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Kinase Inhibitors: the Reality Behind the Success

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Abstract

Tremendous progress has been made by utilizing kinase inhibitors in oncology, and these agents continue to pave the way into other areas of medicine. There are, however, many challenges to the application of kinase inhibitors due to inherent shortcomings of the drugs and lack of comprehensive understanding of tumor and disease biology. The future fate of kinase inhibitors, however, is bright as evidenced from ongoing efforts to increase their efficacy while remediating their weaknesses in order to provide the best quality of care to patients.

“Growth for the sake of growth is the ideology of the cancer cell.”

Edward Abbey

Imatinib (Gleevec) was the first tyrosine kinase inhibitor approved in 2001 for the treatment of Philadelphia chromosome positive chronic myeloid leukemia targeting Bcr-Abl. With the introduction of imatinib, small molecule kinase inhibitors pioneered the field of oncology by shifting the landscape through a shift in standard of care from conventional chemotherapy to the use of targeted therapeutics based on individual genomics.^{1,2} Implementation of orally administered targeted agents in the treatment of a malignant disease was groundbreaking and led one step closer to the application of precision medicine. Just over a decade later, tofacitinib (Xeljanz) was the first tyrosine kinase inhibitor approved in 2012 for a non-malignant indication, moderately to severe active rheumatoid arthritis, and this was followed in 2014 by the approval of nintedanib (Ofev) for idiopathic pulmonary fibrosis. The search for small molecule KIs has remained an active field of research in both academia and industry, and many of these agents have been approved by the US Food and Drug Administration. In the first decade following the approval of imatinib, 8 additional inhibitors were introduced into the clinic. Another 26 kinase inhibitors were approved between 2011 to July 2017 with many more undergoing clinical evaluation (Table 1). With more than 500 known kinases in human genome, the list of kinase inhibitors will only grow as dysregulated cell signaling continues to be implicated in a wide range of disease processes.³ Therefore, elucidating biological and pharmacological properties of these drugs is important to inform correct drug regimens and strategies to treat patients.

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Conflict of interest

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Regardless of their intended molecular targets, the majority of kinase inhibitors share a mode of action whereby they compete with adenosine triphosphate (ATP) at the binding pocket of the catalytic domain of the kinase, thus preventing phosphorylation of target proteins and turning off their downstream signals. Depending on how these kinase inhibitors bind to their targets, they can be largely divided into two classes, namely type I and type II inhibitors. Type I inhibitors bind to the ATP binding site and target the active kinase conformation, whereas type II inhibitors mainly occupy a region adjacent to the ATP-binding site and trap their target kinases in an inactive state.^{3–6} The 35 presently approved kinase inhibitors can alternatively be categorized based on their target kinases, namely tyrosine kinase, serine/threonine kinase, and lipid kinase. The majority of approved kinase inhibitors are tyrosine kinase inhibitors, 2 are serine/threonine kinase inhibitors, and idelalisib, a PI3K inhibitor, is the first and only agent approved as a lipid kinase inhibitor. Usage of kinase inhibitors in patients has brought improved overall outcomes in malignancies and changed the course of progression and management of many diseases.^{2,4,7} Furthermore, agents in this class have utility beyond oncological diseases with new kinase inhibitors being approved for immunological and inflammatory diseases. Despite the success and steady approval rate of kinase inhibitors, scientific and medical communities face great challenges that need to be addressed for better outcomes in patients, including improving efficacy, mitigating toxicities and long term consequences of chronic treatments, and increasing their use in underserved populations.

While more than a decade has passed since imatinib was introduced to the market, with each new kinase inhibitor being extensively studied post-approval, the unpredictability of the pharmacokinetic properties of these agents continues to be problematic.⁸ As discussed in this issue of *Clin Pharmacol Ther* by Verheijen et al,⁹ pharmacokinetic variability poses a great risk for the development of toxicity or suboptimal efficacy. Therapeutic drug monitoring (TDM) is an accepted practice to guide dose adjustments for many marketed drugs, including several anti-microbial agents, antiepileptics, and immunosuppressants, yet a fixed dose regimen is still common practice for kinase inhibitors used in oncology. Drug exposure should be carefully monitored in patients receiving treatment with kinase inhibitors, and if validated prospectively in clinical trials, TDM could be a valuable strategy for treatment optimization of kinase inhibitor-based therapy. Randomized clinical trials evaluating the clinical utility of TDM are uncommon; however, they have been conducted previously for cytotoxic drugs demonstrating feasibility of this approach. Implementation of TDM of kinase inhibitors could contribute minimizing toxicity, and deliver optimized pharmacotherapeutic care.⁹

Monitoring tumorigenesis through biomarkers is also a major factor to consider for providing the best care in patients, as discussed in this issue article by Sumanasuriya et al.¹⁰ Blood-based assays or liquid-biopsies are useful tools to screen a patient's tumor status before, during, and after treatment with targeted therapy. While tissue biopsies remain the standard, liquid biopsies can replace the current practice of tissue biopsies to relieve the patients from burdensome procedures that can reduce treatment-related risks and morbidity. Both nucleic acid and tumor cells circulating in blood samples that are shed from tumors are used for profiling tumor tissue. Recently, companion diagnostics, for instance Cobas (Roche), have become commercially available to easily evaluate tumor mutation status for

EGFR inhibitor treatment, aiding in monitoring tumor response during therapy. Such liquid biopsies can make noninvasive procedures more accessible to patients and be used in clinical decision making that could define the course of treatment care.¹⁰

Another barrier to the clinical efficacy of kinase inhibitors as well as other anti-cancer agents is the occurrence of acquired resistance through various mechanisms. One such mechanism is heterogeneous drug uptake and distribution in tumors to the site of action, which can lead to limited clinical utility of these agents. In this issue, Morosi et al assert that while systemic drug plasma levels can be used as a surrogate point for measuring total drug exposure, it often does not accurately predict tumor concentrations due to the complex nature of the tumor microenvironment.¹¹ The authors propose 3D mass spectrometry imaging as a novel method to visualize localization of drugs in tumor tissues, thus providing precise assessment of drug penetration. With this method, the authors were able to create a 3D representation of imatinib uptake and retention in a resistant tumor xenograft model, highlighting the heterogeneous distribution of this drug in tumor tissue. This procedure provides a platform to depict how kinase inhibitors are physiologically distributed and how quantitative monitoring in the clinical could contribute to treatment optimization in the future.¹¹

With the revolution that was brought by targeted cancer therapies, some agents have produced long and durable responses or even cures, which has brought clinicians and patients to consider the long term consequences of kinase inhibitor usage. In this issue, Ramstein et al discuss the consequences in male reproductive health from kinase inhibitor treatment.¹² While work in this field is still premature, treatment with certain kinase inhibitors could potentially affect the reproductive health of young cancer survivors. As we approach the end of the second decade of kinase inhibitor use, more preclinical and clinical studies are warranted to investigate the lasting effects of these agents not only in reproductive health but in other physiological systems as well.¹²

Substantial advances have been made since the medical community started to incorporate kinase inhibitors into routine treatment modalities. The contribution of scientists and clinicians to the development of such innovative therapies that have improved outcome of many diseases is certainly laudable. However, there is still much to be learned about kinase inhibitor therapy including in terms of their role in acquired drug resistance in cancer, their wide interpatient pharmacokinetic variability, and their unpredictable tissue penetration patterns. With more than 30 agents in the class, only a handful of kinase inhibitors have been tested in pediatric patients, leaving this an underserved patient population. A few kinase inhibitors have brought controversy as being “me-too” drugs with marginal benefit over previously existing agents for the same indication.¹³ Putting past success with these agents behind, further development and characterization of kinase inhibitors in various disease models with interdisciplinary research in all arenas –government, academia, and industry– will propel these novel therapeutics forward and increase our understanding of their optimal use. This, in turn, will ultimately enhance treatment outcomes and offer patients a better quality of life.

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References

1. Wu P , Nielsen TE & Clausen MH . FDA-approved small-molecule kinase inhibitors. Trends. Pharmacol. Sci 36, 422–39 (2015).25975227
2. Drenberg CD , Baker SD & Sparreboom A Integrating clinical pharmacology concepts in individualized therapy with tyrosine kinase inhibitors. Clin. Pharmacol. Ther 93, 215–9 (2013). 23419484
3. Manning G , Whyte DB , Martinez R , Hunter T & Sudarsanam S The protein kinase complement of the human genome. Science. 298, 1912–34 (2002).12471243
4. Zhang J , Yang PL & Gray NS Targeting cancer with small molecule kinase inhibitors. Nat. Rev. Cancer 9, 28–39 (2009).19104514
5. Wu P , Neilsen TE & Clausen MH Small-molecule kinase inhibitors: an analysis of FDA-approved drugs. Drug. Discov. Today 21, 5–10 (2016).26210956
6. Liu Y & Gray NS Rational design of inhibitors that bind to inactive kinase conformations. Nat. Chem. Biol 2, 358–64 (2006).16783341
7. Gross S , Rahal R , Stransky N , Lengauer C & Hoeflich KP Targeting cancer with kinase inhibitors. J. Clin. Invest 125, 1780–9 (2015).25932675
8. Baker S & Hu S , Pharmacokinetic considerations for new targeted therapies. Clin Pharmacol. Ther 85, 208–11 (2009).19092780
9. Verheijen RB , Yu H , Schellens JHM , Beijnen JH , Steeghs N & Huitema ADR Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. Clin. Pharmacol. Ther this issue (2017).
10. Sumanasuriya S , Lambros MB & de Bono J Application of liquid biopsies in cancer targeted therapy. Clin. Pharmacol. Ther this issue (2017).
11. Morosi L , Application of 3D mass spectrometry imaging to TKIs. Clin. Pharmacol. Ther this issue (2017).
12. Ramstein J , Tsai KK & Smith JF Tyrosine kinase inhibitors and male reproductive health. Clin. Pharmacol. Ther this issue (2017).
13. Byawali B & Prasad V Healthy policy: me-too drugs with limited benefits – the tale of regorafenib for HCC. Nat. Rev. Clin. Oncol [Epub ahead or print] (2017).

Table 1.

Kinase inhibitors approved by the US Food and Drug Administration

Initial FDA approval	Generic name (brand name)	Presumed target(s)	Class	Indication
2001	Imatinib (Gleevec)	Bcr-Abl, c-Kit, PDGFR, SCF	TKI	Ph+ CML, Ph+ ALL, MDS/MPD, c-Kit ASM, HES/CEL, DFSP, c-Kit+ GIST
2003/2015	Gefitinib (Iressa)	EGFR	TKI	NSCLC
2004	Erlotinib (Tarceva)	EGFR	TKI	NSCLC
2005	Sorafenib (Nexavar)	Multikinase	TKI	RCC, HCC, DTC
2006	Dasatinib (Sprycel)	Bcr-ABL, SRC, KIT, EPHA2, PDGFR β	TKI	Ph+ CML, Ph+ ALL
	Sunitinib (Sutent)	Multikinase	TKI	GIST, RCC, pNET
2007	Lapatinib (Tykerb)	EGFR, HER2	TKI	HER2+ breast cancer
	Nilotinib (Tasigna)	Bcr-Abl	TKI	Ph+ CML
2009	Pazopanib (Votrient)	Multikinase	TKI	RCC, advanced soft tissue sarcoma
2011	Ruxolitinib (Jakafi)	JAK1/2	TKI	Myelofibrosis, polycythemia vera
	Crizotinib (Xalkori)	ALK, ROS1	TKI	NSCLC
	Vemurafenib (Zelboraf)	BRAF	TKI	BRAF V600 melanoma
	Vandetanib (Caprelsa)	EGFR, VEGFR, RET, BRK TIE2, SRC	TKI	Thyroid cancer
2012	Ponatinib (Iclusig)	Multikinase	TKI	CML, Ph+ ALL
	Cabozantinib (Cabometyx)	Multikinase	TKI	RCC
	Tofacitinib (Xeljanz)	JAK3	TKI	Rheumatoid arthritis
	Regorafenib (Stivarga)	Multikinase	TKI	CRC, GIST, HCC
	Bosutinib (Bosulif)	Bcr-Abl, SRC	TKI	Ph+ CML
	Axitinib (Inlyta)	VEGFR	TKI	RCC
2013	Ibrutinib (Imbruvica)	BTK	TKI	MCL, CLL/SLL, WM, MZL, cGVHD
	Afatinib (Gilotrif)	EGFR, HER2/4	TKI	NSCLC
	Dabrafenib (Tafinlar)	BRAF	TKI	BRAF V600 melanoma
	Trametinib (Mekinist)	MEK1/2	TKI	BRAF V600 melanoma
2014	Nintedanib (Ofev)	Multikinase	TKI	Idiopathic pulmonary fibrosis
	Idelalisib (Zydelig)	PI3K	LKI	CLL, follicular B-cell non-Hodgkin lymphoma, SLL
	Ceritinib (Zykadia)	ALK, IGF1-R, InsR, ROS1	TKI	NSCLC
2015	Palbociclib (Ibrance)	CDK4/6	STKI	HR+ breast cancer
	Lenvatinib (Lenvima)	VEGFR, FGFR, PDGFR, KIT, RET	TKI	DTC, RCC
	Cobimetinib (Cotellic)	MAPK, MEK1/2	TKI	BRAF V600 melanoma
	Osimertinib (Tagrisso)	EGFR	TKI	NSCLC
	Alectinib (Alecensa)	ALK, RET	TKI	NSCLC
2017	Ribociclib (Kisqali)	CDK4/6	STKI	HR+ breast cancer
	Brigatinib (Alunbrig)	ALK, ROS1, IGF-1R	TKI	NSCLC
	Midostaurin (Rydapt)	Multikinase	TKI	FLT3-ITD+ AML

Initial FDA approval	Generic name (brand name)	Presumed target(s)	Class	Indication
	Neratinib (Nerlynx)	EGFR, HER2/4, MAPK, AKT	TKI	HER2+ breast cancer

Abbreviations: TKI: tyrosine kinase inhibitor, STKI: serine/threonine kinase inhibitor, LKI: lipid kinase inhibitor, CML: chronic myeloid leukemia, ALL: acute lymphoid leukemia, ASM: aggressive systemic mastocytosis, HES/CEL: hypereosinophilic syndrome/chronic eosinophilic leukemia, DFSP: dermatofibrosarcoma protuberans, GIST: gastrointestinal stromal tumors, NSCLC: non-small cell lung cancer, RCC: renal cell carcinoma, HCC: hepatocellular carcinoma, DTC: differentiated thyroid cancer, pNET: pancreatic neuroendocrine tumors, HR: hormone receptor, GI- NET: gastrointestinal NET, TSC: tuberous sclerosis complex, SEGA: subependymal giant cell astrocytoma, CRC: colorectal cancer, MCL: mantle cell lymphoma, SLL: small lymphocytic lymphoma, WM: Waldenstrom's macroglobulinemia, MZL: marginal zone lymphoma, cGVHD: chronic graft versus host disease, AML: acute myeloid leukemia.