World Cancer Research Journal WCRJ 2015; 2 (3): e553

OVERVIEW OF FDA-APPROVED ANTI CANCER DRUGS USED FOR TARGETED THERAPY

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Absract – *Rationale:* *Targeted cancer therapies are drugs designed to interfere with specific molecules necessary for tumor growth and progression. Traditional cytotoxic chemotherapies usually kill rapidly dividing cells in the body by interfering with cell division while causing toxicity in normal cells too. Inter-individual pharmacokinetics (PK) variability is often large and variability observed in response to target therapy is influenced not only by the heterogeneity of drug targets, but also by the pharmacogenetic background of the patient (e.g. cytochome P450 and ABC transporter polymorphisms), patient characteristics such as adherence to treatment and environmental factors (drug-drug interactions).*

Upgrading: *This review aim to highlight the most recent FDA-approved anticancer drugs eligible for targeted therapies related to toxicity (i.e. genes of metabolic pathways) and resistance (i.e DNA repair genes). In addition, a comprehensive field related to drug-drug interaction, is proposed and discussed. Moreover, an early outline evaluation of the costs of the therapies were taken in consideration.*

Conclusions: *Based on these fields, the oncologists will have new means to make treatment decisions for their patients in order to maximize benefit and minimize toxicity.*

KEY WORDS: *Monoclonal antibodies, Small molecules, Tyrosine kinase inhibitors, Cost-effectiveness, Genotyping cost, Targeted therapies.*

INTRODUCTION

A primary goal of targeted therapy is to fight cancer cells with more precision and potentially fewer side effects. For this reason it is a promising therapy for the 3rd millennium[1]. Traditional cytotoxic chemotherapy works primarily through the inhibition of cell division. In addition to cancer cells, other rapidly dividing cells (e.g. hair, gastrointestinal epithelium, bone marrow) are affected by these drugs. Drugs for targeted therapies are primarly tyrosine kinase inhibitors (TKIs), monoclonal antibodies (mAbs) interfering RNA molecules, and microRNA. In contrast, targeted therapy blocks the proliferation of cancer cells by interfering with specific molecules required for tumor development and growth. Some of these molecules may be present in normal tissues, but they are often mutated or overexpressed in tumors[2].

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Targeted therapies, which include mAbs and Small molecule inhibitors (SMinhs), have significantly changed the treatment of cancer over the past 15 years. These drugs are now a component of therapy for many common cancers, including breast, colorectal, lung and pancreatic, lymphoma, leukemia and multiple myeloma. The mechanisms of action and toxicities of targeted therapies differ from those of traditional cytotoxic chemotherapy. Targeted therapies are generally better tolerated than traditional chemotherapy, but they are associated with several toxicities, such as acneiform rash, cardiac dysfunction, thrombosis, hypertension and proteinuria, or resistance because acquired mutations on target molecules. The SMinhs are metabolized by cytochrome P450 enzymes and are subject to multiple drug interactions. Targeted therapy has raised new queries about cancer treatment to tailored on individual patient's tumor, the assessment of drug benefits, and the cost-effectiveness of healthcare. As more subjects are diagnosed with cancer and as these patients live longer, primary care physicians will increasingly provide care for patients who have received targeted therapy.

CLASSIFICATION AND NAMING

Targeted cancer agents are broadly classified as either monoclonal antibodies or small molecules.

Therapeutic monoclonal antibodies are immunoglobulin structures designed to target specific antigens found on the cell surface, such as transmembrane receptors or extracellular growth factors. In some cases, monoclonal antibodies are conjugated to radio-isotopes or toxins to allow specific delivery of these cytotoxic agents to the intended cancer cell target.

Small molecules are usually designed to interfere with the enzymatic activity of the target protein. They can penetrate the cell membrane to interact with targets inside a cancer cell.

As with any drug, targeted cancer therapies typically have several different names. One or more names is used to identify the chemical compound during development; if successful, the drug receives a generic name and then a brand name is used by the pharmaceutical company for marketing. For example, the small molecule STI-571 became known as imatinib (generic name) and is marketed by Novartis under the brand name Gleevec™.

The name of a targeted agent provides clues to the type of agent and its cellular target.

Monoclonal antibodies end with the stem "-mab" (monoclonal antibody). Monoclonal antibodies have an additional subsystem designating the source of the compound e.g., "-ximab" for chimeric human-mouse antibodies, "-zumab" for humanized mouse antibodies, and "-mumab" for fully human antibodies.

Small molecules end with the stem "-ib" (indicating that the agent has protein inhibitory properties). Both monoclonal antibodies and small molecules contain an additional stem in the middle of the name describing the molecule's target; examples for monoclonal antibodies include "-ci-" for a circulatory system target and "-tu-" for a tumor target, while examples for small molecules include "-tin-" for tyrosine kinase inhibitors and "-zom-" for proteasome inhibitors. At the beginning of the generic name there is a prefix that is unique for each agent (Table 1).

MONOCLONAL ANTIBODIES

Since ten years, almost 30 monoclonal antibodies have been approved and adopted in clinical therapy, about one half of them for the treatment of cancer (Table 2). Among the earliest targeted therapies were antibodies directed against the cell surface markers cluster of differentiation 20 (CD20), CD33, and CD52, which are present on lymphoma and leukemia cells. Because CD20 is

Table 1. Some examples of target drugs nomenclature.

Monoclonal antibodies	
Bevacizumab	Humanized monoclonal antibody with a circulatory system target (VEGF-A)
Rituximab	Chimeric monoclonal antibody with a tumor target (CD20)
Ipilimumab	Fully human antibody with an immune system target (CTLA-4)
Small molecule inhibitors	
Bortezomib	Small molecule proteasome inhibitor
Imatinib	Small molecule tyrosine kinase inhibitor
Seliciclib	Small molecule cyclin-dependent kinase inhibitor

Table 2. The FDA has approved targeted drug cancer therapies. A partial list of currently approved targeted therapies for cancer and their molecular targets (in alphabetic order).

Targeted Drugs	Target(s)	FDA-approved indication(s)	Annotations
Ado-trastuzumab[$] emtansine (Kadcyla)	HER2 (ERBB2/neu)	Breast cancer (HER2+)	Detection of HER2 by immunohistochemistry (IHC) methods
Afatinib (Gilotrif)	EGFR (HER1/ERBB1), HER2 (ERBB2/neu)	Non-small cell lung cancer (with EGFR exon 19 deletions or exon 21 substitution (L858R) mutations)	
Aldesleukin (Proleukin)	IL2 Receptor	Renal cell carcinoma Melanoma	
Axitinib (Inlyta)	KIT, PDGFRβ, VEGFR1/2/3	Renal cell carcinoma	
Belinostat (Beleodaq)	HDAC	Peripheral T-cell lymphoma	
Bevacizumab (Avastin)	VEGF ligand	Cervical cancer Colorectal cancer Fallopian tube cancer Glioblastoma Non-small cell lung cancer Ovarian cancer Peritoneal cancer Renal cell carcinoma	
Bortezomib (Velcade)	Proteasome	Multiple myeloma Mantle cell lymphoma	
Bosutinib (Bosulif)	ABL	Chronic myelogenous leukemia (Philadelphia chromosome positive)	Monitor acquired mutation of ABL
Brentuximab vedotin (Adcetris)	CD30	Hodgkin lymphoma Anaplastic large cell lymphoma	
Cabozantinib (Cometriq)	FLT3, KIT, MET, RET, VEGFR2	Medullary thyroid cancer	
Canakinumab (Ilaris)	IL-1β	Juvenile idiopathic arthritis Cryopyrin-associated periodic syndromes	
Carfilzomib (Kyprolis)	Proteasome	Multiple myeloma	
Ceritinib (Zykadia)	ALK	Non-small cell lung cancer (with ALK fusion)	
Cetuximab (Erbitux)	EGFR (HER1/ERBB1)	Colorectal cancer (KRAS wild type) Squamous cell cancer of the head and neck	
Crizotinib (Xalkori)	ALK, MET	Non-small cell lung cancer (with ALK fusion)	
Dabrafenib (Tafinlar)	BRAF	Melanoma (with BRAF V600 mutation)	
Dasatinib (Sprycel)	ABL	CML t(9;22) positive Acute lymphoblastic leukemia (ALL) t(9;22) positive	Monitor acquired mutation of ABL
Denosumab (Xgeva)	RANKL	Giant cell tumor of the bone	
Erlotinib (Tarceva)	EGFR (HER1/ERBB1)	Non-small cell lung cancer Pancreatic cancer	
Everolimus (Afinitor)	mTOR	Pancreatic neuroendocrine tumor Renal cell carcinoma Nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis Breast cancer (HR+, HER2-)	
Gefitinib (Iressa)	EGFR (HER1/ERBB1)	Non-small cell lung cancer with known prior benefit from gefitinib (limited approval)	
Ibritumomab tiuxetan (Zevalin)	CD20	Non-Hodgkin's lymphoma	

To be continued

Table 2 *(Continued)*. The FDA has approved targeted drug cancer therapies. A partial list of currently approved targeted therapies for cancer and their molecular targets (in alphabetic order).

Targeted Drugs	Target(s)	FDA-approved indication(s)	Annotations
Ibrutinib (Imbruvica)	BTK	Mantle cell lymphoma Chronic lymphocytic leukemia Waldenstrom's macroglobulinemia	
Idelalisib (Zydelig)	PI3Kδ	Chronic lymphocytic leukemia Follicular B-cell NHL Small lymphocytic lymphoma	Monitor acquired mutation in exon 9 and 20
Imatinib (Gleevec)	KIT, PDGFR, ABL	GI stromal tumor (KIT+) Dermatofibrosarcoma protuberans Multiple hematologic malignancies including Philadelphia chromosome-positive ALL and CML	Monitor acquired mutation of c-kit for resistance prevention
Ipilimumab (Yervoy)	CTLA-4	Melanoma	Monitor polymorphisms of CTLA
Lapatinib (Tykerb)	HER2 (ERBB2/neu), EGFR (HER1/ERBB1)	Breast cancer (HER2+)	
Lenvatinib (Lenvima)	VEGFR2	Thyroid cancer	
Nilotinib (Tasigna)	ABL	CML t(9;22) positive	Monitor acquired mutation of ABL and polymorphisma of UGTA1A
Nivolumab (Opdivo)	PD-1	Melanoma	
Obinutuzumab (Gazyva)	CD20	Chronic lymphocytic leukemia	
Ofatumumab (Arzerra, HuMax-CD20)	CD20	Chronic lymphocytic leukemia	
Olaparib (Lynparza)	PARP	Ovarian cancer (with BRCA mutation)	Detect polymorphisms of PARP1 V762A
Palbociclib (Ibrance)	CDK4, CDK6	Breast cancer (ER+, HER2-)	
Panitumumab (Vectibix)	EGFR (HER1/ERBB1)	Colorectal cancer (KRAS wild type)	
Panobinostat (Farydak)	HDAC	Multiple myeloma	
Pazopanib (Votrient)	VEGFR, PDGFR, KIT	Renal cell carcinoma	Monitor acquired mutation TK domains
Pembrolizumab (Keytruda)	PD-1	Melanoma	
Pertuzumab (Perjeta)	HER2 (ERBB2/neu)	Breast cancer (HER2+)	
Ponatinib (Iclusig)	ABL, FGFR1-3, FLT3, VEGFR2	CML t(9;22) positive and other hematologic malignancies	Monitor acquired mutation TK domains
Ramucirumab (Cyramza)	VEGFR2	Gastric cancer or Gastroesophageal junction (GEJ) adenocarcinoma Non-small cell lung cancer	
Regorafenib (Stivarga)	KIT, PDGFRβ, RAF, RET, VEGFR1/2/3	Colorectal cancer Gastrointestinal stromal tumors	Monitor acquired mutation TK domains
Rituximab (Rituxan, Mabthera)	CD20	Non-Hodgkin's lymphoma Chronic lymphocytic leukemia Rheumatoid arthritis Granulomatosis with polyangiitis	
Romidepsin (Istodax)	HDAC	Cutaneous T-cell lymphoma Peripheral T-cell lymphoma	
Ruxolitinib (Jakafi)	JAK1/2	Myelofibrosis	
Siltuximab (Sylvant)	IL-6	Multicentric Castleman's disease	
Sipuleucel-T (Provenge)	prostatic acid phosphatase (PAP) Antigen	Prostate cancer metastatic, hormone-refractory prostate cancer (HRPC)	Needs leukoaferesys

To be continued

Table 2 *(Continued)*. The FDA has approved targeted drug cancer therapies. A partial list of currently approved targeted therapies for cancer and their molecular targets (in alphabetic order).

Targeted Drugs	Target(s)	FDA-approved indication(s)	Annotations
Sorafenib (Nexavar)	VEGFR, PDGFR, KIT, RAF	Hepatocellular carcinoma Renal cell carcinoma Thyroid carcinoma	Monitor acquired mutation TK domains
Temsirolimus (Torisel)	mTOR	Renal cell carcinoma	
Tocilizumab (Actemra)	IL-6R	Rheumatoid arthritis Juvenile idiopathic arthritis	
Tofacitinib (Xeljanz)	JAK3	Rheumatoid arthritis	
Tositumomab (Bexxar)	CD20	Non-Hodgkin's lymphoma	
Trametinib (Mekinist)	MEK	Melanoma (with BRAF V600 mutation)	
Trastuzumab (Herceptin)	HER2 (ERBB2/neu)	Breast cancer (HER2+) Gastric cancer (HER2+)	
Vandetanib (Caprelsa)	EGFR (HER1/ERBB1), RET, VEGFR2	Medullary thyroid cancer	Monitor acquired mutation TK domains
Vemurafenib (Zelboraf)	BRAF	Melanoma (with BRAF V600 mutation)	
Vismodegib (Erivedge)	PTCH, Smoothened	Basal cell carcinoma	
Vorinostat (Zolinza)	HDAC	Cutaneous T-cell lymphoma	
Ziv-aflibercept (Zaltrap)		PIGF, VEGFA/B	Colorectal cancer

*source: http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet.

$All mAbs are administered intravenously. Infusion reactions may occur with all monoclonal antibodies (more often with murine and chimeric antibodies) and are not listed as toxicities.

NOTE: All SMinhs are administered orally except bortezomib, which is administered intravenously. Most SMinhs undergo metabolism by cytochrome P450 enzymes and are therefore subject to multiple potential interactions (e.g., with anticonvulsants, azole anti-fungals, dexamethasone, isoniazid, macrolide antibiotics, nefazodone, protease inhibitors, rifampin, St. John's wort, verapamil, warfarin, etc.).

also present on normal lymphoid cells, targeting of this molecule affects overall immune function. This observation has led to the use of the anti-CD20 monoclonal antibody rituximab for the treatment of autoimmune diseases such as rheumatoid arthritis[3,4], in addition to non-Hodgkin's lymphoma. The fragment antigen binding (Fab) of a monoclonal antibody, which recognizes and binds to antigens, is responsible for the highly specific targeting that is possible with such therapies. The mAbs exert their antineoplastic effects through a multiplicity of mechanisms: by engaging host immune functions to attack the target cell; by binding either to receptors or ligands, thereby blocking crucial cancer cell processes. Other mechanism include a lethal payload carrier, such as a radioisotope or toxin, to the target cell (i.e., conjugated mAbs)[5]. Because their protein structure is digested by gastrointestinal fluids, mAbs are administered intravenously. In addition, they are not subject to significant drug interactions because they do not undergo hepatic metabolism.

The design of mAbs has changed over the past 20 years as biotechnology has improved. Early drugs in this class were produced by immunizing mice with the target antigen. The resulting mAbs were composed entirely of mouse proteins, which were potentially very antigenic to humans, carrying a risk of hypersensitivity reaction during infusion. Patients treated with these early mAbs could neutralize the effect of the therapeutic antibody because, often displayed anti-mouse Immunoglobulins. To limit these undesirable effects, recently were developed monoclonal antibodies containing a high proportion of human protein sequence and a decreased proportion of murine components; chimeric antibodies are 65% human, humanized antibodies are 95% human, and human antibodies are 100% human[6].

Small molecule inhibitors

The SMinhs differ from mAbs in several ways (Table 2). SMinhs typically interrupt cellular processes by interfering with the intracellular signaling of tyrosine kinases (i.e., enzymes that transfer phosphate groups from adenosine triphosphate to tyrosine amino acid residues in proteins). Tyrosine kinase signaling inductees a molecular cascade that can lead to cell growth, proliferation, migration, and angiogenesis in normal and malignant tissues. For example EGFR, HER2/neu and VEGF receptors are tyrosine kinases and they are the main target of this kind of drugs.

Generally, SMinhs were administered orally because they are not degraded in the gastrointestinal tract. Furthermore, they are manufactured by chemically process that is less expensive than the bioengineering required for mAbs[7]. They achieve less specific targeting than do mAbs[8], as evident in the multitargeting nature of the kinase inhibitors imatinib, dasatinib, sorafenib, and sunitinib. Unlike mAbs, most SMinhs are metabolized by cytochrome P450 enzymes (CYP450), which could result in interactions with the potent inhibitors of CYP450 such as warfarin, macrolide antibiotics, azole antifungals, certain anticonvulsants, protease inhibitors, etc.[9,10]. Whereas mAbs have half-lives ranging from days to weeks (and are therefore usually administered once every one to four weeks), most SMinhs have short half-lives (few hours) and require daily dosing.

Imatinib, one of the first SMinhs, is approved by FDA in 2002 for the treatment of chronic myeloid leukemia (CML). Imatinib inhibits a constitutive active tyrosine kinase of ABL gene that results from the fusion gene BCR/ABL caused by Philadelphia chromosome (translocation chromosome 9 and 22). Because this molecular abnormality occurs in essentially all patients with CML, imatinib therapy results in a complete hematologic response in 98% of patients[11,12].

The second SMinhs FDA-approved, Gefinitib, targeting the EGFR, has been used successfully for the treatment of solid tumors, such as non-small cell lung cancer (NSCLC). Recently, many others congeners molecules were designed to target EGFR pathway.

IMPLICATIONS OF TARGETED THERAPY

As described above, the use of targeted therapy has noticeably changed outcomes for some diseases. In particular, Imatinib has had a dramatic effect on CML and rituximab has revolutionized the treatment of non-Hodgkin's lymphoma (NHL); sunitinib, instead, has improved the renal cell carcinoma treatment while trastuzumab has given high responsiveness for breast cancer[13-15]. In other fields, the degree of clinical benefit is more modest. For example, the addition of erlotinib to standard chemotherapy in patients with advanced pancreatic cancer, increases the survival rate from 17 to 24%, which correlates to an increase in median survival from 24 to 27 weeks[16].

In order to prolonging survival in patients with definite neoplasms, targeted therapies provide treatment options for some patients who may not otherwise be treated with anticancer therapy. For example, elderly patients with NSCLC and NHL, many of whom have comorbidities that limit the use of conventional chemotherapy. In this case, targeted drugs such as erlotinib and rituximab are often less toxic and better tolerated than traditional chemotherapy, offering these patients additional treatment options.

To determine the right dosing and effectiveness of targeted therapies, cancer researchers gradually are turning to pharmacodynamic end points, such as tumor metabolic activity on positron emission tomography (PET) scans, levels of circulating tumor a cells, serial levels and expression of target molecules in tumor tissue, and acquired mutation in cancer cells[17-19].

COST

Targeted therapy also introduce new pharmacoeconomic issues. The use of oral SMinhs for traditional chemotherapy eliminates some treatment costs, including those associated with hospitalizing of the patient. However, targeted therapy is often used in combination to traditional chemotherapy. If targeted therapy includes mAbs, costs can dramatic increase, for example, colorectal cancer treatment regimens containing bevacizumab or cetuximab cost up to $30000 (for eight weeks of treatment), compared with about $60 for fluorouracil/leucovorin based therapy (same weeks)[20-22].

In addition, when conventional chemotherapy is effective, reduction in tumor bulky is anticipated on serial radiographic studies. In contrast, some targeted therapies may impact a clinical benefit by stabilizing tumors, rather than shrinking them. These considerations improve complexity and cost to clinical researchers. In addition, repeated biopsies of tumor tissue could be unacceptable for patients and inconvenient to institutional medical boards.

Although clinical studies may initially increase the time and costs of therapy, they could improve its long-term cost-effectiveness by identifying the subset of patients most likely to maximize benefit from specific drugs

CONCLUSIONS AND FUTURE OUTLOOK

Retrospective studies have proved that targeted drug exposure, indicated in the area under the plasma concentration-time curve (AUC) correlates with treatment response (efficacy/toxicity) in several cancers. Clinical trials of traditional chemotherapeutic drugs generally effect toxicity through the degree of myelosuppression. Targeted therapies, however, often do not cause significant hematologic toxicity nevertheless levels of report for therapeutic drug monitoring (TDM) are however heterogeneous among these agents and TDM is still uncommon for the larger part of them. Now evidence for imatinib exists, others are emerging for compounds including nilotinib, dasatinib, erlotinib, sunitinib, sorafenib and mammalian target of rapamycin (mTOR) inhibitors. Applications for TDM during oral targeted therapies may best be reserved for particular situations including deficiency of therapeutic response, severe or unexpected toxicities, anticipated drug-drug interactions and/or concerns over adherence treatment. Interpatient PK variability noted with mAbs is similar or lower than observed with SMinhs. There are still few data with these agents in favour of TDM procedures, even if data showed encouraging results with rituximab, cetuximab and bevacizumab. At this time, TDM of mAbs is not supported by scientific proof. Remarkable effort should be made for targeted therapies to better define concentration-effect reports and to execute comparative randomised trials of classic dosing versus pharmacokinetically-guided adaptive dosing[23].

Targeted therapy has introduced several new issues for oncologists. Determining optimal dosing is one challenge[24]. Further, effective evaluation of drug design toward the generation of novel and specific therapies focused on molecular targets relating to cancer development, may eventually be personalized and individualized to the patient for maximum efficacy.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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