SMGroup

Targeted Cancer Therapy

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ABSTRACT

Cancer is the one of representative incurable disorders. Numerous research studies and drug discovery have focused on curing cancer; however it still remains to be clarified. First generation therapies of cancer treatment such as surgery, chemotherapy and radiation therapy were used to treat patients with cancer since 1960s. Chemotherapy is the use of chemotherapeutic drug throughout the whole body compared with surgery and radiation therapies by removing or damaging cancers in certain area. However it causes adverse events by attacking normal cells and some patients do not show the expected drug effects. In the early 1990s, basic researches and studies about cancer initiation, promotion and progression have been published and established development of second generation of cancer therapy. Targeted therapy is a type of chemotherapy, which precisely attacks cancer cells and is more like patient-tailored cancer therapy. Targeted therapy stops the action of key proteins involved in cancer growth and progression and attacks cancers by prohibiting cancer division and angiogenesis, promoting suicide of cancer cells or

activating immune system. Recent trend in discovery of targeted therapy is accompanied with a predictive and prognostic biomarker. Since new drug is difficult to be approved by the FDA without specific biomarkers, development of biomarker becomes a critical path for drug discovery. As targeted therapies have reported to develop intrinsic or acquired resistance against drugs, drug development is designed to overcome the resistance issues. One of current trends in the drug discovery area is immune therapy and Protein-Protein Interactions **(PPIs).** Immunotherapy showed anti-cancer effects to overcome conventional therapeutic approaches. PPI inhibitors have reached to clinical trials and these drugs were not involved undesirable side effects for normal cell. In this chapter, we are going to focus on targeted therapies; the most often used therapy at this time.

HISTORY AND CURRENT TRENDS IN TARGETED THERAPY

In 1976, J. Michael Bishop and Harold E. Varmus, the Nobel Prize winners in Physiology or Medicine for 1989, discovered a proto-oncogene c-Src and introduced genes related to cancer initiation and development [1,2]. In the early 1990s, cancer research began an investigation into the diversity of therapeutics. In 2000, Douglas Hanahan and Robert A. Weinberg have published a review article titled "The Hallmarks of Cancer" in the journal Cell [3]. In this study, they characterized cancers with six biological capabilities; insensitivity to anti-growth signal, sustained angiogenesis, limitless replicative potential, tissue invasion and metastasis, evading apoptosis, and self-sufficiency in growth signals. In 2011, they published another review article in the Cell subtitled "The Next Generation", by adding a conceptual research progress in the last decade [4]. Both articles discussed the most essential aspects for understanding of cancers and provided consistent evidence of drug discovery.

As shown in Table 1, the era of first generation therapy chemotherapy began in the 1940s with the use of nitrogen mustard and further introduced with cisplatin, etopside, etc [5]. Since it caused severe side effects, more effective drugs with less severe side effects are required to be investigated. As mentioned above, genes related to cancer development have been identified from numerous studies and the information has been used to develop a second generation cancer therapy. Most importantly, targeted drugs by targeting specific cancer-related genes have improved the excessive toxicity profiles compared to chemotherapy. Since 2000s, targeted drugs are mostly used for cancer patients in clinical use.

Table 1: Trends in cancer therapies. (cancer research institute; www.cancerresearch.org).

	Generation 1 Chemotherapy	Generation 2 Targeted therapy
Drugs	Synthetic drugs (e.g., cyclophosphamide, cisplatin, etoposide, etc)	Antibodies (cetuximab, herceptin, rituxan) & Small molecules
Approach	Using cytotoxic drugs to kill or inhibit rapid proliferation of cancer cells (e.g., nucleoside analogue interrupts DNA replication)	Interfering with a mechanism required for supporting tumor growth
Since	Late 1940s	2000s
Limitations	- Often not destroying the whole tumor with high cytotoxic - Leading to high rates of recurrence - Targeting not only cancer cells but also normal cells, thus high risk of toxicity	- More specific than chemotherapy - Causing less chance of toxicity, but still limited tumor types eligible - High efficiency but short durability driving high rates of recurrence
Administration	Mostly intravenous, some oral agents	Many are oral agents

Targeted therapies are either small molecules or antibodies. Both agents have their pros and cons. Approximately 50 targeted therapies were identified and developed from late 1995 to 2013. Up to now, new and more potent anti-cancer agents are expected under investigation (Table 2) [6,7].

Table 2: Representative targeted drugs and their target proteins.

Drug	Target
Small molecules	
Bortezimib (Velcacle®)	Proteasome
Dasatinib (Sprycel®)	BCR-ABL
Gefitinib (Iressa®), Erlotinib (Tarceva®)	EGFR
Imatinib (Glivec®)	BCR-ABL, PDGFR, c-KIT
Lapatinib (Tykerb®)	EGFR, erbB2
Octreotide (San dostatin®)	Somatostatin receptor
Sunitinib (Nexavar®)	VEGFR, PDGFR, c-KIT, Raf, Scf
Monoclonal antibodies	
Alemtuzumab (Campath®)	CD52
Bevacizumab (Avastin®)	VEGF
Cetuximab (Erbitux®), Panitumumab (Vectibix®)	EGFR
Rituximab (Mabthera®)	CD20
Trastuzumab (Herceptin®)	HER2 (erbB2)

Most of small molecules are targeted drugs, which modulate protein tyrosine phosphorylation in cancer cells. Comparative inhibitors against ATP have been developed and several clinical applicable drugs are under investigation. The first targeted drug is tretinoin (all-trans retinoic acid, ATRA; Vesanoid®; Roche) approved by the FDA in 1995 as the standard induction treatment for Acute Promyelocytic Leukemia **(APL).** Several research groups identified chromosomal abnormalities in patients with APL and confirmed anti-cancer effect of ATRA in patients with APL [8]. Since then, diverse targeted agents have been investigated. The most representative

monoclonal antibodies of targeted therapy is imatinib (Gleevec®; Novartis) used for patients with Philadelphia chromosome-positive (Ph+) Chronic Myelogenous Leukemia **(CML).** The imatinib is the first FDA approved BCR-ABL tyrosine kinase inhibitor [9,10]. It showed anti-cancer effects, but developed resistance to imatinib. Second generation drugs of imatinib have been investigated to overcome resistance and intolerance.

Epidermal Growth Factor Receptor **(EGFR)** is the first target of solid cancers. Anti-EGFRs are either monoclonal antibodies (cetuximab and panitumumab) or first (gefinib and erlotinib) and second generation of small molecules (afatinib). Numerous research studies identified that EGFR is activated in solid tumor, therefore development of anti-EGFRs was focused on inhibition of EGFR activation. Discovery of gefitinib (Iressa®; Astrazeneca) was conducted by screening of chemical compound library consisting of approximately 250,000 molecules. The clinical trials of gefinitinib were designed for patients with Non Small Cell Lung Cancer **(NSCLC)**, however no specific anti-cancer effects was investigated. Further studies have been discovered that EGFR mutation is closely associated with efficiency of gefinitinib. The first clinical trials showed significantly improved Progression-Free Survival **(PFS)** compared with standard chemotherapy. Therefore, gefitinib was approved by the FDA as the first-line therapy for EGFR mutation-positive NSCLC [11]. Cetuximab (Erbitux®; Imclone Systems) is the anti-EGFR antibody, which tightly binds to EGFR and inhibits EGFR activation. Bristol-Myers Squibb **(BMS)** identified that combinational therapy of cetuximab with chemotherapy resulted in prolonged PFS in patients with colon cancers [12]. In 2004, the FDA approved cetuximab for use as a single agent or in combination with irrinotecan (a chemotherapy drug) for patients with EGFR-expressing, (recurrent) metastatic colorectal carcinoma. Further researches clarified that the effect of cetuximab is KRAS genotype dependent. Approximately 50% of colon cancers are KRAS wild type, which means rest of colon cancer patients (50%) with KRAS mutation without cetuximab response. The standard requirement for the prescription of cetuximab is patients with KRAS wild type and treats either single for patients with recurrent metastatic colorectal carcinoma or combinational therapies with irrinotecan for patients with metastatic colorectal carcinoma. However, some patients with KRAS wild type resulted in non-response upon cetuximab treatment. The identification of indicators is useful to classify the standard induction treatments, so-called biomarker, which will be discussed in the next section.

Vascular Endothelial Growth Factor Receptor **(VEGFR)** signaling pathway is known as key players in cancer promotion and progression. VEGFR-2 was identified by Terman, et al. (1992) and Ullrich, et al. (1993) and led to further investigation of angiogenesis signaling. Bevacizumab (Avastin®; Genentech) is a humanized anti-VEGF antibody for cancer treatment with metastatic colon cancer, NSCLC, metastatic renal cell carcinoma, persistent, recurrent, or metastatic carcinoma of the cervix in combination with chemotherapy. As a single agent, bevacizumab is indicated for the second-line treatment of patients with progressive glioblastoma [13,14]. Regorafenib (Stivarga®; Bayer), a multi-kinase inhibitor, has anti-cancer effects on angiogenic

inhibitory and tumor blood vessel penetration. Importantly, regorafenib is effective for patients with metastatic colon cancer who have been previously treated with conventional chemotherapy and showed non-response [15,16]. The FDA expanded the use of regorafenib for patients with advanced Gastrointestinal Stromal Tumors **(GIST)** in 2013. However, predictive biomarkers for treatment of multi-kinase inhibitor regorafenib remain unexplored. Diverse targeted therapies are clinically used for patients.

BIOMARKER DISCOVERY

In general, biomarker is a predictive indicator to detect body composition changes using RNA, DNA, protein or metabolism. In cancer, biomarker is used to distinguish either between normal and disease or predictor of drug response. The discovery of biomarker is essential for development of targeted therapy [17]. Several cases of failure in drug development were reported by having no promising predictive biomarkers. One example is olaparib (Lynparza®; AstraZeneca), the anti- drugs for colon cancer patients. According preclinical research results, olaparib treatment showed Homologous Recombination **(HR)** related gene MRE11 dependent, which led to continue for clinical trial with patients with MRE11 mutation. However, it did not showed clinical efficacy in the clinical trials, which indicated that MRE11 was not a promising biomarker for olaparib.

There is the FDA approved drugs (Olaparib) treatment for patients with breast and ovarian cancers depending on germline mutations in the tumor suppressor genes BRCA1 and BRCA2. In addition, c-Met inhibitor crizotinib (Xalkori®; Pfizer) is used to cure patients with NSCLC harboring chromosome rearrangements of Anaplastic Lymphoma Kinase **(ALK)** gene or the ROS 1 gene. Since echinoderm microtubule-associated protein-like 4 (EML4)-ALK rearrangements are often detected in lung cancer, patients with lung cancers harboring EML4-ALK gene (7% of total population) showed anti-cancer effect upon crizotinib treatment [18,19]. This is the great example of having promising biomarkers. Developed drugs with predictive biomarkers are listed in Table 3.

Table 3: Biomarker discovery for targeted therapies (FDA; http://www.fda.gov/).

Drug	Biomarker	Referenced subgroup
Afatinib	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R) positive
Alectinib	ALK	ALK gene rearrangement positive
Blinatumomab	BCR-ABL1	Philadelphia chromosome negative
Crizotinib	ALK	ALK gene rearrangement positive
Cetuximab (1)	EGFR	EGFR protein expression positive
Cetuximab (2)	KRAS	KRAS codon 12 and 13 mutation negative
Cisplatin	TPMT	TPMT intermediate or poor metabolizers
Dasatinib	BCR-ABL1	Philadelphia chromosome positive, T315I mutation positive
Erlotinib (1)	EGFR	EGFR protein expression positive
Erlotinib (2)	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R) positive
Imatinib	BCR-ABL1	Philadelphia chromosome positive
Gefitinib	EGFR	EGFR exon 19 deletions or exon 21 substitution (L858R) mutation positive
Olaparib	BRCA1-2	BRCA1-2 mutation positive
Panitumumab	EGFR	EGFR protein expression positive
Tamoxifen	ESR1, PGR	Hormone receptor positive
Trametinib	BRAF	BRAF V600E/K mutation positive
Tretinoin	PML-RARA	PML-RARα translocation positive

Biomarker discovery is the critical path for new drug discovery as the FDA does not approved drugs without a specific biomarker. The global biomarkers market is expected to increase at $ 53.8 billion by 2018. Genotyping and diagnostic markets are also estimated to growth at 11% annually and rapidly spread worldwide in pharmaceutical markets. The identification of biomarkers is expected to be a huge market in drug discovery and development. In addition, the biomarker discovery promotes the discovery of patient-tailored cancer therapy for individual patients.

LIMITATIONS OF TARGETED THERAPPIES: DRUG RESISTANCE

The fact is that treatment of targeted therapies eventually causes drug resistance in certain situations. The presence or development of intrinsic resistance to drugs has been investigated to identify key players associated with resistance and to identify new drug or combinational treatments. In case of acquired resistance, it is more difficult to understand as an effective drug is not sufficient anymore. Efforts to understand the evolution of acquired resistance lead to diverse researches and development of gene analysis techniques. The studies of signaling pathway in drug resistance of cancers are under active investigation. Gefitinib is the FDA approved tablets for first-line treatment of patients with advanced EGFR mutation-positive NSCLC. After a year of gefitinib treatment, approximately 50-60% of NSCLC patients develop acquired resistance to EGFR T790M mutation. AZD9291 (Tagrisso®; AstraZeneca) was developed to overcome EGFR

T790M mutation [20]. In addition, imatinib is treated for patients with Gastrointestinal Stromal Tumor **(GIST)** and reported intrinsic resistance by developing PDGFRA D842V mutation and NR1. Acquired resistance to imatinib in GIST occurs by c-KIT mutation [21]. For the acquired resistance, patients treated with sunitinib (Sutent®; Pfizer) showed the improved PFS. It seems very susceptible at the moment; however it still has probability to develop another resistance. A current challenge in drug development is to improve limitations of targeted therapy. It could be a third generation drug development or identify alternative way of new drug development.

CHALLENGE IN OVERCOMNG RESISTANCE TO TARGETED THERAPIES

The immunotherapy is the so-called 'the next generation" therapeutic agents [22]. Immunotherapeutic drugs stimulate human immune system and cause less side effects and better anti-cancer efficacy. Most targeted therapies showed better initial response, however survival of stage IV cancer patients rapidly declined. Immunotherapy continued initial response after 2-4 years and showed significant anti-cancer effects on stage late III and IV cancer patients who developed cancer progression or could not apply with conventional therapies. As current immunotherapy has no promising biomarker, it has made limited to apply on different stages of cancer patients.

Alternative targeted therapies are interfering with PPIs**.** Small molecule inhibitors of p53-MDM2 PPIs have been investigated in clinical trials for cancer treatment. Several research groups have been working on to identify blockers of diverse PPIs. PPIs are fascinating targets because it showed no significant adverse events. Therefore, PPI inhibitors have a potential to become "first-in-class" therapies [23].

Current and further aspects of drug development will provide new insights of anti-cancer drugs in combination with discovery of diagnostics and biomarkers.

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