

## Molecularly Targeted Therapy: Great Progress or Evil Cycle

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### Editorial

Therapeutic mode of cancer patients have shifted during a past few decades from the administration of broadly effective conventional anti-cancer agents towards the more-specific therapies in individual case and each cancer. This strategy derived from the notion that cancer cells usually become more dependent on and addicted to the activity of a specific molecule which in most cases, is an oncogene product. Along with the prevalence of this concept “oncogene addiction”, this novel and specific therapy called “tailored targeted therapy” came true for each patient [1,2]. The rationale of targeting the molecule selectively overexpressed or activated in cancer cells is that cytotoxicity will be selective/specific for cancer cells, minimizing potential adverse events (AEs). Therefore, effective tailored targeted therapy requires the initial and essential effort to identify the key molecule(s) by which downstream pathways are activated. The representative target molecule has been protein kinase, and thus, receptor tyrosine kinases and the downstream effectors (phosphoinositide-3 kinases [PI3-K], Ras and Raf, etc.) have been attractive therapeutic targets. The highly conserved ATP-binding site within the catalytic domain of most kinases was initially viewed as an appropriate target for the development of selective small-molecule kinase inhibitors. Later, the non-ATP-competitive kinase inhibitors were found to show the higher selectivity without affecting other protein kinases. Eventually, this trial spurred the development of more than 500 molecularly targeted pharmacological agents and about 150 kinase-targeted drugs, and ushered in an era of “molecularly targeted therapy” (MTT) [3].

Imatinib for chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GIST) with mutated c-KIT, gefitinib for non-small cell lung carcinoma (NSCLC) with mutated EGFR, trastuzumab for breast carcinomas overexpressing human-EGFR2 (HER2), crizotinib for NSCLC with fusion gene of the Anaplastic lymphoma kinase (ALK) and rituximab for B-cell lymphomas are the fruits of great progress in MTT. During the history of MTT, the first application of imatinib in CML and association between EGFR mutations and gefitinib sensitivity in NSCLC were breakthrough discoveries. These genetic lesions are activating aberrations within or involving the target kinase genes and have prompted efforts to stratify patients based on the specific genomic profile of the cancer [2]. The pitfall of not establishing such an identification system was seen in the trials of gefitinib, which involved a large number of NSCLCs with EGFR over-expression that subsequently demonstrated only a small fraction of responsive population. Thus, approaches should be taken to carefully identify individual determinants of therapeutic sensitivity and outcome in order to maximize the benefits and keep AEs to a minimum. In fact, in the majority of cancers, large effort is required to specify the addiction of tumor on a specific molecule due to a high degree of complexity: since multiple aberrations of different genes are involved in carcinogenesis and progression, the responsive kinase often remains unclear. Nonetheless, exploration of the single addicting gene has been the initial step as the standard strategy, and many agents targeting single molecule still show clinical responses even in cancers harboring genetically complex aberrations. The success of these agents further triggered many trials leading to the development of broad-spectrum inhibitors against drug-resistant mutants.

AEs and drug resistance represent consistent obstacles in MTT, since a substantial proportion of patients should discontinue the therapy by these reasons. There seems to be the endless evil circle composed by new drug design and development of resistance as observed in the history of antibiotics. Thus, the most important issue at present is to further develop the knowledge about the mechanisms of AEs/drug resistance rather than novel drug design.

With regards to the first obstacle, AEs, clinically approved agents should be qualified not only in the efficacy, but also in the greater tolerability for potential AEs. One of the reasons why agents specifically inhibiting one target kinase were highly evaluated was that a narrow window is less likely to cause unexpected AEs. However, there has been the avalanche of reports dealing with AEs by almost all targeting agents. The most popular and serious AE is interstitial pneumonia (IP) in gefitinib. In recently approved anti-VEGF monoclonal antibody bevacizumab for colorectal, lung, and breast cancers, extensive hemorrhage from the tumor was occasionally noted, and thus, its application in NSCLC was limited to non-squamous cell carcinomas. Altogether, it is mandatory to explore if there are risk factors for developing AEs, such as gender, ethnicity, past history, smoking habit and histopathology of cancer.

The second obstacle is the resistance. Even by imatinib, although 80% of the patients with GIST have significant benefit, while the rest of 20% exhibit primary resistance and 50% show progressive disease due to the acquired resistance [4]. In addition to the causative mutation of the responsible gene, the intrinsic heterogeneity of cancers that harbor multiple gene aberrations could cause resistance. Moreover, in clinical samples, many studies generally affirmed the crosstalk between the various levels of different signal pathways [2]. Despite the wealth of information, a global understanding of the mechanism of resistance is sometimes hard, and thus, the combating resistance is still the important issue and the strategies have been conducted.

First, even when acquired resistance is noted, restarting of the agents after cessation is proposed in imatinib or trastuzumab, depending on the case, since some tumor cells still remain sensitive to the agents.

Second, exploitation of the combination treatments along with the switch of addiction, and chasing the process of cancer escapes from the addicted pathway is prevalent. Generally, the larger population of the patients has malignancies harboring complex genetic aberrations, and the effect by a single targeted agent is often unsatisfactory. Multi targeted kinase inhibitors or agents targeting intracellular signaling

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molecules have been found to overcome these complex pathobiological circumstances. Those include sunitinib (against VEGFR, PDGFR, c-Kit, etc.), sorafenib (Raf, VEGFR-2/3, PDGFR-B, etc.) and dasatinib (SRC, ABL, c-KIT, etc.).

Third, the “second-generation” kinase inhibitors that can form covalent bonds with the target have been highly regarded against gefitinib-resistant NSCLC, i.e., a dual EGFR/HER2 inhibitor BIBW 2992 (afatinib) [3].

Lastly, other sorts of broad-targeting agents entered into the trials: the inhibitors of HSP90 of which many cancer-related proteins are client, miRNAs and proteasome inhibitors. A unique agent T-DM1 represents a novel approach to drug delivery in which trastuzumab is conjugated to an anti-microtubule agent (DM1, maytansine) to efficiently deliver DM1 to HER2-overexpressing cancer cells [5].

Combination of two or more agents could theoretically lower the effective dose of each agent, but retain comparable or enhanced activity, thus are expected to reduce the toxicity. However, unequal potency of multi-targeted agents against each target may result in unsatisfactory results. Indeed, AEs have not decreased as remarkably as expected. One study in combined regimen with gefitinib and rapamycin derivative (rapalog) for 31 patients of NSCLC reported one patient each exhibited rapalog lung toxicity and the gefitinib-associated IP [6]. Since gefitinib-induced IP generally occurs in 1%, the rate of gefitinib-induced AE was enhanced.

MTT made a great progress, but must be further refined in the forthcoming age of cancer therapy. The ultimate task is the identification in advance, of the subpopulation of patients who respond to a therapy so as to derive greater benefit and simultaneously to avoid unnecessary treatment of patients who have little hope of benefiting. At present, the established kinase inhibitors cover a small fraction of

the whole kinome, and many of kinase inhibitors in clinical trials did not achieve the anticipated results. The impediments, i.e., limitation due to AEs or drug resistance, could emerge in clinical application of any agents. However, this situation will be improved by the upcoming kinase inhibitors with a better selectivity. The DNA-microarray enabled to obtain the expression patterns of millions of genes, and comprehensive analysis on cancer samples demonstrate characteristic expression profiles specific to particular cancer traits. Ongoing efforts using genome-wide screening and its integration with targeted agent-responsive phenotypes have been under way.

There is no return from this ideal methodology for cancer therapy.

#### Declaration of Interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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