

Review

From dominance to decline: can we reverse the trend in small molecule and TKI cancer therapies?

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Summary

Over the past two decades, precision oncology has seen unprecedented advances, particularly with the rise of small molecule drugs. These drugs have significantly benefitted patients with cancer harboring somatic genomic alterations, contributing to precision cancer medicine. Despite their early promise, there is a growing concern that major pharmaceutical companies are recently moving away from developing small molecules and tyrosine kinase inhibitors (TKIs) due to market saturation, primary and secondary resistance, and economic factors. The Inflation Reduction Act (IRA) further threatens innovation by reducing incentives for small molecule drug development. Additionally, patient access to comprehensive genomic testing remains a significant barrier. To reverse this trend, a multifaceted approach is urgently needed. Embracing cutting-edge technologies, fostering collaborations, and regulatory innovation are essential. Addressing systemic deficiencies, improving patient access, and ensuring ongoing investment in personalized medicine are crucial for realizing the full potential of small molecule oncology drugs and improving patient outcomes. Collaboration among stakeholders is imperative for advancing effective cancer treatments.

Key words: small molecule inhibitors, TKI, precision medicine, tyrosine kinase inhibitors, precision oncology

Introduction

Over the past two decades, we have witnessed unprecedented advances and remarkable strides in precision oncology. Among the most notable advancements is the rise of small molecule drugs. The advent of small molecules spearheaded the era of precision oncology, particularly benefiting cancer patients with somatic genomic alterations. Of the 160 approved oncology drugs between 2001 and 2021, 68% were small molecules, contributing to the realization of precision cancer medicine based on an individual patient's genetic alteration features ¹. A quarter-century back, Christopher A. Lipinski crafted a series of principles aimed at defining the traits of effective orally administered "small molecules". Known as the Rule of 5, these guidelines emerged from the observation that promising drug candidates typically had a molecular mass under 500 g/mol and exhibited lipophilicity. However, it's important to note that not all medicinal chemists' drug developments conformed to these standards, and indeed, they never have.

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However, it is becoming increasingly concerning that major pharmaceutical companies are moving away from developing small molecules and tyrosine kinase inhibitors (TKIs) for cancer treatment, driven by emerging trends and challenges². In this discussion, we explore the present obstacles facing small molecule drug development and consider potential strategies to reverse these trends in the future.

Historical perspective

The significance of personalized medicine's rise, marked by the introduction of drugs like Gleevec, is immense³. The treatment of chronic myeloid leukemia (CML) was revolutionized, showcasing a groundbreaking approach to fighting cancer. What was once a fatal disease has now been transformed into a condition where patients on TKIs can anticipate nearly normal lives. This development undeniably represents the creation of a new paradigm in cancer therapy. It is not an overstatement to say that a new paradigm in cancer therapy has emerged. Starting with first-generation small molecules such as crizotinib for *ALK* fusions and erlotinib for *EGFR* mutations, the development has progressed to newer-generation better-in-class to best in class molecules like lorlatinib and osimertinib. These advancements have offered significant benefits to specific groups of patients with advanced or metastatic non-small cell lung cancer (NSCLC) harboring specific genomic alterations.

The initial triumphs and promise of TKIs drew significant attention and investment to this burgeoning field. Combining a deeper understanding of cancer and its targets with technological advancements in drug discovery was viewed as the key to accelerating the next generation of small-molecule oncology drugs. Innovative small-molecule drugs are now emerging across various therapeutic domains, particularly in oncology, immunology, and neurology. Their superior efficacy and safety compared to traditional chemotherapy have established them as essential treatments for cancer. In recent years, the surge in FDA-approved targeted cancer therapies has highlighted the growing use of small-molecule drugs to pinpoint specific pathways or molecules involved in cancer progression. The rise of modern molecular biology and advanced molecular pathology testing, including next-generation sequencing (NGS) for target identification, has propelled the rapid development of these drugs. This progress is further bolstered by cutting-edge technologies, computer-aided drug design, structural biology, and combinatorial chemistry⁴. Moreover, initiatives like the US FDA's accelerated approval program have spurred the

development of small molecule drugs targeting cancers identified by specific biomarkers.

A shift in mood and direction?

In recent years, there has been a noticeable decline in the focus on small molecules and TKIs. This shift has partly been driven by positive factors, such as the exploration of other promising new approaches in cancer treatment. However, negative factors have also played a significant role. Commercial considerations, such as market saturation and competition, have influenced this decline. Additionally, many patients exhibit primary resistance to TKIs despite the presence of the molecular target, leading to higher toxicity and lower efficacy, thus creating an urgent need for alternative treatments for these patients. There are more fundamental concerns as well. Multiple pharmaceutical companies are targeting the same cancer populations with same biomarkers, resulting in the neglect of other patient groups. Advances in cancer understanding have led to more refined diagnoses and correspondingly narrower patient populations, which affects the potential returns on investment in a system not designed for long-term innovation⁵.

Small-molecule-targeted anti-cancer drugs face inherent challenges, such as drug resistance linked to gene mutation, gene amplification or gene fusion, or dysregulation of apoptosis. TKIs are also associated with varying therapeutic responses among individual patients and across patient populations. Factors like potency, selectivity, individual drug metabolism profiles, pharmacokinetics, and tumor heterogeneity, add to these complexities. Preventing both primary and secondary resistance and developing more selective TKIs could provide solutions, but market dynamics may be jeopardizing this exploration. These circumstances have fostered the rise of smaller biotech companies that are developing new molecules. The introduction of "fast follower" drugs – new products targeting validated cancer vulnerabilities – is disrupting the U.S. market. These drugs often have shorter development times and conduct clinical trials in less costly countries, such as China, aiming for similar clinical outcomes as more expensive, approved options. This trend is intensifying market competition⁶. The reason for this shift is clear: smaller biotech firms tend to be more agile than large pharmaceutical companies in an environment characterized by rapid innovation. While innovation is welcome, it is crucial for health-care policy to realistically address the complexities of drug development and provision.

Challenges in patient testing and identification

The advancement of small molecules faces another significant obstacle: their reliance on comprehensive genomic testing and precise patient identification. Central to their efficacy is NGS testing, and for these treatments to be widely adopted, NGS testing must be broadly accessible. Beyond the scientific aspects of drug discovery, improving patient access to genetic testing and approved medications is essential to fully realizing future benefits. Currently, this is not a given. While NGS is becoming standard in some highly developed healthcare systems for high-burden cancers like NSCLC, significant limitations remain in patient testing for other conditions. These gaps inevitably impact patient identification and treatment outcomes. Despite the evident benefits for patients, widespread NGS adoption is hindered by multiple barriers. Issues of cost and accessibility persist, often exacerbated by a lack of awareness and infrastructure in certain regions⁷. Moreover, the trajectory of cancer treatments is influenced by a variety of external factors, most notably economic and regulatory considerations.

Effect of the Inflation Reduction Act

Currently, legislation in the world's largest pharmaceutical market – the United States – is exerting a profound influence through the Inflation Reduction Act (IRA). This legislation is expected to impose constraints on profitability, particularly for the top 30 drugs with the highest gross spending by Medicare, many of which are small molecule drugs with multiple indications⁸. The IRA is seen as a threat to innovation in small molecule drugs by reducing the economic incentives to develop these therapies for multiple uses. The non-partisan Congressional Budget Office has estimated that this law could result in the approval of 15 fewer drugs over a 30-year span. The law is expected to affect timelines for initial launches, post-approval research toward additional indications, and ultimately, patient access to new treatments. This poses an immediate threat to revenue streams and is also likely to impact research and development (R&D) investments in small molecules and TKIs.

A policy brief by Tomas J. Philipson, Yier Ling, and Ruiquan Chang from The University of Chicago examines the potential impacts of the IRA's policy to set prices for select small molecule drugs nine years after FDA approval⁹. The study suggests that such price controls undermine existing intellectual property laws, reducing incentives for investment in R&D. They con-

servatively estimate an 8.0% reduction in expected revenues for small molecule drugs in the U.S. market, leading to a 12.3% decrease in R&D investment, or \$232.1 billion over 20 years. This reduction in investment could result in 188 fewer small molecule treatments, including 79 fewer new drugs and 109 fewer post-approval indications, ultimately causing 116.0 million life years lost due to missed opportunities for health improvements. The brief emphasizes the importance of small molecule drugs in treating critical conditions such as cancer and mental health disorders, highlighting their advantages like ease of production, stability, and the ability to penetrate cell membranes and the blood-brain barrier. The study criticizes the Congressional Budget Office's estimate of 15 fewer new drugs over 30 years as a significant underestimate. The authors argue that the IRA's price-setting provisions, which reduce the time for manufacturers to earn returns from an average of 12-14 years to a maximum of 9 years, will disproportionately impact small molecule drug innovation. They conclude that the IRA will not only hinder new drug development but also discourage post-approval research, negatively affecting patient health and exacerbating health inequities. This unexpected shift was an inadvertent consequence that likely escaped everyone's foresight. It has the potential to impact the development of drugs for rare diseases and pediatric conditions, and it is already influencing future investments in small molecule drug development.

Emergence of other therapeutic areas

Broader economic factors further complicate the landscape, leading to shifts in market dynamics and investment priorities. Comparisons with other therapeutic areas suggest that the continued development of small molecule therapies may be particularly at risk. In 2023, oncology dominated FDA approvals with 15 novel therapies, accounting for over 20% of all approvals. Notably, small-molecule approvals outnumbered biologics. However, the rise of alternative cancer treatments and renewed focus on other therapeutic categories may signal a waning interest in small-molecule therapies. Innovations such as T cell-engaging bispecific antibodies, gene therapies, blood products, antibody-based treatments including antibody-drug conjugates, radiopharmaceuticals and oligonucleotide-based drugs suggest shifting expectations that could reallocate research spending and reimbursement funding¹⁰. Several specific case studies highlight the challenges faced. Targeted therapies for ultra-rare genetic alterations, such as *NTRK* and

ROS1 alterations, have struggled to gain a foothold in the market. Contributing factors include the limited size of the patient populations and the high development costs compared to the potential revenue¹¹.

Conclusion

Over the last two decades, cancer treatment has been revolutionized, particularly through the introduction of small molecules. However, a confluence of factors now threatens the continued development and optimization of these promising therapies. The risk is that the full potential of one of the most exciting advancements in cancer treatment may remain untapped. The pressing need is for the frequent creation of transformational medicines for underserved patient populations. These should feature better drug profiles, offering wider therapeutic windows, improved tolerability, longer treatment durations, greater efficacy, and the ability to combine new small molecules with other drug classes for optimized therapy and, ultimately, the potential to cure diseases. The theoretical outlook for cancer therapy development is promising, with a steady stream of potential growth areas and innovative breakthroughs. However, looming challenges cast a shadow over these prospects, not just for small molecules but for innovative cancer treatments at large. If the adverse factors impacting small molecule development extend to the broader cancer therapy landscape, the future's brilliance may be somewhat dimmed. Addressing the extensive and severe challenges common to many aspects of innovative therapy requires a proportional response, going beyond mere individual problem-solving. Strategic approaches are necessary, involving all stakeholders to tackle systemic deficiencies underlying current challenges. Pricing systems should be evaluated to create incentives for developing and launching new indications based on unmet medical needs and supported by real-world evidence. Improved patient outcomes – and potentially reduced healthcare costs – also depend on other conditions. Earlier diagnosis enables more efficient treatment, which in turn necessitates adequate numbers of oncology specialists, broader availability and access to high-quality oncology facilities, quality-assured molecular pathology laboratories, reduced waiting times, increased health literacy, and expanded access across socioeconomic groups. National cancer programs informed by epidemiological data and adherence to recognized guidelines can overcome unplanned healthcare provision. Strengthened research capacity is fundamental to the innovation that cancer patients desperately need.

Reversing the current decline in small molecule drugs in oncology requires a multifaceted approach that leverages advances in technology, collaborative research, and regulatory innovation. Firstly, embracing cutting-edge technologies such as artificial intelligence and machine learning can streamline the drug discovery process, identifying promising small molecules with greater efficiency and accuracy. Second, fostering collaborations between academic institutions, biotech companies, and pharmaceutical giants can pool resources and expertise, greatly accelerating the development pipeline. Third, regulatory bodies can also play a pivotal role by adopting more flexible and adaptive frameworks that facilitate faster approval processes for promising small molecule candidates. Fourth, investment in understanding the molecular mechanisms of cancer and identifying novel targets will also be crucial in developing next-generation small molecule therapies. Finally, a dedicated carve-out in the IRA could significantly boost innovation, providing financial incentives for research and development in rare and pediatric diseases. By understanding cancer at a molecular level and identifying new therapeutic targets, we can revive the small molecule oncology sector, ultimately leading to better patient outcomes and better quality of life, and a broader spectrum of treatment options.

Collaboration among all stakeholders – healthcare policymakers, government administrators, regulators, pharmaceutical companies, healthcare professionals, and patients – is crucial for improving access to oncology treatments. A call to action is needed, directed at everyone with a stake in and influence over the development of effective cancer responses.

This appeal must stress the crucial need for ongoing investment in personalized medicine, irrespective of the mechanism of action, as long as it provides clinical benefits. It should also champion policies and practices that ensure thorough patient testing and fair access to innovative treatments. By tackling the various issues that impact all facets of cancer responses, we can aspire to achieve satisfactory outcomes for cancer patients around the globe.

CONFLICTS OF INTEREST STATEMENT

Vivek Subbiah reports:

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AUTHORS CONTRIBUTIONS

Conceptualization, D.H.; methodology, D.H.; validation, formal analysis, investigation and data curation, D.H., P.F., D.S., U.M., and V.S.; resources, D.H. and V.S.; writing—original draft preparation, D.H., V.S., and D.H.; writing—review and editing, D.H. and V.S.; visualization, D.H.; supervision, D.H.; project administration, D.H.; funding acquisition, D.H. All authors have read and agreed to the published version of the manuscript.

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ETHICAL CONSIDERATION

Not applicable

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