Chinese Journal of Cancer

Editorial

Targeted cancer therapies

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Abstract

With unprecedented understanding of molecular events underlying human cancer in this genomic era, a large number of drugs specifically targeting hypothesized oncogenic drivers to which tumors are potentially addicted to have been developed and continue to be developed. These targeted cancer therapies are being actively tested in clinical trials with mixed successes. This editorial provides an overview on successful targeted cancer drugs on the market and those drugs that are in late clinical development stages. Importantly, the article lays out main challenges in developing molecular targeted therapies and potential path forward to overcome these challenges, as well as opportunities for China in this new era of targeted agents. The editorial serves as an introduction to the Targeted Cancer Therapies series that will review in depth of major pathways and drugs targeting these pathways to be published in the coming issues of the *Chinese Journal of Cancer*.

The first targeted cancer therapy was tamoxifen approved in 1970s. Tamoxifen binds to the estrogen receptor (ER), prevents estrogen from binding to ER, and therefore modulates ER activity. By interfering estrogen's ability to stimulate cancer cell growth, tamoxifen provides an effective treatment option for patients with ER-positive breast cancer. Following tamoxifen, multiple ER-targeting drugs were developed to include toremifene, fulvestrant, anastrozole, exemestance, and letrozole, forming the basis of endocrine therapies for ER-positive breast cancer.

In the past two decades, the discovery of oncogenes and tumor suppressor genes, and the completion of human genome sequencing fueled some major advances in our understanding of the molecular mechanisms leading to cancer. Subsequently, such newly emerging biological and genetic information rapidly prompted the introduction of a large number of new targeted cancer therapies.

Signaling pathways regulated by protein kinases are the frequent targets of somatic mutations, leading to many human cancers. Of the more than 100 dominant oncogenes known to date, many encode protein tyrosine kinases. Several mechanisms lead to aberrant function by protein tyrosine kinases and subsequent oncogenic transformation. These include (1) genomic rearrangements resulting in oncogenic fusion proteins that include the kinase catalytic domain and an unrelated protein that provides a constitutive activation/dimerization function, (2) gain-of-function mutations in the juxtamembrane or kinase domains or small deletions of regulatory regions, (3) overexpression with or without gene amplification, and (4) loss of the normal autoinhibitory and regulatory constraints of kinase activation. At this time, several tyrosine kinase inhibitors of variable target specificity have been approved by the Food and Drug Administration (FDA) for treatment of patients with a variety of cancers (Table 1).

Several receptor protein and cytoplasmic kinases are known to be mutated and/or overexpressed in human cancer. These include the epidermal growth factor receptor (EGFR; ErbB1), HER2/neu (ErbB2), insulin and insulin-like growth factor (IGF) receptors, fibroblast growth factor receptor-2 (FGFR-2), FGFR-4, Src, ABL, phosphoinositide 3-kinase (PI3K), MEK, RAF, among others. In many examples to be reviewed, inactivation of several of these kinases with exogenous inhibitors has resulted in an antitumor effect in preclinical models of cancer. And most importantly, some of these agents have shown promising clinical activity in patients with cancer and are in late development (Table 2). Several conditions are generally considered prior to the selection of a kinase as a therapeutic target against which drugs are developed. First, the kinase should be a "gain-of-function" oncogene and/or causal to tumor

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Table 1. US FDA approved targeted cancer therapies

Brand name	Compound name	Company	Target(s)	Indication*
Xgeva	Denosumab	Amgen	RANK ligand	Bone metastases
Istodax	Romidepsin	Gloucester	HDAC	Cutaneous T cell lymphoma
Arzerra	Ofatumumab	Genmab	CD-20	Chronic lymphocytic leukemia
Votrient	Pazopanib	GSK	VGFR-1, -2 and -3, c-kit, PDGF-R	Renal cell carcinoma
Affinitor	Everolimus	Novartis	mTOR	Renal cell carcinoma
Tasigna	Nilotinib	Novartis	BCR-ABL	Philadelphia chromosome positive chronic myelogenous leukemia
Torisel	Temsirolimus	Wyeth	mTOR	Renal cell carcinoma
Tykerb	Lapatinib	GlaxoSmithKline	HER-2/EGFR	Breast cancer
Sutent	Sunitinib malate	Pfizer	VGFRs, PDGFR	Gastrointestinal stromal tumor
Sprycel	Dasatinib	Bristol-Myers Squibb	Src, BCR-ABL	Chronic myeloid leukemia
Zolinza	Vorinostat	Merck	HDAC	Cutaneous T-cell lymphoma
Vectibix	Panitumumab	Amgen	EGFR	Colorectal carcinoma
Nexavar	Sorafenib Tosylate	Bayer	RAF, VEGFR-2 and -3, PDGFR-b, c-kit	Renal cell carcinoma
Tarceva	Erlotinib Hydrochloride	OSI Pharms	EGFR	Non–small cell lung cancer
Avastin	Bevacizumab	Genentech	VEGF	Colorectal cancer
Erbitux	Cetuximab	ImClone Systems	EGFR	Colorectal cancer
Bexxar	Tositumomab and iodine ^{131}I tositumomab	Corixa Corporation	CD-20	Non-Hodgkin's lymphoma
Velcade	Bortezomib	Millennium Pharms	Proteasome	Multiple myeloma
Iressa	Gefitinib	AstraZeneca	EGFR	Non–small cell lung cancer
Zevalin	Ibritumomab tiuxetan	IDEC Pharms	CD-20	B-cell non-Hodgkin's lymphoma
Campath	Alemtuzumab	Berlex Laboratories	CD-52	B-cell chronic lymphocytic leukaemia
Gleevec	Imatinib	Novartis	BCL-ABL, c-kit, PDGGR	Chronic myeloid leukaemia
Mylotarg	Gemtuzumab ozogamicin	Wyeth/Pfizer	CD-33	Acute myeloid leukaemia
Ontak	Denileukin diftitox	Eisai	IL-2	Cutaneous T-cell lymphoma
Herceptin	Trastuzumab	Genentech	HER2	Breast cancer
Rituxan	Rituximab	Genentech/Biogen Idec	CD-20	Non-Hodgkin's lymphoma

*First indication approved by the United States Food and Drug Administration (US FDA).
HDAC, histone deacetylase; VGFR, vascular endothelial growth factor receptor; PDGF-R, platelet derived growth factor receptor; EGFR, epithelial growth factor receptor.

development and tumor maintenance. It should be differentially expressed in tumor vs. non-tumor tissue and identifiable in cancer tissues. Although the kinase target may have a critical role in postnatal or adult physiology, it should provide a therapeutic window such that "tumor toxicity" occurs before prohibitive host tissue toxicity. Structure-function knowledge of the molecular target should be in hand in order to develop mechanism-based inhibitors. In general, kinase inhibitors have consisted of neutralizing antibodies, or low molecular weight ATP-mimetics and allosteric inhibitors.

Challenges in Targeted Cancer Drug Development

Despite the advancement in targeted therapy, treatment of cancer still remains as a huge unmet medical need. Multiple factors, in addition to the complexity of cancer biology, contribute to this unsatisfactory state.

Lack of reliable preclinical models to predict anti-cancer drug efficacy

Cancer development in human patients is a long multi-step process. The resulting malignant tumors are intimately intertwined with surrounding "normal" tissues. Such close tumor-host interactions are vitally important in determining the sensitivity of tumor cells to cancer treatments. However, such complex tumor context is not replicated either *in vitro* or *in vivo* in transgenic or xenograft models. Genetically engineering mouse tumor models provide a potentially promising alternate to assess preclinical cancer drug efficacy. But their true value has yet to be validated by clinical successes.

Inefficient clinical development

Near 30% of the 98 000 clinical trials listed on Clinicaltrials.gov were related to cancer drugs. Such a large number not only reflects the huge unmet medical

needs, but also stems from the low success rate of cancer medicine development. It is estimated that only 10% of the cancer drug candidates entering clinical stage ultimately gain market approval. New trial approaches are urgently needed especially for the development of targeted cancer therapies that will only benefit a subset of patients. Prospectively identifying sensitive or excluding resistant patient populations to achieve definitive clinical benefit led to successful development of several targeted therapies. Such successes include the use of HER2 fluorescent in situ hybridization (FISH) assay for selecting HER2-positive breast cancer patients receiving Herceptin treatment, EGFR mutation assay for selecting non–small cell lung cancer patients to be treated with gefitinib/erlotinib, and applying KRAS mutation assay to avoid exposing colorectal cancer patients with KRAS mutations to anti-EGFR mAbs. Recently, such biomarker-based prospective patient selection strategy was applied to Phase 1 studies to expedite clinical development of several new targeted agents. Overall response rates from 50% to near 80% were achieved in early phase trials of crizotinib (ALK inhibitor), as well as PLX-4032 (R7204) and GSK2118436 (bRAF V600E inhibitors). Such dramatic early efficacy data prompted sponsors launching Phase 3 registration trials based on Phase 1 and Phase 2 results (Table 2). For compounds lacking definitive biomarkers for identifying sensitive/resistant subpopulation, adaptive trial design to incorporate biomarker identification and validation into one single trial may represent an effective and efficient approach[1].

Limited single agent activity

Most human tumors harbor numerous mutation events leading to activation of multiple signaling pathways. The redundancy in the signaling systems at the disposal of the cancer cells often render individual targeted agents inactive in treating most cancers. Even in rare exceptions, such as narrowly defined patient populations, single agent activities could be dramatic, but cancers still recur. Combinations of targeted agents represent a potentially effective approach to simultaneously inhibiting multiple pathways, suppressing feedback reactivation of compensatory signaling network, and therefore to prevent recurrence. The parallels between clinical development of combinations and understanding of cancer resistance will ultimately lead to personalized medicine, such as matching targeted therapy with cancer patients based on molecular events underlying their malignancies.

Opportunities for China

The era of targeted cancer therapies brings unique opportunities to China. The already saturated clinical trial density in well established oncology trial regions such as

Table 2. Selected targeted cancer therapies in late stage development

Compound name	Company	Major indication	Target	Stage
Antibody				
Ipilimumab	Bristol-Myers Squibb	Melanoma	CTLA4	BLA submitted
Tremelimumab	Pfizer/Debiopharm	Melanoma	CTLA4	Phase III
Zalutumumab	Genmab	Head and neck cancer	EGFR	Phase III
Pertuzumab	Genentech	Breast cancer	HER2	Phase III
Trastuzumab-DM1	Genentech/Immunogen	Breast cancer	HER2	Phase III
Small molecule				
Omacetaxine	ChemGenex	CML with T315I BCR-ABL mutation	MCL1	NDA submitted
BSI-201	Sanofi-Aventis	Triple-negative breast cancer	PARP1	Phase III
ZD6474	AstraZeneca	Failure of previous EGFR therapy	EGFR	Phase III
IPI-504	Infinity	GIST	HSP90	Phase III
Ridaforolimus	Ariad/Merck	Sarcoma	mTOR	Phase III
XL184	Exelixis	Medullary thyroid cancer	MET, VEGFR2, RET	Phase III
PLX-4032 (R7204)	Roche/Plexxikon	Melanoma	BRAF V600E	Phase III
GSK2118436	GSK	Melanoma	BRAF V600E	Phase III
Crizotinib (PF02341066)	Pfizer	Non–small cell lung cancer	EML4-ALK	Phase III
ARQ197	ArQule/Daiichi Sankyo	Non–small cell lung cancer	c-MET	Phase III

This table was modified from *Targeted cancer therapies* by Saurabh Aggarwal[3].
BLA, biologic license application; CML, chronic myeloid leukemia; CTLA4, cytotoxic T-lymphocyte protein 4; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor receptor 2 (also known as ERBB2); HSP90, heat-shock protein, 90 kDa; IGFR1, insulin-like growth factor receptor 1; MCL1, myeloid cell leukemia sequence 1; mTOR, mammalian target of rapamycin; NDA, new drug application; NSCLC, non–small cell lung cancer; PARP1, poly (ADP-ribose) polymerase 1.
Sources: company reports, ClinicalTrials.gov, American Society of Clinical Oncology, American Society of Hematology.

North America and Western Europe poses an impassable challenge to accruing patients with proper molecular characteristics to match targeted agents. For example, nearly 7 000 patients need to be screened to identify the 5% patients with tumors harboring the EML4-ALK fusion event for the crizotinib Phase 3 trial of 320 patients. The success in contributing patients to the I-PASS trial is a beginning for China to play a more active role in global development of new anti-cancer agents [2]. In preparation for this new era, it is vital for investigators in China to master the knowledge in new cancer biology, pharmacokinetics, pharmacodynamics, innovative trial design of both early and late phases, as well as to establish core capabilities in molecular testing of tumor samples in real time fashion to support prospective patient selection.

In collaboration with US Chinese Anti-Cancer Association (USCACA), *Chinese Journal of Cancer* has organized a series of review articles to cover a broad spectrum of topics in targeted cancer therapies. These articles will analyze each major pathway or target class with an emphasis on mechanism of action, translational medicine, and clinical development. This series of reviews will provide a basis for our readers, especially clinical investigators, to develop a comprehensive appreciation of these targets and pathways in cancer as well as relevant targeted therapies being developed.

Acknowledgement

Authors would like to acknowledge Ms. Debbie Allison for her contribution and advice on the tables summarizing targeted agents.

Received: 2010-11-29; revised: 2010-11-30; accepted: 2010-12-01.

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