WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 09, 131-148. Conference Article ISSN 2277–7105

MOLECULAR TARGETED THERAPY OF CANCER: THE PROGRESS AND FUTURE PROSPECT

Deepak Kashyap*, Dheeraj Ahirwar, Jhakeshwar Prasad and Ashish Kumar Netam

School of Pharmacy, Chouksey Engineering College Bilaspur (C.G.), India.

Article Received on
18 March 2018,
Revised on 08 April 2018,
Accepted on 29 April 2018
DOI: 10.20959/wjpr20189-12089

***Corresponding Author**
Deepak Kashyap
School of Pharmacy,
Chouksey Engineering
College Bilaspur (C.G.),
India.

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.

KEYWORDS: Cancer, Molecular Targeted Therapy, And Drug resistance.

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] 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, antiangiogenesis 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 crossresistance during treatment. The mechanisms of cross-resistance are complicated and may be 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.

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 over expression, 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[18], RAS/Raf/MAPK pathway and the cell survival PI3K/Akt paBreast cancers are divided into four subtypes: luminal A (Estrogen Receptor (ER)+, Progestogen Recep- tor (PR)+, HER2 and Ki67 (which is a proliferation marker) <14%), luminal B (ER+,PR+, HER2 and Ki67 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 chal- lenge 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 tyrosine kinase inhibitors (TKIs), antibody–drug conjugates (ADC) and other anti-HER2 agents.

Trastuzumab (Herceptin, Genetech) and pertuzumab (Perjeta, Genetech) are the first FDA approved monoclonal antibody agents that are specific for tyrosine kinase. Lapatinib (Tykerb, GlaxoSmithKline) is the second FDA approved HER2 targeted agent, which is a small molecule TKIs. Neratinib (HKI-272, Puma Biotechnology) and Afatinib (BIBW-2992, Boehrin- ger Ingelheim) are another two dual TKIs. Trastuzumab–emtansine (T-DM1, Genetech) is an antibody drug conjugate combining an anti-microtubule cytotoxic chemical agent with trastuzumab. Combination therapies are often adopted by clinical practice to achieve higher synergistic response. Trastuzumab is often com- bined with pertuzumab or lapatinib, and the combination of anti- body drug conjugate with anti-HER2 agents. Perez EA et al.[20] demonstrated that antibody-drug conjugate trastuzumab encour- aged efficacy and safety in a phase II study of patients with previ- ously untreated HER2-positive metastatic breast cancer. Combination T-DM1 and pertuzumab showed an acceptable safety profile in a phase Ib and II study. Welslau M et al.[21] supported the concept that T-DM1 has greater efficacy and tolerability than cape- citabine plus lapatinib, which may translate into improvements in health-related quality of life.

Molecular Targeted Therapy For EGFR-Mutated Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. NSCLC is frequently diagnosed at a late stage and has a high mortality rate. Genetic mutations in DNA found in the serum of patients with NSCLC were first observed in 1998. The ErbB fam- ily of tyrosine kinases includes epidermal growth factor receptor (EGFR), HER2, ErbB3 and ErbB4. Dysregulation of these tyrosine kinases and their downstream PI3K/AKT pathway is implicated in cancer cell metastasis, proliferation and angiogenesis. EGFR signal- ing is triggered by the binding of growth factors, such as epidermal growth factor (EGF), resulting in the dimerization of EGFR molecules or hetero dimerization with other closely receptors (e.g. HER2/neu). Autophosphorylation and transphosphorylation of the receptors through their tyrosine kinase domains cause the recruitment of downstream effectors and the activation of proliferative and cell-survival signals.[22] Exon 19 deletion (Del19) and exon 21 Leu858Arg substitution

(L858R) account for 90% of EGFR mutations as common mutations. Although activating EGFR mutations occur in only 1–3% of patients with NSCLC, the ErbB family still represents a rational therapeutic target. EGFR-TKIs are used for the first-line treatment of advanced NSCLC and activating EGFR mutations. Patients with EGFRm+ could achieve good responses to the treatment with the first-generation EGFR-TKIs, such as erlotinib and gefitinib. The use of EGFR-TKIs was associated with dramatic, durable, and tol- erable responses and side effect profiles when applied to the pal- liation of advanced EGFRm+ NSCLC.[23] However, despite initial benefit, the majority of patients treated with an EGFR-TKI devel- oped resistance to therapy within about 12 months, approxi- mately 50% of patients due to a second-site mutation, the T790M mutation occurring within exon 20.[24] Clinical trials have shown that EGFR-TKIs did not improve the survival of patients with EGFRm+ NSCLC because of the high crossover of treatments. Zhao et al.[25] put forward that EGFR-TKI therapy was an indepen- dently prognostic factor for NSCLC with mutated EGFR. A more effective therapy was needed for patients with wild-type EGFR. Gefitinib targeted the ATP cleft within the tyrosine kinase, which was overexpressed in 40 to 80 percent of NSCLC and many other epithelial cancers.[26]

Molecular Targeted Therapy For FLT3-ITD Mutation In Acute Myeloid Leukemia.

Acute myeloid leukemia (AML) has achieved a high prevalence of complete remission (CR) with the gold standard for induction chemotherapy using daunorubicin and cytarabine. However, 20– 30% AML patients harbor an internal tandem duplication mutation of the FMS-like tyrosine kinase receptor (FLT3-ITD mutation).[27] FLT3 is a proto-oncogene involved in crucial steps of haematopoi- esis such as proliferation, differentiation and survival. FLT3 muta- tions have been associated with the clinical prognosis, treatment and survival of patients. The most common form of FLT3 mutation is internal tandem duplication (ITD) that promotes ligand- independent auto-phosphorylation and constitutive activation of the receptor.[28] The CR rate was lower and the overall and disease-free survival was shorter than those of non-FLT3-ITD AML patients.[29] Homoharringtonine (HHT) was a natural alkaloid and used in China for the treatment of hematological diseases for the past 30 years. It may work in the way of inhibiting protein syn- thesis by preventing the initial elongation step of protein synthesis via an interaction with the ribosomal A-site and by reducing p-eIF4E levels.

This leaded to a rapid loss of proteins with short half-lives such as c-Myc, Mcl-1 and CyclinD1. HHT has been reported to act against AML, MDS and CML cells. In an open-label, randomized, controlled phase III study performed by Xia Li's group,[30] with the homoharringtonine-based induction regi- men HAA (homoharringtonine, cytarabine and aclarubicin), it showed 73% of patients (150/206) with AML (non-acute promyelo- cytic leukemia (APL)) achieved CR, which was significantly higher than that in the DA (daunorubicin and cytarabine) group (61%, 125/205). Also, 40 FLT3-ITD mutant patients were included and the HAA regimen showed good curative effect of treatment. Recently, as reported by Xu G et al.,[31] sorafenib in combination with low-dose homoharringtonine as a salvage therapy was suc- cessfully administrated and obtained CR in primary refractory FLT3-ITD mutant AML. In conclusion, regimen including HHT has been used as an alternative valid front line chemotherapy for AML in China. Pillinger G et al. and Wu H et al. found ibrutinib was particularly effective in inhibiting FLT3-ITD mutant AML cell survival.[32,33] They have confirmed that ibrutinib blocks the FLT3 mutation signaling pathway and inhibits the expression of STAT5, ERK, AKT, and C-Myc to suppress FLT3-ITD mutant.

Molecular targeted therapy for VEGF and mTOR pathway in renal cell carcinoma

Renal cell carcinoma (RCC) is the seventh most common cancer in men and the ninth most common in women and accounts for 2–3% of all malignant diseases in adults. In the treatment of patients with RCC, partial nephrectomy for small tumors and radical nephrectomy for large tumors were the gold-standard treatments. The standard of care for RCC has evolved rapidly with the approval of six targeted therapies by the US FDA and European Medicines Agency since 2006. One of most important treatments is aimed to block the activity of vascular endothelial growth factor (VEGF), which is also a major tumor growth factor for RCC. The TKIs (sorafenib, sunitinib, and pazopanib) and anti-VEGF antibody bevacizumab are commonly used drugs that have a direct effect on the VEGF pathway. mTOR inhibitors (Temsirolimus and everoli- mus) are also used in clinic.[34] Regulation of the activation of the mammalian target of rapa- mycin (mTOR) pathway was mediated through a series of complex signaling interactions that linked growth factor receptor signaling (e.g. activation of the Akt/protein kinase-B pathway and phosphoinositide-3 kinase activation). Temsirolimus showed anti-tumor activity in a

phase II trial in patients with treatment- refractory metastatic RCC that seemed pronounced in a retrospec- tive analysis of a poor-risk subset of patients. VEGF and mTOR pathways have been established to be the relevant therapeutic targets based on the underlying molecular biology of RCC.[35] Sunitinib-treated patients had a longer median overall survival for interferon-treated patients. Of note, several patients who were randomly assigned to interferon received sunitinib or other active targeted treatment, or both, on disease progression, probably under powering this trial to detect a difference in overall survival. The very high median numbers noted for overall survival in this trial in comparison with historical controls support that targeted treatment has extended the lives of patients with metastatic RCC. Sunitinib has emerged as a front-line standard of care in metastatic RCC.[36]

Molecular targeted therapy for VEGFR in hepatocellular carcinoma:

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths accounting for approximately 80% of primary liver cancer cases and usually develops as a conse- quence of underlying liver disease. The majority of HCC is diag- nosed at an advanced stage of disease and is not a candidate for surgical interventions. VEGF is the primary stimulus for tumor angiogenesis and an endogenous cytokine that induces capillary endothelial cell proliferation. VEGF binds to vascular endothelial growth factor receptor (VEGFR) and promotes cell proliferation and angiogenesis by activating the MAPK pathway (also known as Ras/Raf/MEK/ERK pathway). FGF2 is a potent angiogenic factor in HCC and can augment VEGF-mediated HCC angiogenesis. It may evade resistance to VEGFR modulating agents.[37] Sorafenib (Nexavar; Whippany, NJ), the only approved agent, is the inhibitor of platelet-derived growth factor receptor (PDGFR) and VEGFR.[38]

It was showed to be the first effective antiangiogenic therapy for advanced RCC and HCC. Sorafenib induces tumor cell proliferation and tumor angiogenesis by inhibiting the Raf/MEK/ extracellular signal-regulated kinase pathway. It also inhibits intracellular Raf kinase (Raf-1) to target the MAPK signal transduc- tion pathway. Dovitinib is a potent inhibitor of VEGFRs, FGFRs, and PDGFRb, which are related to antitumor activity such as antiproliferative and antiangiogenic effects. Preliminary efficacy for dovitinib has been also reported in patients with metastatic melanoma, metastatic RCC, breast cancer, and acute myeloid leukemia. Cheng AL et al.[38] demonstrated antitumor

activity of dovitinib was superior to that of sorafenib and antiangiogenic effects that correlated with FGFR, PDGFRb, and VEGFR2 signaling pathway activation.

Mechanisms of anticancer drug resistance

Tumor resistance to anticancer drug was a well-known clinical phenomenon that was yielding its secrets to investigation at the molecular level. It was important to validate the important mechanisms from the resistance situation of the patient. Several mechanisms involved in resistance to anticancer drug, including an increase in drug efflux, alteration or mutation of drug targets, drug detoxification and inactivation, impact on apoptosis, interference with DNA replication and many other ways.

Expression of drug efflux pumps

One of the main causes for the failure of cancer therapy was multidrug resistance (MDR). MDR occurred at the beginning of the treatment or during treatment when cells resist to the treatment. One of the mechanisms was the increased expression of drug efflux pumps, such as P-glycoprotein (P-gp).[39,40] P-gp was one of the ATP-binding cassette (ABC) transporters and was encoded by the MDR1 (ABCB1) gene.[41] A previous study has revealed that over 96% of cells expressed P-gp in colorectal cancer. P-gp serves an important role in the generation and maintenance of colorectal cancer drug resistance.[42] P-gp became a target of several studies to identify novel compounds to counteract MDR. Wang S et al.[43] reported MRP1 acted as an efflux pump, which rapidly extruded various anticancer drugs from the targeted cancer cells. Azzariti A et al.[44] suggested that both Gefitinib and Vandetanib may act as inhibitors of P-gp and transported substrates for Breast Cancer Resistance Protein (BCRP, ABCG2). Short periods of exposure to TKIs could provide insights into the nature of the binding to MDR-related proteins, either as inhibitors or as substrates, The analysis of exposure periods was needed in order to optimize future development in combination with established chemotherapeutic approaches.

It has also been reported[45] that aberrantly regulated Wnt/beta-catenin and Notch1 signaling in carcinoma stem cells (CSCs) were involved in MDR. The MDR properties of CSC were due to the overexpression of the ABC transporter protein ABC sub-family G member 2 (ABCG2), which acted as a drug efflux pump for DNA-targeting drugs. Some researchers also studied the mechanisms responsible for the onset of resistance to drug therapy by EGFR inhibitors such as TKIs. Among ABC transporters involved in MDR, P-gp and BCRP have been considered as the pumps responsible for TKIs treatment failure, including gefitinib and

erlotinib. Moreover, two subtypes of EGFR mutations have been described: mutations of the exons coding for tyrosine kinase domain (18 to 21) and truncating mutations (exons 2 to 7) that involved downstream effectors such as MAPK, PI3K/Akt and STAT. The first group of mutations could be considered as a hallmark of NSCLC and were responsible for the failure of TKIs while the second group of mutations led to resistance.[46] Galetti M et al.[47] indicated that gefitinib inhibited ABCG2 activity in lung cancer cells and ABCG2 silencing or overexpression affects intracellular gefitinib content by modulating the uptake rather than the efflux. Overexpression of ABCG2 affected the expression of a number of drug transporters, altering the functional activities of nutrient and drug transport systems.

Alteration or mutation of drug targets

Drug resistance in anticancer therapy could be greatly affected in the molecular level of drug targets. Generally, the mutations of functional targets or some alterations of expression levels dramatically influenced drug resistance. Recently, new anticancer drugs that targeted oncogenic signaling pathways have been developed. Two representative examples of such drugs were cetuximab and panitumumab, two monoclonal antibodies (moAbs) against the EGFR, which have been proven to be effective for patients with RAS wild type (RAS-WT) metastatic colorectal cancer (mCRC). However, a large part of unselected mCRC patients were not benefit from but resistant to the anti-EGFR therapy. It suggested that the primary resistance to anti-EGFR therapy is common in CRC.[48] Trastuzumab, a recombinant anti-HER2 agent, was the first biological drug approved and remained the gold standard for the treatment of HER2+ BC. Though many studies have proved the satisfactory therapeutic efficacy of trastuzumab, some HER2+ BC patients showed intrinsic or acquired resistance to it.[49,50] Resistance mechanisms to trastuzumab develop often as a result of HER2 gene amplification or protein overexpression. The increased PI3K signaling and the presence of alternative forms of HER2 are not detected by trastuzumab.[51] The modulation of Cdk inhibitor p27 by insulin-like-growth-factor 1 (IGF-1) may be a key player in resistance to trastuzumab as overexpressed IGF-1 is responsible for the activation of the PI3K downstream signaling pathway and further effects on Akt. The specific mutations in the EGFR gene of NSCLC are correlated with clinical responsiveness to the TKI gefitinib. These mutations lead to the increase of growth factor signaling and susceptibility to the inhibitor. Such mutations in NSCLC lead to the good response to cetuximab and panitumumab that could bind to the extracellular domain of EGFR. Among the downstream pathways, the RAS RAF-MAPK, PI3K-PTEN-AKT, and JAK/STAT pathways have also been implicated in the resistance

mechanisms against antibody-mediated EGFR inhibition.[52] Any alterations or mutations in their components, such as KRAS, NRAS, BRAF, and PIK3CA gene, can influence the activation of EGFR and lead to drug resistance. Recently, the third-generation EGFR inhibitors, such as osimertinib, rociletinib and olmutinib were developed in targeting T790M. These mutant-selective EGFR-TKIs expressed a good effect in overcoming T790M-mediated resistance in patients with NSCLC.[53]

Drug detoxification and inactivation

Tumor resistance may be present at the beginning of treatment, develop during treatment, or become apparent on re-treatment of the patient. The mechanisms involved are usually inferred from experiments of Di Nicolantonio F et al.[54] Clonal selection in this process was that cell lines produced highly resistant sub-clones on the low concentrations of drugs exposure. However, cells may be able to adapt by regulation of expression of resistance or target molecules individually if they survived the initial exposure to the drug and did not require clonal selection. This required changes in molecular levels such as epigenetic change and mutation mechanisms. Glutathione S-transferase (GST) was important for the development of drug resistance via direct detoxification. It may decrease the concentration of anticancer drugs via the glutathione (GSH)-conjugate export pump and special emphasis has been put on the function of GSTs in Phase II detoxification.[55] Drozd E et al.[56] indicated that expression of GSTM1 and GSTA1-3 genes was up-regulated by doxorubicin treatment and suggested that activity of these genes may be associated with drug resistance.

It has been shown that cancer cells could develop cisplatin resistance through enhancing the drug detoxification system by elevating the levels of intracellular scavengers such as GSH in treatment in ovarian, testicular, cervical cancer and other cancer types. The detoxification of cisplatin by its interaction with GSH may be catalyzed by GST.[57] Other GSH-related enzymes may be also important in this resistance process. In the research of Khalil et al.,[58] they showed that Nuclear erythroid related factor-2 (NRF2) was known to promote cancer therapeutic detoxification and crosstalk with growth-promoting pathways. Here they reported HER2 targeting by antibodies (eg. Trastuzumab and Pertuzumab) inhibited growth in association with persistent generation of reactive oxygen species (ROS), GSH depletion, reduction in NRF2 levels and inhibition of NRF2 function in ovarian cancer cell lines. Several therapeutic strategies such as anticancer chemotherapy largely depended on ROS

generation to induce cytotoxicity. Hyperactivation of NRF2 dependent AR pathway would attenuate the potency of such agents.

Impact on apoptosis

The suppression of apoptosis is one mechanism by which tumor cells become drug resistant. Why cytotoxic drugs fail to kill sufficient tumor cells in the major human solid cancers, such as the carcinomas, was suggested to be due to the inherent inability of these cells to engage apoptosis after drug-induced damage.[59,60] Drug resistance mediated by anti-apoptosis is also a key MDR mechanism. B-cell leukemia/lymphoma-2 (BCL-2) was considered to be one of the primary anti-apoptotic proteins. The BCL-2 family of proteins regulated cell fate by controlling the mitochondrial apoptotic pathway. When activated, the pro-apoptotic members Bak and Bax could form high molecular weight oligomers on the mitochondrial membrane, which promoted dissipation of mitochondrial membrane potential and allowed the release of cytochrome to the cytoplasm and consequently activating the caspases. In turn, the pro-survival members, such as Bclxl, Bcl2, and Mcl-1, binded Bak and Bax and prevented their activation and oligomerization. Thus, this family of proteins served as rheostats for mitochondrial membrane stability and is critical in the cell's life or death decisions.

Indeed a significant amount of research was underway in developing therapeutic modalities that targeted these proteins in apoptotic pathway.[61] The data from Taylor ST et al.[62] demonstrated that JLP119 B lymphoma cells underwent apoptosis after the exposure to the topisomerase II inhibitor etoposide and this was dramatically reduced when the cells were cultured in the germinal centre (GC) system. They thought that combined effects of three microenvironmental signals on the Bcl-2 family illustrated the potential importance of such signaling pathways in drug resistance. Chresta CM et al.[63] reported that 60%-70% of bladder carcinomas had mutant p53 and this could prevent the response to the topoisomerase II poison etoposide. Lines with mutant or non-functional p53 low showed the constitutive expression of bcl-2 and bcl-XL with low and non-inducible levels of bax. Guo P et al. observed that changes of intracellular ROS levels may secondarily regulate the expression of Bcl-2, Bax and P-gp, affecting apoptosis and drug resistance.[41] Cardenas C et al. observed chemoresistant EOC stem cells expressed higher levels of the pro-apoptotic members Bak and Bax compared to the chemosensitive CD44/MyD88 EOC cells.[61]

Interference with DNA replication

On the stress of DNA damage of cancer cells by chemotherapeutic agents, cancer could make changes in some genes to produce the mutator phenotype. The obtaining of further mutations could repair DNA damage to make resistance to drug agents. Irinotecan promoted cancer cell death by interfering with the topoisomerase type 1b enzyme (TOP1) on DNA, generating cytotoxic proteinlinked DNA breaks (PDBs). Meisenberg et al.[64] reported that the resistance is neither due to the downregulation of the main cellular target of irinotecan TOP1 nor the upregulation of the key TOP1 protein-linked DNA breaks (PDBs) repair factor tyrosyl DNA phosphodiesterase 1 (TDP1). Instead, the faster repair of PDBs underlies the resistance, which was associated with chromatin acetylation landscape, in particular H4K16ac. CRC cells with histone deacetylase (HDAC) inhibitors could effectively overcome resistance in subsequent treatment of irinotecan-resistant.[64] PARP or HDAC inhibitors were already approved by FDA and should be examined the efficacy in both irinotecan responsive and non-responsive patients.

Topoisomerase-II (Topo-II) was the primary target for various anticarcinogens (e.g. anthracyclines, epipodophy and amsacrine). Through forming drug-Topo-II complexes in cancer cells, these agents promoted DNA strand breaks and affected DNA replication. Decreased sensitivity and activity of Topo-II were important in the development of drug resistance.[43] DNA damage repair played a vital role in drug resistance, especially resistance to Poly (ADPribose) polymerase (PARP) inhibitors in the clinic. The DNA repair proteins, Breast cancer gene 1 (BRCA1), BRCA2 and RecA homolog (RAD51) were client proteins of heat shock protein 90 (Hsp90). Clearance of these proteins by inhibition of Hsp90 was an effective method for overcoming drug resistance to PARP inhibitors. Jiang J et al.[65] provided a novel strategy for the treatment of breast cancer with wild type BRCA1 using the combination therapy targeting Hsp90 to overcome resistance to PARP inhibitors.

CONCLUSION

The molecular diagnostics of cancer rapidly developed in recent years. Molecular targeted anticancer drugs make effect on the basis of their high precision in the treatment of cancer disease. The novel treatment agents of targeted immunotherapy always contain the most cancer subtypes. The cellular signaling targets are important and essential to tumor proliferation, survival and development and are genetically altered in cancer cells. Targeted treatment represents a promising therapeutic approach for patients with diverse cancers.

Mechanisms of chemotherapeutics drug resistance are complex in many fields and cannot be easily solved in clinic. For example, even though numerous studies have been conducted to explore resistance mechanisms to EGFR blockade, it seemed that several biomarkers and pathways were involved in the development of resistance to anti-EGFR therapy. New drugs that aim to a single target still have great limitations in the treatment of cancer. As a result, drug resistance may therefore arise rapidly following treatment with targeted treatment therapy. MDR may occur due to variation in the expression levels of MDR protein. On the basis of individual markers or tumor type alone, adaptation to treatment agents may be explained that why prediction of resistance mechanisms is difficult. It suggests that more complex predictive methods are required to improve the response rates to targeted therapy. Our understanding of the cellular mechanisms underlying death and survival has allowed the development of rational approaches to overcome drug resistance. It is also believed that more factors regulating and controlling the expression of the targeted drug resistance genes will be discovered in the future.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin, 2015; 65: 87–108.
2. Gainkam LO, Huang L, Caveliers V, et al. Comparison of the biodistribution and tumor targeting of two 99mTc-labeled anti-EGFR nanobodies in mice, using pinhole SPECT/micro-CT. J Nucl Med, 2008; 49: 788–795.
3. Friedman M, Ståhl S. Engineered affinity proteins for tumour-targeting applications. Biotechnol Appl Biochem, 2009; 53: 1–29.
4. Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, McLennan MT. Nitrogen mustard therapy; use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemiaand certain allied and miscellaneous disorders. J Am Med Assoc, 1946; 21: 126–132.
5. Jackson JR, Patrick DR, Dar MM, Huang PS. Targeted anti-mitotic therapies: can we improve on tubulin agents? Nat Rev Cancer, 2007; 7: 107–117.
6. Ruegg C, Mutter N. Anti-angiogenic therapies in cancer: achievements and open questions. Bull Cancer, 2007; 94: 753–762.
7. Blattman JN, Greenberg PD. Cancer immunotherapy: a treatment for the masses. Science, 2004; 305: 200–205.

8. Noguchi T, Toiyama Y, Kitajima T, et al. MiRNA-503 promotes tumor progression and is associated with early recurrence and poor prognosis in human colorectal cancer. Oncology, 2016; 90: 221–231.
9. Levitzki A, Klein S. Signal transduction therapy of cancer. Mol Aspects Med, 2010; 31: 287–329.
10. Herr R, Brummer T. BRAF inhibitors in colorectal cancer: Toward a differentiation therapy? Mol Cell Oncol, 2015; 2: e1002709.
11. Weber WA, Morris MJ. Molecular imaging and targeted radionuclide therapy of prostate cancer. J Nucl Med, 2016; 57(Suppl. 3): 3S–5S.
12. Lv Q, Meng Z, Yu Y, et al. Molecular mechanisms and translational therapies for human epidermal receptor 2 positive breast cancer. Int J Mol Sci, 2016; 17.
13. González-Cao M, Karachaliou N, Viteri S, et al. Targeting PD-1/PD-L1 in lung cancer: current perspectives. Lung Cancer (Auckl), 2015; 6: 55–70.
14. Dholaria B, Hammond W, Shreders A, Lou Y. Emerging therapeutic agents for lung cancer. J Hematol Oncol, 2016; 9: 138.
15. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol, 2005; 205: 275–292.
16. Nishida S, Tsubaki M. Exploration of molecular targets in the development of new therapeutics aimed at overcoming multidrug resistance. Yakugaku Zasshi, 2017; 137: 145–149.
17. Wahler J, Suh N. Targeting HER2 positive breast cancer with chemopreventive agents. Curr Pharmacol Rep, 2015; 1: 324–335.
18. Ménard S, Pupa SM, Campiglio M, Tagliabue E. Biologic and therapeutic role of HER2 in cancer. Oncogene, 2003; 22: 6570–6578.
19. Orphanos G, Kountourakis P. Targeting the HER2 receptor in metastatic breast cancer. Hematol Oncol Stem Cell Ther, 2012; 5: 127–137.
20. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab emtansine with or without pertuzumab versustrastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. J Clin Oncol, 2017; 35: 141–148.
21. Welslau M, Diéras V, Sohn JH, et al. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib inhuman epidermal growth factor receptor 2- positive locally advanced ormetastatic breast cancer. Cancer, 2014; 120: 642–651.

22. Keating GM. Afatinib: A review in advanced non-small cell lung cancer. Target Oncol, 2016; 11: 825–835.
23. Rangachari D, Drake L, Huberman MS, et al. Rapidly fatal advanced EGFRmutated lung cancers and the need for rapid tumor genotyping in clinical practice. Cancer Treat Commun, 2016; 9: 41–43.
24. Castellanos EH, Horn L. Generations of epidermal growth factor receptor tyrosine kinase inhibitors: perils and progress. Curr Treat Options Oncol, 2015; 16: 51.
25. Zhao D, Chen X, Qin N, et al. The prognostic role of EGFR-TKIs for patients with advanced non-small cell lung cancer. Sci Rep, 2017; 12: 40374.
26. Zhang H. Three generations of epidermal growth factor receptor tyrosine kinase inhibitors developed to revolutionize the therapy of lung cancer. Drug Des Devel Ther, 2016; 24: 3867–3872.
27. Li X, Yin X, Wang H, et al. The combination effect of homoharringtonine and ibrutinib on FLT3-ITD mutant acute myeloid leukemia. Oncotarget, 2017; 8: 12764–12774.
28. Lagunas-Rangel FA, Chávez-Valencia V. FLT3-ITD and its current role in acute myeloid leukaemia. Med Oncol, 2017; 34: 114.
29. Azari-Yam A, Tavakkoly-Bazzaz J, Semnani Y, et al. FLT3 gene mutation profile and prognosis in adult acute myeloid leukemia. Clin Lab, 2016; 62: 2011–2017.
30. Jin J, Wang JX, Chen FF, et al. Homoharringtonine-based induction regimens for patients with de-novo acute myeloid leukaemia: a multicentre, open-label, randomised, controlled phase 3 trial. Lancet Oncol, 2013; 14: 599–608.
31. Xu G, Mao L, Liu H, Yang M, Jin J, Qian W. Sorafenib in combination with lowdose-homoharringtonine as asalvage therapy in primary refractory FLT3-ITDpositive AML: a casereport and review of literature. Int J Clin Exp Med, 2015; 8: 19891–19894.
32. Pillinger G, Abdul-Aziz A, Zaitseva L, et al. Targeting BTK for the treatment of FLT3-ITD mutated acute myeloid leukemia. Sci Rep, 2015; 21: 12949.
33. Wu H, Hu C, Wang A, et al. Ibrutinib selectively targets FLT3-ITD in mutant FLT3-positive AML. Leukemia, 2016; 30: 754–757.
34. Négrier S, Gravis G, Pérol D, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol, 2011; 12: 673–680.
35. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet, 2009; 373: 1119–1132.
36. Afriansyah A, Hamid AR, Mochtar CA, Umbas R. Targeted therapy for metastatic renal cell carcinoma. Acta Med Indones, 2016; 48: 335–347.

37. Antoniou EA, Koutsounas I, Damaskos C, Koutsounas S. Remission of psoriasis in a patient with hepatocellular carcinoma treated with sorafenib. In Vivo, 2016; 30: 677–680.
38. Cheng AL, Thongprasert S, Lim HY, et al. Randomized, open-label phase 2 study comparing frontline dovitinib versus sorafenib in patients with advanced hepatocellular carcinoma. Hepatology, 2016; 64: 774–784.
39. Zhao B, Wang L, Qiu H, et al. Mechanisms of resistance to anti-EGFR therapy in colorectal cancer. Oncotarget, 2017; 8: 3980–4000.
40. Lopes-Rodrigues V, Oliveira A, Correia-da-Silva M, et al. A novel curcumin derivative which inhibits P-glycoprotein, arrests cell cycle and induces apoptosis in multidrug resistance cells. Bioorg Med Chem, 2017; 25: 581–596.
41. Guo P, Wang S, Liang W, et al. Salvianolic acid B reverses multidrug resistance in HCT-8/VCR human colorectal cancer cells by increasing ROS levels. Mol Med Rep, 2017; 15: 724–730.
42. Salphati L, Plise EG, Li G. Expression and activity of the efflux transporters ABCB1, ABCC2 and ABCG2 in the human colorectal carcinoma cell line LS513. Eur J Pharm Sci, 2009; 37: 463–468.
43. Wang S, Meng Q, Xie Q, Zhang M. Effect and mechanism of resveratrol on drug resistance in human bladder cancer cells. Mol Med Rep, 2017.
44. Azzariti A, Porcelli L, Simone GM, et al. Tyrosine kinase inhibitors and multidrug resistance proteins: interactions and biological consequences. Cancer Chemother Pharmacol, 2010; 65: 335–346.
45. Lu BC, Li J, Yu WF, Zhang GZ, Wang HM, Ma HM. Elevated expression of Nrf2 mediates multidrug resistance in CD133+ head and neck squamous cell carcinoma stem cells. Oncol Lett, 2016; 12: 4333–4338.
46. Colabufo NA, Contino M, Niso M, Berardi F, Leopoldo M, Perrone R. EGFR tyrosine kinase inhibitors and multidrug resistance: perspectives. Front Biosci, 2011; 1: 1811–1823.
47. Galetti M, Petronini PG, Fumarola C, et al. Effect of ABCG2/BCRP expression on efflux and uptake of gefitinib in NSCLC. Cell lines. PLoS One, 2015; 10: e0141795.
48. Yang J, Li S, Wang B, et al. Potential biomarkers for anti-EGFR therapy in metastatic colorectal cancer. Tumour Biol, 2016; 37: 11645–11655.
49. Toomey S, Madden SF, Furney SJ, et al. The impact of ERBB-family germline single nucleotide polymorphisms on survival response to adjuvant trastuzumab treatment in HER2-positive breast cancer. Oncotarget, 2016; 7: 75518–75525.

50. Maximiano S, Magalhães P, Guerreiro MP, Morgado M. Trastuzumab in the treatment of breast cancer. Biodrugs, 2016; 30: 75–86.
51. Masoud V, Pagès G. Targeted therapies in breast cancer: New challenges to fight against resistance. World J Clin Oncol, 2017; 8: 120–134.
52. Proto C, Imbimbo M, Gallucci R, et al. Epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of central nervous system metastases from non-small cell lung cancer: the present and the future. Transl Lung Cancer Res, 2016; 5: 563–578.
53. Minari R, Bordi P, Tiseo M. Third-generation epidermal growth factor receptortyrosine kinase inhibitors in T790M-positivenon-small cell lung cancer: review on emerged mechanisms of resistance. Transl Lung Cancer Res, 2016; 5: 695–708.
54. Di Nicolantonio F, Mercer SJ, Knight LA, et al. Cancer cell adaptation to chemotherapy. BMC Cancer, 2005; 18: 78.
55. Di Pietro G, Magno LA, Rios-Santos F. Glutathione S-transferases: an overview in cancer research. Expert Opin Drug Metab Toxicol, 2010; 6: 153–170.
56. Drozd E, Krzyszton´ -Russjan J, Marczewska J, et al. Up-regulation of glutathionerelated genes, enzyme activities and transport proteins in human cervical cancer cells treated with doxorubicin. Biomed Pharmacother, 2016; 83: 397–406.
57. Sirota R, Gibson D, Kohen R. The timing of caffeic acid treatment with cisplatin determines sensitization or resistance of ovarian carcinoma cell lines. Redox Biol, 2016; 7: 170–175.
58. Khalil HS, Langdon SP, Goltsov A, et al. A novel mechanism of action of HER2 targeted immunotherapy is explained by inhibition of NRF2 function in ovarian cancer cells. Oncotarget, 2016; 7: 75874–75901.
59. Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer, 1972; 26: 239–257.
60. Makin G, Dive C. Modulating sensitivity to drug-induced apoptosis: the future for chemotherapy? Breast Cancer Res, 2001; 3: 150–153.
61. Cardenas C, Montagna MK, Pitruzzello M, Lima E, Mor G, Alvero AB. Adipocyte microenvironment promotes Bclxl expression and confers chemoresistance in ovarian cancer cells. Apoptosis, 2016.
62. Taylor ST, Hickman JA, Dive C. Survival signals within the tumour microenvironment suppress drug-induced apoptosis: lessons learned from B lymphomas. Endocr Relat Cancer, 1999; 6: 21–23.

63. Chresta CM, Arriola EL, Hickman JA. Apoptosis and cancer chemotherapy. Behring Inst Mitt, 1996; 97: 232–240.
64. Meisenberg C, Ashour ME, El-Shafie L, et al. Epigenetic changes in histone acetylation underpin resistance to the topoisomerase I inhibitor irinotecan. Nucleic Acids Res, 2016.
65. Jiang J, Lu Y, Li Z, et al. Ganetespib overcomes resistance to PARP inhibitors in breast cancer by targeting core proteins in the DNA repair machinery. Invest New Drugs, 2017.