Special Article

Targeted Therapy: Novel Agents against Cancer

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Nowadays, malignancies still are crucial problems of healthcare system in many aspects including efficacy of therapeutic modalities, quality of patients' life and cost of treatment. The understanding of genetic alterations and intracellular pathways are very helpful to define the pathologic abnormalities specific to each cancer. Consequently, there have been recently discovered agents which destroy the cancer cells with higher specificity than previously used agents. "Targeted therapy" is established to call this group of drugs because its mechanism of action selectively targets on tumor-specific abnormal cellular processes. These aimed extracellular or intracellular mechanisms are mainly divided into 3 groups; 1) activating natural immune system directly against tumor cells, 2) inhibiting cellular proliferation, 3) inducing tumor anti-angiogenesis. The targeted drugs are currently studied to establish the appropriate regimens for cancers with or without concurrent chemotherapy. It is important to understand and keep updated in these novel agents for better clinical outcome of cancer patients.

***Keywords**: Targeted therapy, HER2 inhibitor, EGFR inhibitor, Anti-angiogenesis, Multikinase inhibitor*

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Since cancer remains an utterly important health problem, there have been many treatments trying to overcome it including advanced surgery techniques, radiation and various chemotherapeutic agents. As we all know, the so called chemotherapy takes its effect by interfering DNA synthesis or cellular mitosis and the most worrying side effect is that it also destroys other normal cells, especially those with rapid proliferation rates. Moreover, it has no specificity to a certain type of cancer. In the two recent decades, a new way of selective cancer killing called "targeted therapy" has been developed with ever high precision. It has proven itself useful in combination with the previous anti-neoplastic drugs. This contributes to profound changes in drug formulas, disease progression and treatment outcomes. This literature will review the general information about targeted therapy-groups, mechanism of actions, and clinical trials.

Pathophysiology

Given detailed analysis on cellular and molecular activities, the proteins involving cancer cell growth and proliferation are identified, also factors promoting angiogenesis. It can be either structural abnormalities or overproduction of these substances that lead to uncontrollable cell replication. And if these proteins are discovered, the therapeutic agents could be designed to target such proteins. A large group of the important proteins in proliferative process is tyrosine kinase which is composed of several members in this family. Tyrosine kinase family is divided by structural similarity into many subfamilies as shown in Fig. 1[1].

As shown in Table 1[2], an abnormality in a chromosome or protein can lead to several types of cancer, thus one drug can be used to combat many cancers. On the other hand, one cancer can be caused from various abnormalities, so it can be treated by a number of drugs.

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Mechanism of Action

To destroy only cancer cells, targeted therapy is designed to have as high selectivity as possible and is divided into 3 groups according to each different mechanism. The first mechanism is to attach to the cell surface and activate the immune system in order to kill cancer cells. The second action is inhibition of signal pathways for cell growth and proliferation. And the last one is to inhibit tumor angiogenesis. Besides, some drugs with multiple sites of antitumor activity are called "Multikinase Inhibitor", and there are some drugs with

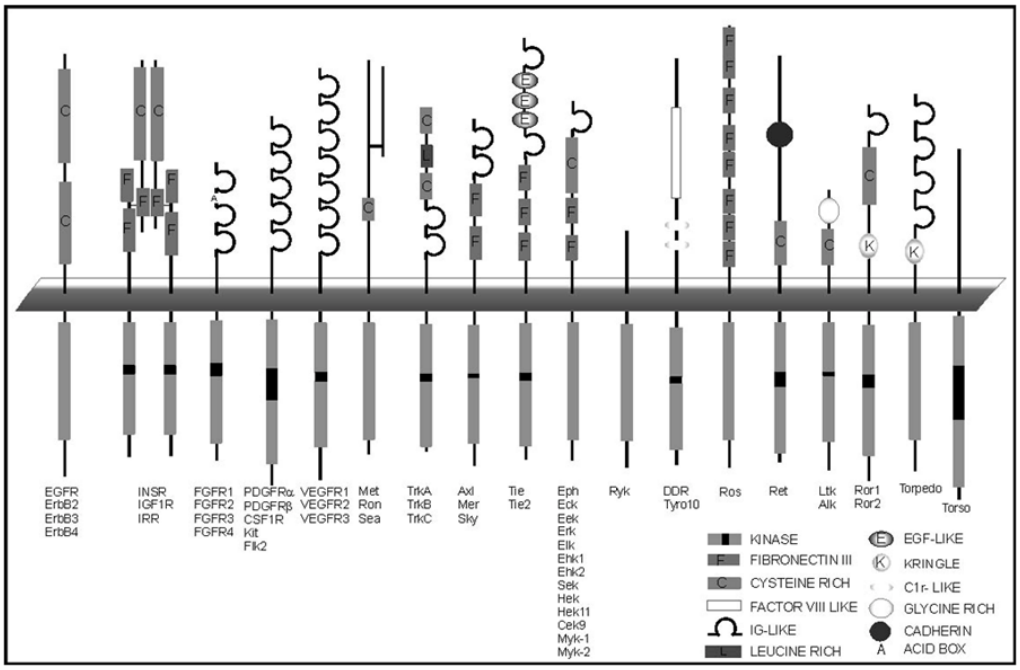

Fig. 1 Tyrosine kinase receptor family members[1].

other methods than the three mentioned above, which will be discussed later on.

There are 2 main different sites of action: extracellular and intracellular. The agents which take their actions outside cell membrane act as "monoclonal antibody". Other substances penetrating cell membrane to block intracellular cascades are called "small-molecule inhibitor". The drugs which attach and directly activate immune system have to be only monoclonal antibody. But the anti-proliferative and anti-angiogenesis groups have members in either of them as shown in Table 2.

Drugs activating immune system

These drugs resemble the monoclonal antibody, binding to a surface antigen. For example, Rituximab, which is the first one that received the United States of America FDA approval, acts as monoclonal antibody of CD20[3]. This antigen expresses on more than 90% of mature B cells in non-Hodgkin lymphoma, but is not found on other normal tissues. As well as non-Hodgkin lymphoma, chronic lymphocytic leukemia (CLL) has CD20 on cell surface and partially responds to the drug. The antigen-antibody complex stimulates immunologic responses via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) for better cancer cell destruction. Similar to Rituximab, Alemtuzumab binds to CD52 on leukemic B-cells in CLL and Gemtuzumab to CD33 on myeloid blast cells in AML.

Drugs inhibiting cell growth and proliferation

The complex cascades of growing and dividing cells need activation of receptors and intracellular signaling pathways. Many novel agents affecting these processes are grouped by site of action to be extracellular and intracellular sites.

Extracellular Targets

The agents inhibit receptors at cell membrane such as EGFR (Epidermal Growth Factor Receptor) and PDGFR (Platelet-Derived Growth Factor Receptor). These receptors are tyrosine kinase receptors and are composed of 3 parts as follow: extracellular ligand binding domain, transmembrane portion, and intracellular tyrosine kinase domain (Fig. 2). Activated kinase molecule induces sequential signaling reactions through several pathways, such as mitogen-activated protein kinase (MAPK) and PI3-kinase/Akt/mTOR, finally tribute to cellular division and differentiation. The drugs in this group are designed to directly target receptors at outer surface of cell membrane as monoclonal antibody.

In the HER (Human Epidermal Growth

Table 1. Abnormal tyrosine kinase molecules identified in many types of cancer[2].

yrosine kinase	malignant disease	
	hematologic malignancy	solid tumor
ALK	anaplastic large cell lymphoma	inflammatory myofibroblastic tumor
ARG	AML	-
BCR-ABL	CML, ALL, AML	-
c-FMS	MDS, AML	-
c-KIT	AML, SM	GIST, seminoma, SCLC, soft-tissue sarcoma
c-MET	-	SCLC, gastric cancer, malignant melanoma
ERB-B1(EGFR)	-	NSCLC, Gliobastoma, CRC, renal cell cancer, pancreatic cancer, ovarian cancer
ERB-B2 (HER-2)	-	breast cancer
ERB-B3		soft tissue sarcoma
FGFR1	EMS, CML	-
FGFR3	MM, T-cell lymphoma	-
FLT3	AML	-
JAK2	CML, ALL, AML	-
NTRK1	-	papillary thyroid carcinoma
NTRK3	AML	fibrosarcoma, breast cancer
PDGFRα	HES, SM, CML	glioblastoma, osteosarcoma, dermatofibrosarcoma, GIST
PDGFRβ	CMML, CML, AML	
RET	-	MEN-2A, MEN-2B, familial medullary thyroid carcinoma
ROS	-	glioblastoma, astrocytoma
SYK	MDS	-
VEGFR1, VEGFR2	-	NSCLC, breast cancer, CRC, prostate cancer

(AML acute myeloid leukemia, ALL acute lymphoblastic leukemia, CMML chronic myelomonocytic leukemia, CML chronic myeloid leukemia, CRC colorectal cancer, EMS 8p11 myeloproliferative syndrome, GIST gastrointestinal stromal tumor, HES hypereosinophilic syndrome, MEN multiple endocrine neoplasia, MDS myelodysplastic syndrome, MM multiple myeloma, NSCLC non-small cell lung cancer, SCLC small cell lung cancer, SM systemic mastocytosis)

Table 2. Sites of mechanism of action of targeted therapy.

sites of mechanism	monoclonal antibody	small-molecule inhibitor
EGFR	Cetuximab, Panitumumab	Gefitinib, Erlotinib, Lapatinib
HER2	Trastuzumab	Lapatinib
SCR	-	Dasatinib, Bosutinib
mTOR	-	Temsirolimus
RAF	-	Sorafinib
VEGF	Bevacizumab	-
VEGFR	-	Sorafenib, Sunitinib

Receptor) group, there are 4 subgroups that share similar structures – Epidermal Growth Factor Receptor (EGFR;ERB-B1), HER2/neu (ERB-B2), HER3 (ERB-B3) and HER4 (ERB-B4). As shown in table 1, both EGFR and HER2/neu are found overactive or overexpressed in many epithelial cell cancers.

HER2 Inhibitor:

Trastuzumab is monoclonal antibody blocking HER2 (as demonstrated in Fig. 3) which is discovered that increases in 15-30% of breast cancer[3,4]. It is very helpful in combination with Taxane-based chemotherapy for metastatic HER2-positive breast

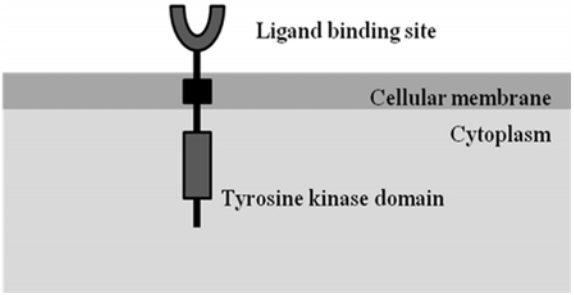

Fig. 2 Molecular structure of tyrosine kinase (adapted from Rosa DD et al[4])

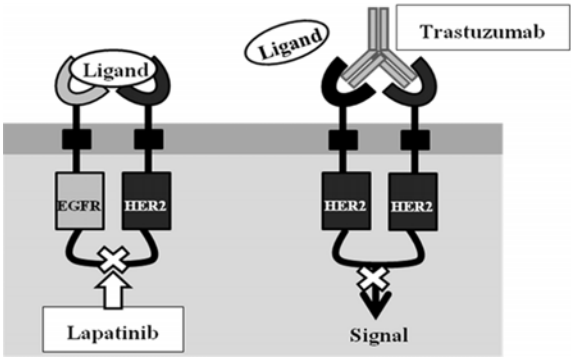

Fig. 3 Mechanism of action of HER2 inhibitor (adapted from Rosa DD et al[4])

cancer[5,6]. The less relapsed rate, longer disease-free survival time and median survival time were found in Trastuzumab and chemotherapy compared to chemotherapy alone. The recent studies also demonstrate clinical benefit of Trastuzumab combining in the adjuvant therapy for HER2-overexpressed non-metastatic breast cancer[7-9].

EGFR inhibitor:

EGFR is found in several types of malignancy as shown in Table 3[12] and EGFR inhibitor can treat many cancers, however the clinical trials have proven the clinical usefulness in few diseases. For example, metastatic colorectal cancer with resistance to Irrinotecan alone is beneficially treated by Cetuximab combined with Irrinotecan with higher response rate[10]. Because inhibiting EGFR reduces cellular integrity of skin, rash is the major side effect of which more severity correlates with greater clinical response and survival rates. Besides, studies showed that Cetuximab was also beneficial in combination with platinum-based chemotherapy for metastatic and relapsed squamous cell carcinoma of head and neck and provided

Table 3. Proportion of EGFR expression in various tumor types[12].

Malignancy	EGFR expression percentage
Head and neck	80-100
Renal	50-90
Lung	40-80
Breast	14-91
Colon	25-77
Ovary	35-70
Prostate	39-47
Glioma	40-63
Pancreas	30-50
Bladder	31-48

radiosensitization effect for locally advanced tumor[11].

Panitumumab is proven beneficial in metastatic colorectal cancer expressing EGFR and refractory to Oxaliplatin and Irrinotecan. Although this new agent improves progression-free survival time, it does not affect overall survival rate[13].

Intracellular Targets

Receptor kinase inhibitors:

As mentioned above, tyrosine kinase receptor has 3 parts on cell membrane. Its function can be blocked at intracellular site by the agents with small molecule, then the downstream cascades can not be activated.

The intracellular inhibitors for EGFR are Gefitinib and Erlotinib (Fig. 4). They provide the better response and outcome of treatment for patient with chemotherapy-refractory non-small cell lung cancer. The group of patient with EGFR mutation has higher response rate than the other group without mutation. There is no significant change in overall survival rate from both of them, however, the favorable outcome of survival benefit is found in Erlotinib compared with placebo[14,15].

Lapatinib, as shown in Table 2, inhibits both EGFR and HER2. It is used to treat metastatic breast cancer with HER2 overexpression, especially in brain metastasis, and those do not response to Trastuzumab. This is because Lapatinib is one of the small molecule inhibitors which can pass through the blood-brain barrier better[16].

Signaling kinase inhibitors:

After the activation of transmembranous kinase receptor, there are many downstream processes

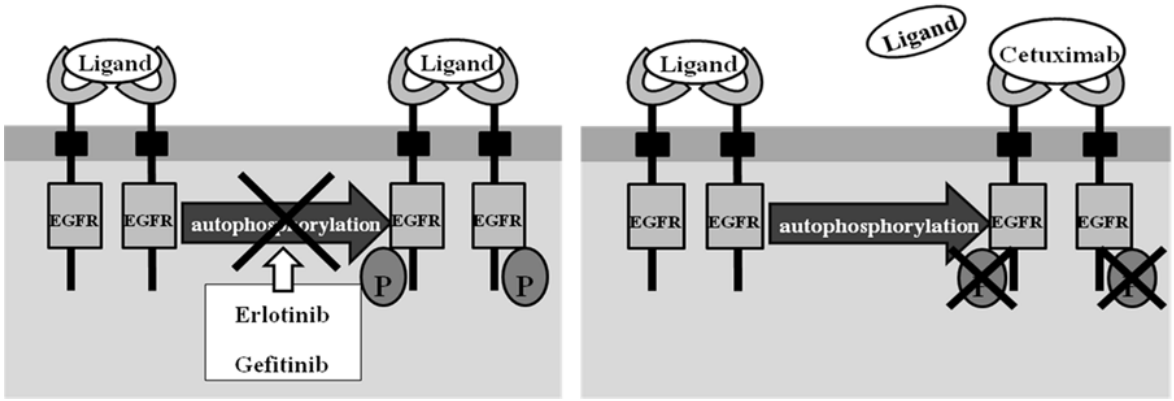

Fig. 4 Mechanism of action of EGFR inhibitor (adapted from Rosa DD et al[4]).

responsible for cell growth, proliferation, differentiation and even angiogenesis of tumor, as shown in Fig. 5[12]. PI3k/Akt/mTOR and mitogen-activated protein kinase (MAPK) pathway are the complicated processes and involve various substances which are non-receptor kinase proteins within the cell such as PI3k, Akt, mTOR, RAS, and RAF. Effective drugs have to be small-molecule inhibitors in order to provide their function at the intracellular sites.

SRC:

The c-SRC is the first discovered proto-oncogene. Its producing protein is a non-receptor tyrosine kinase. Once SRC is stimulated, there will be cell growth and division. Dasatinib inhibits both SRC and ABL. This drug significantly profits in Philadelphia-chromosome-positive chronic myeloid leukemia (Ph+ CML) and acute myeloblastic leukemia (Ph+ ALL) which resist to Imatinib[17]. Bosutinib aiming to treat breast cancer and CML is in the study phase.

PI3k/Akt/mTOR Pathway:

PI3k (phos- phoinositide3'-kinase), Akt, and mTOR (mammalian target of Rapamycin) are non-receptor serine/threonine kinases which gather and amplify signals from other receptor kinases resulting in cellular proliferation. The process starts from PI3k activation by receptor kinases, changing to 3'-phosphoinositides (PIP3). While phosphoinositide-dependent kinase 1 (PDK1) is produced increasingly. Then both PIP3 and PDK1 stimulate Akt and mTOR. This consequently leads to excessive intracellular protein synthesis. Many studies indicate that the increased activation of PI3k/Akt/mTOR pathway relates to carcinogenesis, also bad prognosis and chemotherapy-resistance of tumor[17].

Various agents inhibiting this pathway target at different sites in the downstream flow such as PI3k, PDK1, Akt or mTOR. Two mTOR inhibitors approved by FDA, Temsirolimus and Everolimus, are proven to prolong the median overall survival in terminal stage renal cell carcinoma[18,19]. Rapamycin is formerly used as an immunosuppressive drug for patients undergone organ transplantation, but the indication for cancer treatment is controversial. Other drugs in this group are in the study phase, for example, Deforolimus (mTOR inhibitor) and Perifosine (Akt inhibitor).

Mitogen-Activated Protein Kinase (MAPK) Pathway:

This pathway starts from RAS, which is an intracellular protein, receiving the aggravation from growth factor or cytokines, then sends signal to the RAF, MEK, and ERK (extracellular signal-regulated kinase) respectively, as shown in Fig. 5[12]. It regulates numerous functions such as gene transcription, cellular proliferation and differentiation. Drugs in the RAS inhibitor group (also known as farnesyl transferase inhibitor; FTI), such as Tipifarnib and Lonafarnib, and MEK inhibitor group are still in clinical trial phase. There is one FDA approved RAF inhibitor, Sorafenib, which will be discussed later in the section "Multikinase inhibitor".

Drugs inhibiting tumor angiogenesis (Anti-angiogenesis)

Angiogenesis is the production of new vessels beyond normal vasculature of organ because any tissue changing to tumor needs more oxygen and nutrients. Folkman J reported in 1971 that the tumor 2 mm^3 of size

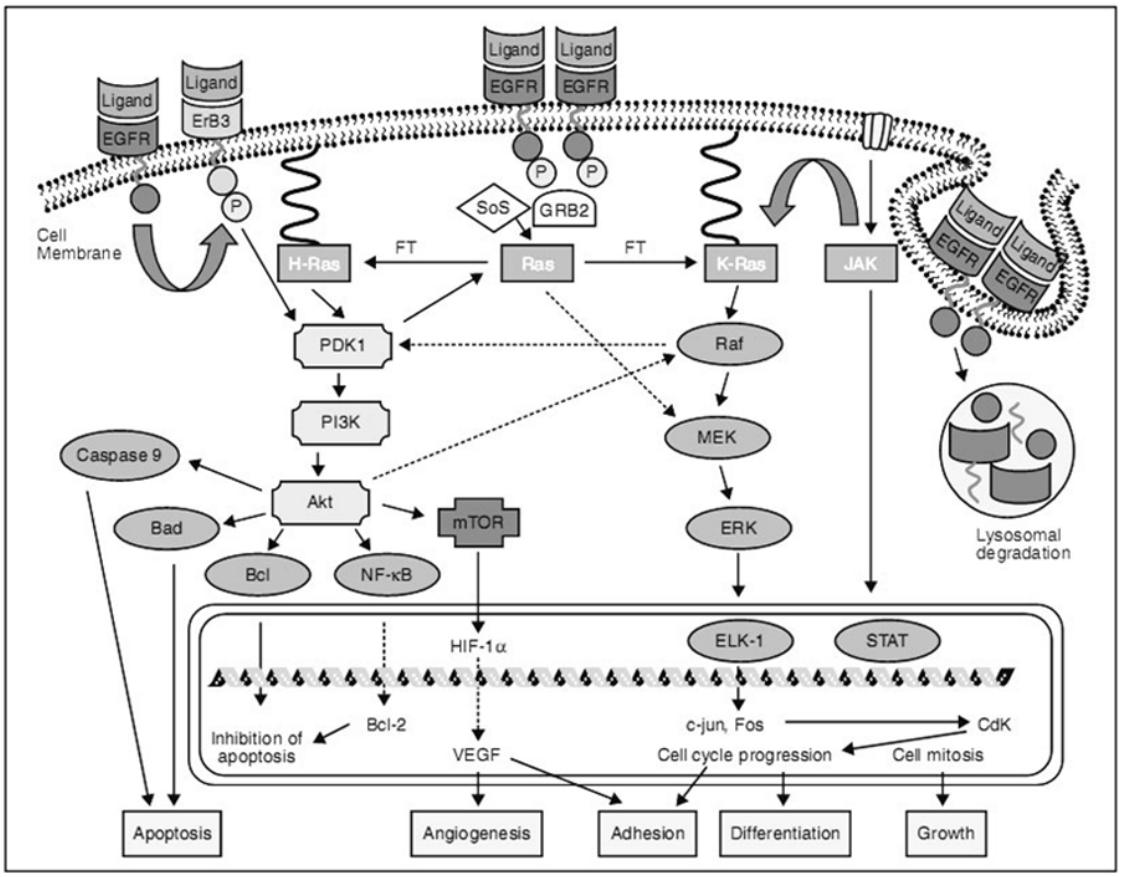

Fig. 5 Intracellular signaling pathways involving cellular proliferation[12]

started its neovascularization for further growth. Then inhibition of angiogenesis is cessation of tumor progression[17].

VEGF (vascular endothelial growth factor), PDGF (platelet-derived growth factor), and FGF (fibroblast growth factor) are some examples of factors involving in angiogenesis. VEGF is divided into 6 subtypes " VEGF-A (known as VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PlGF (placenta growth factor). Many studies showed that VEGF played an important role in neovascularization and endothelial cell growth. Moreover, both VEGF-C and VEGF-D promote lymphagiogenesis which is important for tumor cells to spread to distant organs. These VEGFs bind to VEGFR-1 (*fms*-like tyrosine kinase; flt-1), VEGFR-2(KDR/flk-1), or VEGFR-3(flt-4), as shown in Fig. 6. After VEGF-VEGFR binding, PI3k/Akt/mTOR and MAPK pathways are activated, then induce other substances involving neovascularization such as hypoxia-induced factor (HIF-1, HIF-2), PDGF, and basic fibroblast growth factor (bFGF). Anti-angiogenesis can reduce tumor

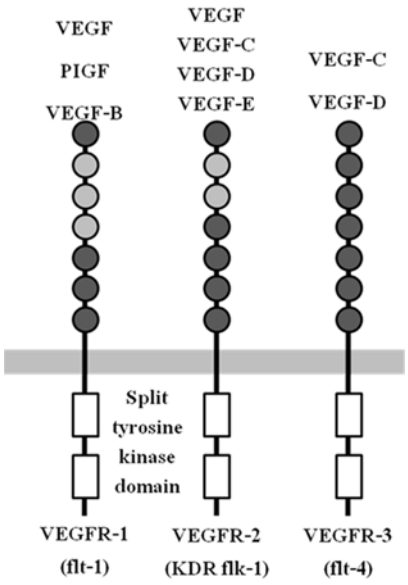

Fig. 6 Structure of VEGFR (adapted from Neufeld G et al[22])

neovascularzation by blocking either VEGF or VEGFR.

There are evidences supporting that the additional effect of anti-angiogenesis drugs is the normalization of blood vessels. It means less fluid and protein leakage are observed with the decrease in interstitial pressure, then chemotherapeutic substances can be better delivered to the target tissue. As a result, anti-angiogenesis is claimed to enhance the effect of concurrent chemotherapy and radiation.

The one widely used and very important anti-angiogenesis is Bevacizumab, a monoclonal antibody binding to VEGF[21]. By combining Bevacizumab with a chemotherapy containing 5-fluouracil/leucovorin to treat metastatic colorectal cancer, it is proven beneficial in increasing response rate, prolonging progression-free survival and overall survival period[23,24]. For patients with non-small cell lung cancer, using Bevacizumab, Paclitaxel, and Carboplatin together is also found helpful in adenocarcinoma cell type by increasing both response and overall survival rates[25]. Besides, there are ongoing clinical studies in using Bevacizumab as a combination with Interferon in renal cell cancer, and with Paclitaxel in breast cancer.

In angiogenesis, the pericytes play important roles including endothelial cells signaling, capillary growth and blood flow controlling. Abnormal pericytes within tumor have bizarre morphology and loose association with endothelial cells. Its function is regulated through PDGFR signaling. Then any agents which target PDGFR provide additional effect in normalization of blood vessels[26]. The combination of anti-VEGF (*e.g.* Bevacizumab) and anti-PDGF (*e.g.* Imatinib) should be more effective than anti-VEGF monotherapy. The other way for combined therapy is the agent affecting both VEGFR and PDGFR in single drug such as Sunitinib and Sorafenib (Table 4). They are "multikinase inhibitors" and are mentioned below.

Multikinase Inhibitors

As previously shown in Table 1, a certain drug can be applied to various types of cancer, because the overexpressed tyrosine kinase is found in different cancer cell types. On the other hand, there can be various abnormal tyrosine kinases in a certain type of cancer. Chronic myeloid leukemia is an exception since abnormal BCR-ABL is up to 90% responsible for it. For other cancers, several tyrosine kinase abnormalities are found in different proportions such as gastrointestinal stromal tumor (GIST) which contains c-KIT (CD117) and PDGFR (as shown in Fig. 7) about 80% and 5-8%, respectively[27,28]. That fact explains why a drug inhibiting a single site of tyrosine kinase may not be enough, so multitargeted therapy is invented with the aim to stop cancer growth in many ways with several mechanisms of action as shown in Table 4. Some drugs inhibit cell proliferation by taking action at tyrosine kinase and intracellular signaling pathway altogether, while others provide both cellular proliferative inhibition and anti-angiogenesis. Similarly, multikinase inhibitors with anti-angiogenetic effect can attack many sites such as VEGFR and PDGFR. Multitargeted therapy reduces a number of

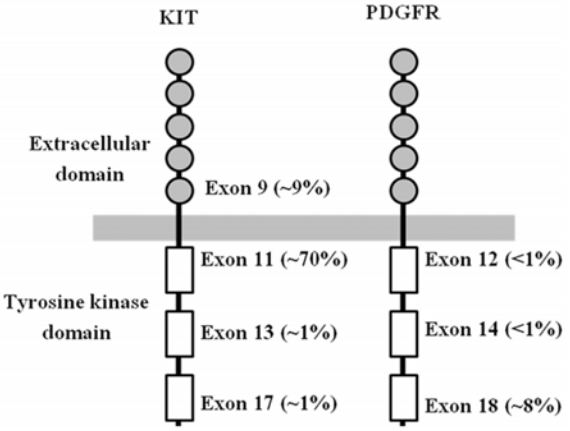

Fig. 7 Distribution of KIT and PDGFR mutations found in GIST (adapted from Bauman JE et al[26])

Table 4. Affecting sites for action of multikinase inhibitors[31].

Drugs	Mechanism of Action							
	VEGFR	PDGFR	KIT	FLT3	RET	RAF	SRC	BCR-ABL
Imatinib		✓	✓					✓
Sunitinib	✓	✓	✓	✓	✓			
Sorafenib	✓	✓	✓		✓	✓		
Dasatinib		✓	✓				✓	✓

Table 5. Drugs in targeted therapy with FDA approval[17, 41-43].

Generic name	Trade name	Target	Type	Approved indication	Toxicity	US FDA approval
Rituximab	Mabthera, Rituxan	CD20	monoclonal antibody	B-cell NHL CD20 positive: relapsed or refractory low-grade or follicular type	fever, chill, nausea, urticaria	November 1997
Trastuzumab	Herceptin	HER2	monoclonal antibody	Breast cancer with HER2-overexpression: adjuvant in node- positive; metastatic disease	cardiotoxicity	October 1998
Imatinib	Glivec, Gleevec	c-KIT (CD117), BCR-ABL, PDGFR	Small-molecule inhibitor	CML Philadelphia positive: chronic phase newly diagnosed or after IFN-a failure; blast crisis, accelerated phase ALL Philadelphia positive: relapsed or refractory GIST c-KIT positive: unresectable or metastatic disease; adjuvant therapy after resection	nausea, diarrhea, myalgia, edema	May 2001
Bortezomib	Velcade	Proteosome	Small-molecule	Multiple myeloma: initial treatment; relapsed Mantle cell lymphoma: relapsed disease after at least 1 prior treatment	GI symptoms, fatigue, sensory thrombocytopenia neuropathy	May 2003
Gefitinib	Iressa	EGFR	Small-molecule inhibitor	Non-small cell lung cancer: locally advanced or metastatic disease after failure of platinum-based and docetaxel chemotherapy	diarrhea, nausea, rash, pulmonary toxicity	May 2003
Bevacizumab	Avastin	VEGF	Monoclonal antibody	Colorectal cancer: first-line for metastatic disease Non-small cell lung cancer: unresectable, recurrent or metastatic disease Breast cancer: metastasis of HER2-negative Renal cell carcinoma: metastatic disease	hypertension, intestinal perforation	February 2004
Cetuximab	Erbitux	EGFR	Monoclonal antibody	Colorectal cancer: metastatic disease Squamous cell carcinoma of head and neck: locally advanced disease combined with radiation; recurrence, metastasis after platinum-based therapy	acneiform rash, folliculitis, hypersensitivity reaction	February 2004
Erlotinib	Tarceva	EGFR	Small-molecule inhibitor	Non-small cell lung cancer: locally advanced or metastatic disease after at least 1 chemotherapy Pancreatic adenocarcinoma: combined with gemcitabine for first-line in unresectable or metastatic disease	diarrhea, acne-like skin rash	November 2004
Azacitidine	Vidaza	DNMT	Nucleoside analogue	poor-risk MDS	BM suppression, GI disturbance, fever, arthralgia, petechiae	May 2004

Table 5. Cont.

Generic name	Trade name	Target	Type	Approved indication	Toxicity	US FDA approval
Sorafenib	Nexavar	VEGFR-2,-3, PDGFR-b, FLT-3, RET, RAF	Small-molecule inhibitor	Renal cell carcinoma: advanced or metastasis disease Hepatocellular carcinoma: advanced or unresectable disease	diarrhea, anorexia, rash, hand foot syndrome, hyper-tension, fatigue	December 2005
Sunitinib	Sutent	VEGFR-1,-2, -3, PDGFR-a, -b, c-KIT, FLT3, RET	Small-molecule	GIST: refractory to Imatinib Renal cell carcinoma: advanced or metastatic disease	hypertension, bullous skin lesion, yellow stomatitis, skin coloration, hair depigmentation, hand foot syndrome	January 2006
Dasatinib	Sprycel	BCR-ABL, c-KIT, SRC, PDGFR-b	Small-molecule inhibitor	CML: chronic, accelerated, blast phase with intolerance or resistance to Imatinib ALL Philadelphia positive: refractory to Imatinib	myelosuppression, fluid retention, GI bleeding	June 2006
Panitumumab	Vectibix	EGFR	Monoclonal antibody	Colorectal cancer: metastatic disease refractory to chemotherapy with no KRAS mutation	acneiform rash, diarrhea paronychia, fatigue	September 2006
Decitabine	Dacogen	DNMT	Nucleoside analogue	poor-risk MDS	hyperbilirubinemia, pneumonia	May 2006
Lapatinib	Tykerb	EGFR, HER2	Small-molecule inhibitor	Breast cancer HER2 overexpression: advanced or metastatic disease after chemotherapy Trastuzumab failure	diarrhea, rash, anorexia, nausea, vomitingor	March 2007
Temsirolimus	Torisel	mTOR	Rapamycin analogue	Renal cell carcinoma: recurrent or metastatic disease	asthenia, anemia, dyspnea	May 2007
Everolimus	Afinitor	mTOR	Rapamycin analogue	Renal cell carcinoma: advanced disease after failure of Sunitinib or Sorafenib	anorexia, rash, mucositis, headache hyperlipidemia	March 2009

chemotherapy exposure, decreases drug interaction, reduce side effects, is easily administered, and is less likely to cause drug resistance.

As mentioned earlier, BCR-ABL abnormality is found up to 90% in CML, then Imatinib is a good choice especially in chronic-phase CML which resists to Interferon. Imatinib is also used in GIST (gastrointestinal stromal tumor) by inhibiting both KIT and PDGFR which are found in the percentages as mentioned above. This fact explains that Imatinib can also provide clinical benefit in c-KIT negative tumor. It is highly recommended for unresectable tumor or metastatic disease. Studies showed 52-54% tumor shrinkage, 28-32% stable tumor size, and only 12-14% primary resistance[29,30]. The resistance could be found after previously-used responsive patient group, called secondary resistance, about 40%[31]. In resistant group, it is considerable for Sunitinib which is proven to slow down disease progression by 4 times and improve overall survival rate[32]. Besides, studies comparing Interferon therapy with Sunitinib in metastatic renal cell carcinoma revealed better response rates using Sunitinib[31].

Sorafenib is another drug belonging to multikinase inhibitor group with clinical application to improve progression-free survival in metastatic renal cell carcinoma[33]. It is investigated in ongoing trial phase for the treatment of hepatocellular carcinoma, and is found to significantly slow tumor progression and prolong survival time[34].

Miscellaneous

Ubiquitin-Proteosome Inhibitors

Ubiquitin-Proteosome system is the cellular protein degradation especially those built with abnormal structures, damaged ones, and oncogenic proteins. These proteins are marked by ubiquitin, then are directly degraded by proteosome complex. The function of this system is needed for cell cycle regulation, proliferation and differentiation. To inhibit the ubiquitin-proteosome system is to stop cell growth and division; moreover, it induces apoptosis and decreases chemotherapy resistance.

Bortezomib, a boronic acid derivative, is the first proteosome inhibitor. Its action is blocking proteosome, thus increase the level of cyclin-dependent kinase inhibitor (CDKI) p21. A rise in CDKI p21 level ceases cellular proliferation in G2-M phase leading to apoptosis[4]. Bortezomib has its clinical use in multiple myeloma (MM) as both second-line for refractory disease[35] and initial treatment in combination with Melphalan and Prednisolone. There are higher response and overall survival rates compared to the control group without Bortezomib[36].

Epigenetic Modulators

Agents in this group involve in the changes in gene expression without alteration of genetic DNA sequence itself. The "turning on" and "shutting down" of tumor suppressor gene expression are the result of many processes such as DNA methylation and histone

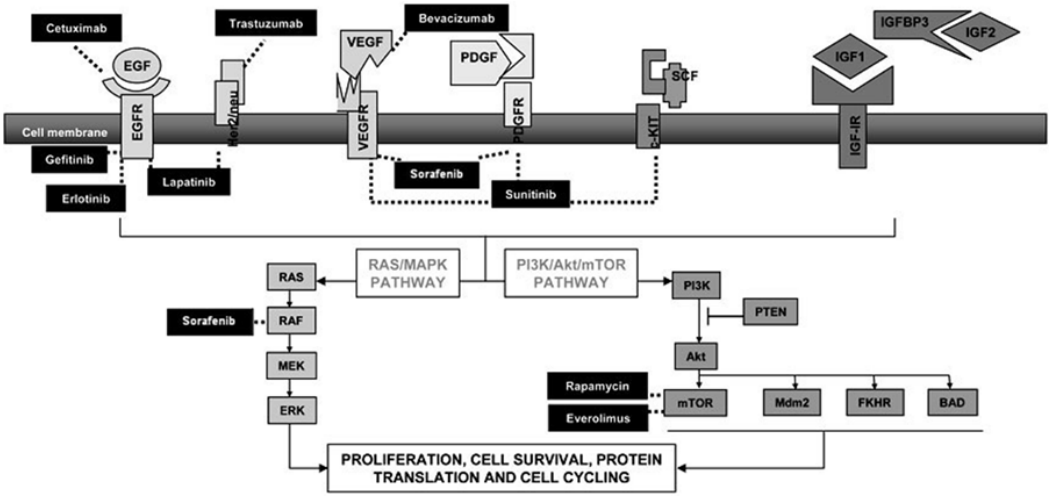

Fig. 8 Variety of targeted therapy and mechanism of action[21]

modification. Both DNA methylation by DNA methyltransferases (DNMTs) and histone deacetylation by histone deacetylases (HDACs) inhibit RNA translation and protein production from tumor suppressor gene. All of the mentioned finally result in malignant change of the cell. Thus, the purpose of epigenetic modulators is inhibiting both DNMTs and HDACs, enabling the tumor suppressor gene to express and regain proper function.

DNA Methyltransferase Inhibitors (DNMTis)

The addition of a methyl group to a specific location of DNA sequence induces the DNA strands to wrap around histones tightly. The tumor suppressor gene, which is nearby the attached sequence, will be blocked and cannot express its function. The two FDA-approved DNMTis are Azacitidine and Decitabine which are used in treating poor-risk myelodysplastic syndrome with significant higher response rate and longer median time to leukemic transformation[37-39]. They also improve quality of life of these patients.

Histone Deacetylases Inhibitors

Histone acetylation by histone acetyltransferases (HATs) adds acetyl group to histone, loosens the complex and allows gene expression. On the contrary, deacetylation enhances the tightening of complex and can induce tumor formation. Although HDAC inhibitors act as epigenetic modulators, they also inhibit other proteins by hyperacetylation such as Raf, Akt, ErbB2, and Bcr-Abl. Their actions targeting multiple pathways enhance the antitumor effect. So far there is only one FDA-approved drug called Vorinostat which is a hydroxamine acid derivative, used in cutaneous T-cell lymphoma after the second failure to chemotherapies. Studies showed approximately 30% response rate[40].

Conclusion

Given details about mechanism of action and clinical application of targeted therapy, it is helpful in many types of cancer. Most of the recent studies demonstrated clinical benefit of targeted therapy in advanced stage cancers, inoperable tumor or metastatic disease, by single drug administration with or without chemotherapy. Nevertheless, targeted therapy is recently discovered and developed, so there need to be more studies about indications in early stage of cancer, combination with chemotherapy regimens or other targeted agents, and also drug interactions. It is crucial for physicians treating patients with cancer to keep updated for better treatment outcomes and quality of life.

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การรักษาแบบมุ่งเป้า : ยากลุ่มใหม่ในการรักษาโรคมะเร็ง

อัสนี ทองอยู่

โรคมะเร็งยังคงเป็นปัญหาด้านสาธารณสุขที่สำคัญ ทั้งในเรื่องของผลการรักษา คุณภาพชีวิตของผู้ป่วย และค่าใช้จ่ายในการรักษาพยาบาล ความรู้ความเข้าใจในการเปลี่ยนแปลงในสารพันธุกรรม และกระบวนการต่าง ๆ ภายในเซลล์ มีประโยชน์อย่างมากในการระบุความผิดปกติที่ก่อให้เกิดโรคมะเร็งขึ้น และนำไปสู่การคิดค้นยาชนิดใหม่ที่สามารถทำลายจำเพาะต่อเซลล์มะเร็ง เรียกว่า "การรักษาแบบมุ่งเป้า" โดยออกฤทธิ์ผ่านกระบวนการหลัก ๆ 3 แบบ ได้แก่ 1) กระตุ้นระบบภูมิคุ้มกันให้ทำลายเซลล์มะเร็งโดยตรง 2) ยับยั้งการเจริญเติบโตของเซลล์ และ 3) ยับยั้งการสร้างหลอดเลือดใหม่ที่เข้าไปเลี้ยงเซลล์มะเร็ง ยาในกลุ่มนี้ยังอยู่ในระหว่างการศึกษาอีกมาก เพื่อค้นหาวิธีการบริหารยาที่เหมาะสม ทั้งที่ให้ยาเพียงชนิดเดียวหรือให้ร่วมกับยาเคมีบำบัด จึงจำเป็นที่จะต้องติดตามผลการศึกษาที่ทันสมัยเพื่อให้การรักษาผู้ป่วยโรคมะเร็งได้ผลที่ดีขึ้น