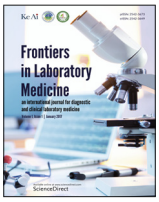
Frontiers in Laboratory Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Frontiers in Laboratory Medicine

journal homepage: www.keaipublishing. com/FLM; www.frontlabmed.com



Molecular targeted therapy of cancer: The progress and future prospect

Xing Ke, Lisong Shen *

Department of Clinical Laboratory, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

ARTICLE INFO

Article history:
Received 9 March 2017
Received in revised form 26 April 2017
Accepted 16 May 2017
Available online xxxx

Keywords:
Cancer
Targeted therapy
Drug resistance

ABSTRACT

Cancer has become a major public health problem worldwide. Researches focus on the new approaches for cancer treatments that involve the specific targets of the cancer disease. The premise of targeted therapy in oncology is the fundamental reliance of tumor cells on biological pathways to which drugs inhibiting those pathways can be applied. Tumor resistance to anticancer drugs is a well-known clinical phenomenon that is now yielding its secrets to investigation at the molecular level. Resistance of immunotherapeutic agents is a matter of concern that is believed to influence the effectiveness of anticancer therapies. The intrinsic or acquired drug resistance directly impacts on the survival and the prognosis of patients with cancer. This review presents the application of molecule targeted therapy in cancer treatment. A particular focus is on the potential mechanism that can facilitate further improvement of anticancer.

Contents

Introduction

Cancer is one of the most common diseases and a major public health problem in China and worldwide. Based on GLOBOCAN estimates, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide. Over the years, the burden has shifted to the developing countries, which currently account for about 57% of cases and 65% of cancer deaths worldwide.[1] The high morbidity and mortality of cancer are related with the increasing prevalence of risk factors such as overweight, smoking, the increased aging and growth of the population.[2]

* Corresponding author at: Department of Clinical Laboratory, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, 1665 Kong Jiang Road, Shanghai 200092, China.
E-mail address: lisongshen@hotmail.com (L. Shen).

http://dx.doi.org/10.1016/j.flm.2017.06.001

There are many effective methods to treat the cancer disease. Surgery, radiation therapy and chemotherapy are the major methods in the treatments of cancer today. Primary tumors and large metastases often depend on surgery and radiation therapy. Some disseminated tumors such as breast, prostate and colorectal cancer are treated mainly by chemotherapy.[3] Traditional anticancer chemotherapy agents block cell division and DNA replication.[4] Many of these agents could also target the microtubule dynamics of the mitotic spindle. These early anticancer drugs such as platinum derivatives, nucleoside analogues, topoisomerase inhibitors, taxanes and vinca alkaloids are widely used today. They have great curative effects and slightly prolong survival among patients with childhood leukaemias and testicular carcinoma. However, they are not effective for all types of cancer.[5]

Regarding the background and disadvantage of chemotherapy, complementary treatment modalities are being widely explored in recent years. For example, molecular therapy, anti-angiogenesis therapy,[6] immunotherapy,[7] apoptosis regulation,[8] signal-transduction therapy,[9] differentiation therapy,[10] targeted radionuclide therapy[11] and nucleic-acid-based therapies[12] have attracted more attention from the public. Researches are focusing on some new approaches for cancer treatments that involve the specific targets of the cancer disease. Multiple molecular targets and signaling pathways were related to the action of targeted treatment. Targeted treatment exerted its anticancer effects through multiple mechanisms, including proliferation inhibition, apoptosis induction, metastasis suppression, immune function regulation and multidrug resistance reversal.

Increased understanding of tumor immunology leads to the development of effective targeted therapies.[13] The molecular diagnostic of cancer is also rapidly developed recently. More and more targeted therapeutic agents across various cancer subtypes have been approved by the US Food and Drug Administration (FDA) in the recent years than in previous two decades. These drugs which are effective and safe provide new treatment opportunities to patients who could not receive suitable conventional chemotherapy.[14] Drugs targeting signaling oncoproteins that have gained tumor-driving functions through mutations or overexpression are subsequently developed to increase specificity and thus reduced the side effects, but have limitations such as the formation and development of drug resistance.

Resistance of therapeutic agents is an important problem in the treatment of cancer disease that is believed to influence the effectiveness of targeted therapies and the prognosis of patients with cancer.[15] Drug resistance in cancer inevitably emerges during treatment, particularly with novel targeted therapies designed to inhibit specific molecules. Although a patient initially was sensitive to some chemotherapeutic agents, he may also acquire cross-resistance during treatment. The mechanisms of cross-resistance are complicated and maybe different from the single drug resistance. According to incomplete statistics, above 80% of patients with metastatic cancer were acquired single or multiple drug resistance. Drug resistance directly causes treatment failure in cancer disease especially in metastatic tumor.[16] Tumor resistance to anticancer drug is a major clinical phenomenon. Several mechanisms involve in anticancer resistance, including an increase in drug efflux, alteration or mutation of drug targets, drug detoxification and inactivation, impact on apoptosis, interference with DNA replication and other ways. Cancer cell resistance to chemotherapy could occur at a lot of molecular levels. The overcome of drug resistance could impact on survival of patients with cancer.

This review shows the application of molecule targeted therapy in cancer treatment. A particular focus is on the mechanism of tumor resistance to anticancer drugs. The premise of targeted therapy in oncology is inhibiting the biological pathways of tumor cells. Here, we also provide an overview of these potential resistance mechanisms that can facilitate further improvement of anticancer.

Molecular targeted therapy in anticancer

Researchers have developed anticancer drugs with a higher precision of molecular targeting. The cellular targets are genetically altered in cancer cells and are essential to tumor development and survival. Oncoprotein or oncogenes targets, which are mainly involved in various signaling pathways, are primarily products of gene fusions, obtained or functional mutations or overexpressed oncogenes. The molecular targets and approved agents in anticancer therapy are showed in table 1.

Molecular targeted therapy for HER2 positive breast cancer

Apart from lung cancer, death rate of breast cancer among women in the world is higher than that of other cancers. Human epidermal receptor 2 (HER2) positive breast cancer (HER2+ BC) belongs to a subtype of breast cancer with *HER2* gene amplification and HER2 protein overexpression, and accounts for about 25% of all breast cancers.[17] HER2-containing heterodimers are capable of activating both of the key signaling pathways: the cell proliferative RAS/Raf/MAPK pathway and the cell survival PI3K/Akt pathway.[18] HER2 is an ideal target for developing therapeutic strategies for the treatment of HER2+ BC. Breast cancers are divided into four subtypes: luminal A (Estrogen Receptor (ER)+, Progestogen Receptor (PR)+, HER2 and Ki67 (which is a proliferation marker) <14%), luminal B (ER+, PR+, HER2 and Ki67 $\geq$14% or ER+, PR+, HER2+), HER2 positive breast cancer (HER2+, ER and PR) and basal-like (ER, PR and HER2).[19] Due to these complex subtypes, it is a challenge to diagnose and cure different molecular subtypes of breast cancers.

For the treatment of HER2+ BC, HER2 targeted therapeutic methods are divided into monoclonal antibodies, small molecule

Table 1
Molecular targeted therapy in anticancer.

Molecular targets	Tumor types	Signaling pathways	Approved agents	References
HER2	Breast Cancer	RAS/Raf/MAPK and PI3K/Akt pathways	Trastuzumab and pertuzumab (monoclonal antibody); apatinib, afatinib and neratinib (TKIs); T-DM1 (antibody drug conjugate)	Perez EA et al.[20]; Welslau M et al.[21]
EGFR	Non-Small Cell Lung Cancer	PI3K/AKT pathways	Erlotinib and gefitinib; afatinib, dacomitinib and neratinib; simertinib, rociletinib and olmutinib (TKIs)	Zhao D et al.[25]; Zhang H[26]
FLT3-ITD	Acute myeloid leukemia	STAT, ERK, AKT, and C-Myc pathways	Homoharringtonine sorafenib, daunorubicin, cytarabine and inib	Li X et al.[27]; Pillinger G et al.[32]; Wu H[33]
VEGF and mTOR	Renal cell carcinoma	VEGF and mTOR pathways	Sorafenib, sunitinib and pazopanib (TKI); bevacizumab (anti-VEGF) temsirolimus and everolimus (mTOR inhibitors)	Négrier S et al.[34]; Rini BI et al.[35]
VEGFR	Hepatocellular carcinoma	Ras/Raf/MEK/ERK pathways	Sorafenib (multikinase inhibitor); dovitinib (receptor inhibitor)	Antoniou EA et al.[37]; Cheng AL et al.[38]

Please cite this article in press as: Ke X., Shen L. Molecular targeted therapy of cancer: The progress and future prospect Frontiers in Laboratory Medicine (2017), http://dx.doi.org/10.1016/j.flm.2017.06.001