Emerging Role of Tyrosine Kinases as Drugable Targets in Cancer

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Supplementary Issue: Tyrosine Kinases in Cancer

ABSTRACT: Tyrosine kinases (TKs) play a significant role in cancerogenesis and cancer cell function. Initial developments in this field go back to the early 80s, but the success story really started with the selective BCR-ABL inhibitor, imatinib. Owing to the cancer-driving role of BCR-ABL in chronic myeloid leukemia (CML), excellent response rates lead to fast FDA approval in both the first and second treatments of CML patients. Since then, numerous TKs were identified. TK inhibitors have been developed accordingly, and technology to test for ideal drug–target interactions has profoundly improved. By now, medical oncologists and hematologists struggle to have a pool of potential TK inhibitors, where the most efficient one could be picked out to treat a specific cancer patient, which might also help overcome the occurring resistance mechanisms against TK inhibitors. Whether disease eradication can be achieved via single or sequential TK inhibitor treatment(s) needs to be tested in the present and in the future.

KEYWORDS: tyrosine kinase inhibitors, targeted therapy, cancer

Early Steps

Identification of tyrosine kinases with a critical role in cancer. As cloning technologies improved over the past few decades, cloning of large gene transcripts became available and allowed for the identification of cDNA, encoding for biologically relevant physiological peptide kinases and growth factors, including the group of tyrosine kinases (TKs). TKs are involved in multiple aspects of a "normal cell life." They take part in essential processes, including cell signaling, differentiation, proliferation, and survival. Most receptor TKs are transmembrane proteins that bind extracellular ligands and hand over the signal to cytoplasmic effector and adaptor proteins to regulate biological processes. Nonreceptor TKs, typically, are located in the cytoplasm and include many well-characterized proteins, such as the Src family kinases, c-Abl, and Jak kinases.

Their potential participation in cancer development and cancer cell function was suggested when a close relationship of epidermal growth factor receptor (EGFR) and *the viral oncogene v–erbB*[1,2] was revealed, and cloning of chromosomal translocations associated with malignancies enabled the characterization of oncogenic gene alterations.

Enhanced TK activity or constitutively active kinase activity with quantitatively and qualitatively altered downstream signaling has been regularly found in human malignancies.

These dysregulations are caused by gene amplification or overexpression of protein tyrosine kinases (PTKs) as in the case of HER2 and breast cancer and genomic rearrangements or chromosomal translocations resulting in fusion proteins as in the case of BCR-ABL and chronic myeloid leukemia (CML). Another example in this direction is the anaplastic lymphoma kinase in anaplastic large cell lymphoma.[3] Furthermore, gain of function mutations or deletions in PTKs within the kinase domain or extracellular domain play a role as in the case of *EGFR* mutations and certain types of lung cancer. Mutations causing aberrant B-cell receptor activation are also relevant as in the case of Bruton's tyrosine kinase (BTK) and B-cell lymphomas.[4]

Past Era

Development of specific TK inhibitors for known TK targets. The first targeted antikinase therapeutic agent was the monoclonal antibody trastuzumab used in the treatment of breast cancer. The discovery of *HER2* gene amplification in breast and ovarian cancers was the basic finding that triggered the development of this antibody.

With advanced technologies, analysis of TK transforming properties became possible, and structure–function studies facilitated the development of small molecule inhibitors, specifically targeting constitutively activated protein kinases.

Specific TK inhibitors were developed to interfere with TK enzymes that are aberrantly activated in tumor cells and are critical to tumor growth. Antibodies against TK receptors or their ligands interrupt TK signaling through interference of the ligand-receptor binding. Many other TK inhibitors are designed to directly block the catalytic activity of the kinase by interfering with the binding of ATP or substrates. In 2001, imatinib was the first selective TK inhibitor that was approved by the FDA for use in patients with CML.[5,6] This small molecule revolutionized the treatment and prognosis of Philadelphia chromosome-positive CML.[7] Since imatinib potently inhibited the TKs such as Platelet-derived growth factor receptor (PDGFR) and KIT, the FDA approved its use also for patients with advanced GIST. Up to now, numerous anti-TK small molecules or monoclonal antibodies were integrated into therapeutic guidelines in different cancer entities, solid tumors (eg, bevacizumab, sunitinib, and gefitinib), and hematological malignancies (eg, ruxolitinib,[8] ibrutinib, and idelalisib[9]).

TK inhibitors, typically, are orally administered and generally exhibit good tolerability that distinguishes these agents from conventional cytotoxic chemotherapies. However, as also seen with other drugs, efficacy of TK inhibitors is limited by the development of resistance. Mechanisms leading to drug resistance of tumor cells are manifold, often described are mutations, mostly point mutations that impede TK inhibitor binding,[10,11] altered gene copy numbers, and protein expression level, which lead to restoration of oncogenic signaling in the presence of a given drug concentration (eg, *bcr–abl* amplification)[12] or increased drug efflux via increased MDR-1 expression.[13] In order to overcome mutational escape routes, TK inhibitor designs were optimized and second/third-generation TK inhibitors became available.[14] Since second-generation TK inhibitors induced better responses compared to imatinib in patients with newly diagnosed chronic-phase CML, nilotinib and dasatinib were also approved for first-line treatment. However, there is less clinical experience and long-term effects need to be compared to imatinib. Ponatinib, as a third-generation TK inhibitor, was the effective TK inhibitor in patients with T315I so far.

Present and Future Steps

Application of available TK inhibitors across different tumor stages and cancer entities. Some TKs like BCR-ABL are restricted to specific types of cancer, but others are commonly expressed and exhibit tumor-promoting activity in many solid tumors, such as EGFR. Targeting EGFR, therefore, affects various tumor cell types. However, efficiency is not as striking compared to BCR-ABL, because EGFR is not the only molecule driving the tumor growth.

As TKs are essential in many physiological functions and are involved, if dysregulated, in many general tumorigenic processes like invasion, metastasis, and prolonged survival, targeting TK activity is successful across disease stages and also across different cancer entities (eg, anti-EGFR in NSCLC, colon cancer, etc, as well as anti-BTK in diffuse large cell lymphoma, mantle cell lymphoma, etc). Therefore, current studies address the search for new TK targets to broaden TK inhibitor application by analyzing tyrosine kinomes in different cancers using high-throughput sequencing technologies or microarray-based technologies combined with bioinformatics.

Another option could be "drug repositioning" on the search for the ideal TK inhibitor out of the already existing pool of TK inhibitors. An unbiased drug sensitivity and resistance testing of patient-derived cancer cells could reveal new drug–target interactions and, thereby, provide a basis for different and/or broader clinical applicability of TK inhibitors. One example is axitinib, an antiangiogenic drug already approved for renal cancer, that has recently been shown to potently inhibit the highly resistant T315I mutation of the bcr-abl gene.[15]

Beside the "effectiveness" criterion, safety/clinical applicability is also of great importance. Different TK inhibitors exhibit unique toxicity profiles and – given a comparable efficiency – selection of the ideal TK inhibitor can be adapted to individual patients with certain comorbidities, for example, in the case of a CML with T315I mutation: ponatinib with side effects like hypertension, rash, and abdominal pain versus axitinib with side effects like cardiac insufficiency, embolic/thrombotic events, and bleedings.

Perspective

TK inhibitors proved to be very efficient and established a new treatment option in various cancer entities. However, to which extent TK inhibitors can facilitate disease eradication is still unclear. Results from both the STOP-Imatinib study and the TWISTER study showed that molecular remissions sustained in 40%–50% of the patients for at least 12–24 months after imatinib cessation.[16,17] To estimate the long-term efficacy of TK inhibitor cessation, more discontinuation studies and especially longer follow-ups are necessary. More studies are necessary to determine the best time point to restart TK inhibitor treatment for optimal outcome.[18] Moreover, trials addressing this issue for solid tumor entities are missing so far. Apart from their imminent clinical relevance, these strategies are also of biological interest as they address the question, whether TKI may ultimately result in chronic disease control or may even have the potential to trigger cure.

Author Contributions

Wrote the first draft of the manuscript: IKN. Contributed to the writing of the manuscript: PlC. Jointly developed the structure and arguments for the paper: IKN, PlC. Made critical revisions and approved final version: IKN, PlC. Both authors reviewed and approved of the final manuscript.

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