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Tyrosine kinase inhibitors in cancer therapeutics: great expectations from small molecules

Zeeshan A Ansar

tariq moatter
aga khan university, tariq.moatter@aku.edu

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In the last two decades, biomedical scientists have made extraordinary efforts to unravel molecular intricacies underlying carcinogenesis, thus providing a strong foundation for the development of targeted cancer therapies. Application of latest molecular technologies have transformed our understanding of cancer pathogenesis and mechanisms involved in neoplastic transformation. Cancer, as known today, is a disease that has its origin embedded in the alteration of specific genes. This hypothesis was held true because several “cancer genes” have been discovered and characterized using high throughput molecular technologies. Moreover, the completion of human genome sequencing has placed a major milestone on this path and as was anticipated in the initial phase of the genome project, its completion has led to significant advancements in our understanding of cancer biology.

Over the last few decades, the identification and characterization of the genetic changes in malignant transformation have progressed rapidly. On the other hand, failure of response to therapy has been progressively detected; these failures could be due to drug intolerance, lethal toxicities, insensitivity of target receptors and genetic changes or alteration in cell signaling pathways.

Cell surface receptors play crucial role in cancer biogenesis, especially those receptors that encode for enzymatic activities, such as tyrosine kinases, commonly known as receptor tyrosine kinases (RTKs). These are membrane-spanning cell proteins that play critical role in transduction of extracellular signals to cytoplasm. There are approximately sixty RTKs, which are divided into twenty sub-families as defined by their ligands. Among these receptors three features including immunoglobulin like sequence having amino terminal extracellular domain, lipophilic transmembrane segment and an intracellular carboxyl terminal domain which contain tyrosine kinase catalytic site are found common.

The RTKs are activated through binding with their ligands, hormones, peptide or growth factors and trigger a cascade of signaling molecules subsequently leading to transcription of genes, which regulate cell growth, proliferation, differentiation, migration and apoptosis. In addition, RTKs can also become activated by somatic mutations, which are identified as a common mechanism of carcinogenesis, whereby they play an important role in the modulation of growth factors signaling under pathological conditions. Activated forms can cause increased tumor cell proliferation, growth induce anti-apoptotic effects and promote angiogenesis. Therefore, detection of RTK variants in malignancies is not only useful for the diagnosis but also becomes helpful in their treatment, as specific markers of targeted therapies.

In cancer therapy, during the last decade, a major development was the advent of Tyrosine Kinase Inhibitors (TKI), these small molecules inhibit pathologically induced activation of RTKs. Till date, several RTKs can be targeted by small molecule inhibitors, and clinical evidence indicates that tumors carrying mutations involving RTK genes are particularly susceptible to such inhibitors, most probably because of tumors becoming “addicted” to specific kinase pathways. The advantages of TKI over conventional chemotherapy are numerous; such as this treatment is specific for cancer cells and it is less toxic and it can be utilized at any age and every stage of the disease with minimal harm to body’s physiological functions. TKIs have been approved for several malignancies in both hematolymphoid and solid tumor groups.

The first successfully used TKI, Imatinib Mesylate (Gleevec), was very effective in treating Chronic Myeloid Leukemia (CML). This success led to an accelerated approval of this drug in 2001. Currently, the predicted survival time of CML patients has improved from 15 months before Imatinib to a projected 15 years after the latter’s introduction. With the passage of time, the list of TKIs have expanded as well as their application in various cancers particularly lung cancer, breast cancer, gastrointestinal stromal tumor, and female genital tumors.

One of the disadvantage of this biological treatment, which by definition is non-cytotoxic and can thus be chronically administrated, is the development of resistance. During the course of treatment, response to
TKI is generally slow, which could be due to extrinsic mechanisms involving metabolism of drug, bioavailability or systemic deterioration due to progressive illness. In addition, intrinsic factors can also have major impact on drug response, like acquired mutations developed during the course of therapy seen in CML, lung tumors, breast tumors, hepatic and renal cancers. In a tumor where a single dominant oncogene, such as the RTK, is activated by mutations; acquired resistance is the consequence of secondary mutations generally affecting the kinase domain of the receptors. This ultimately results in the modification of the kinase conformation, which becomes no longer compatible with the TKI-binding.

To overcome the failure of therapy, the initial approach includes escalation of TKI dose, but it is usually associated with side effects and intolerance. New emerging second line TKIs are more potent, most of them have dual target/receptor action with high efficacy. The combination of second line with first line TKIs was found significantly more effective and less toxic in various clinical trials.

In future, prospective use of molecular modeling and simulation for the selection of new TKIs is likely to pave the way towards a truly personalized treatment. The upcoming future technologies have the potential for designing multi-targeted therapeutic agents with the ability to effectively inhibit both primary and/or expected secondary mutations. The new agents in the pipeline include multi-targeted TKIs and non-selective inhibitors of tyrosine kinases. Majority of these are currently in preclinical workup or phase I/II trials and hopefully, these agents will soon become available for treatment of cancer patients as mono or combination therapies.

REFERENCES