequent mutations in the ligand-binding domain of PML-RARalpha after multiple relapses of acute promyelocytic leukemia: analysis for functional relationship to response to all-trans retinoic acid and histone deacetylase inhibitors in vitro and *in vivo*. [J]. Blood. 2002; 99: 1356-1363.

28. Goto E, Tomita A, Hayakawa F, et al. Missense mutations in PML-RARA are critical for the lack of responsiveness to arsenic trioxide treatment. [J]. Blood. 2011; 118: 1600-1609.

29. Lou Y, Qian W, Meng H, et al. High efficacy of arsenic trioxide plus all-trans retinoic acid based induction and maintenance therapy in newly diagnosed acute promyelocytic leukemia. [J]. Leuk Res. 2013; 37: 37-42.

30. Berndt N, Karim RM, Schönbrunn E. Advances of small molecule targeting of kinases. [J]. Curr Opin Chem Biol. 2017; 39: 126-132.

31. Soverini S, Mancini M, Bavaro L, et al. Chronic myeloid leukemia: the paradigm of targeting oncogenic tyrosine kinase signaling and counteracting resistance for successful cancer therapy. [J]. Mol Cancer. 2018; 19: 49.

32. Dwivedi S, Purohit P, Misra R, et al. Diseases and Molecular Diagnostics: A Step Closer to Precision Medicine. [J]. Indian J Clin Biochem. 2017; 32: 374-398.