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Review Article

Medicinal Chemistry of Anticancer Drugs

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ABSTRACT

In recent decades, combating cancer and preventing its onset have become major priorities for healthcare systems worldwide. Significant progress has been made in both treating various types of cancer and improving survival rates, thanks to advancements in therapeutic methods and the development of effective antitumor drugs. Today, the discovery and creation of anticancer medications are key areas of focus for pharmaceutical companies, research institutions, and both government and non-government organizations globally. Remarkable strides have been made in identifying and developing drugs that can target cancer cells. Numerous chemical compounds—whether synthetic or derived from natural sources—have been tested for their potential to fight cancer. However, despite these efforts, the pace of discovering truly successful anticancer agents remains slow. In fact, the failure rate for new cancer drugs is alarmingly high, with approximately 95% of drug candidates not making it past clinical trials, a much steeper decline compared to other medical fields. The costs involved in developing these drugs are also significant. It can take millions of dollars and many years of research to bring a promising anticancer drug to market. Despite these challenges, the relentless pursuit of effective cancer therapies continues, offering hope for better treatments and a future where cancer can be managed more successfully. Developing anticancer drugs is a complex and time-consuming process. After a drug candidate is identified, it must undergo extensive toxicological testing and pass through three phases of clinical trials before it can be approved for use. This review explores several crucial aspects of anticancer drug research, including the discovery, development, marketing, and the high costs associated with their therapeutic use over the past decade. It also discusses the approval process by three key regulatory bodies: the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).The review highlights the advances in cancer treatment that have been explored in the last ten years, focusing on the identification of specific biochemical characteristics of cancer cells that can be targeted more effectively. These discoveries are key to developing

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therapies that selectively attack tumor cells, reducing damage to healthy tissue. Market research shows that the global anticancer drug market has grown at a remarkable pace. However, the rise of counterfeit drugs, particularly those sold online, has created significant challenges for both pharmaceutical companies and the safety of cancer patients. In 2012, the total sales of anticancer drugs worldwide reached $80 billion, with these drugs leading the global market in terms of spending by therapeutic class. This highlights the immense financial stakes and the increasing demand for effective cancer treatments.

INTRODUCTION

Introduction: Discovery and Development of New Anticancer Drugs

Cancer remains a major global health challenge, ranking as the second leading cause of death after cardiovascular diseases, especially in developed regions such as Western Europe and North America. Over the past few decades, the fight against cancer has been a top priority for medical research and healthcare systems worldwide. Numerous organizations, both governmental and non-governmental, have made the discovery and development of new anticancer drugs a central focus. Key institutions such as the National Cancer Institute (NCI) in the United States, the European Organization for Research and Treatment of Cancer (EORTC), and other national research centers like the British Cancer Research Campaign (CRC) have driven this effort. In many developed countries, there has been significant investment in cancer research, prevention, diagnosis, and treatment. New research institutes and specialized laboratories have emerged to discover innovative ways to combat cancer. However, despite these advances, progress in cancer treatment has often been slow due to the complex nature of cancer biology. The unique biochemical characteristics of cancer cells make it challenging to target them selectively without affecting normal cells.

Challenges in Drug Discovery

Over the past 50 years, tremendous progress has been made in the discovery, development, and use of oncology drugs. By the late 1990s, over 600,000 compounds, including bioactive natural products, had been screened for potential anticancer properties, but fewer than 40 drugs were widely used in clinical settings. This highlights the difficulty of translating initial findings into effective treatments. In recent decades, thousands of promising molecular compounds have been tested as potential anticancer agents. The development of cancer drugs differs significantly from other types of drug discovery. The process is long and costly, requiring rigorous toxicological testing and several stages of clinical trials. Typically, the journey of developing an anticancer drug spans many years, with a significant number of candidates failing along the way. Conventional approaches to drug discovery in oncology have focused on cytotoxic agents—substances that kill or inhibit the growth of tumor cells. These drugs have often been identified by studying the biochemical pathways essential to cancer cell division. In recent years, advancements in molecular biology and a deeper understanding of the molecular mechanisms driving tumor development have provided new opportunities for targeted therapy.

Targeted Therapy and Precision Medicine

The concept of targeted therapy has emerged as a groundbreaking approach to cancer treatment. These drugs are designed to interfere with specific molecular targets associated with cancer progression, growth, and metastasis. Targeted therapy is different from traditional chemotherapy, which broadly attacks rapidly dividing cells, often causing significant side effects. Instead, targeted

therapies focus on the unique molecular signatures of cancer cells, minimizing damage to healthy cells and offering the potential for more precise and effective treatment. Several anticancer drugs currently approved for clinical use are based on this targeted approach. These drugs work by inhibiting specific enzymes or proteins that are critical to cancer cell survival. For example:

- **Imatinib mesylate (Gleevec)**: A small-molecule drug that inhibits the Bcr-Abl fusion protein, a type of tyrosine kinase. It is primarily used to treat gastrointestinal stromal tumors (GISTs) and chronic myeloid leukemia (CML).
- **Gefitinib (Iressa)**: A drug that targets the epidermal growth factor receptor (EGFR), which is often overactive in certain cancers like non-small-cell lung cancer (NSCLC).
- **Bortezomib (Velcade)**: A proteasome inhibitor used in the treatment of multiple myeloma, particularly in cases resistant to other therapies.
- **Rituximab (Rituxan)**: A monoclonal antibody that targets the CD20 antigen on B-cells, used to treat B-cell non-Hodgkin's lymphoma and B-cell leukemia by inducing the destruction of these cells.

Looking Ahead: The Future of Cancer Drug Discovery

The landscape of cancer drug development continues to evolve rapidly, with ongoing breakthroughs in molecular oncology and new compounds entering clinical trials. While many of these drugs are still in the early stages of development, the success of targeted therapies like Imatinib, Gefitinib, and Rituximab highlights the potential for personalized cancer treatments that are tailored to the genetic profile of an individual's cancer. The discovery and development of new anticancer drugs remains a complex and resource-intensive process. Yet, as our understanding of cancer biology deepens, the future holds great promise for the creation of even more effective and less toxic therapies.

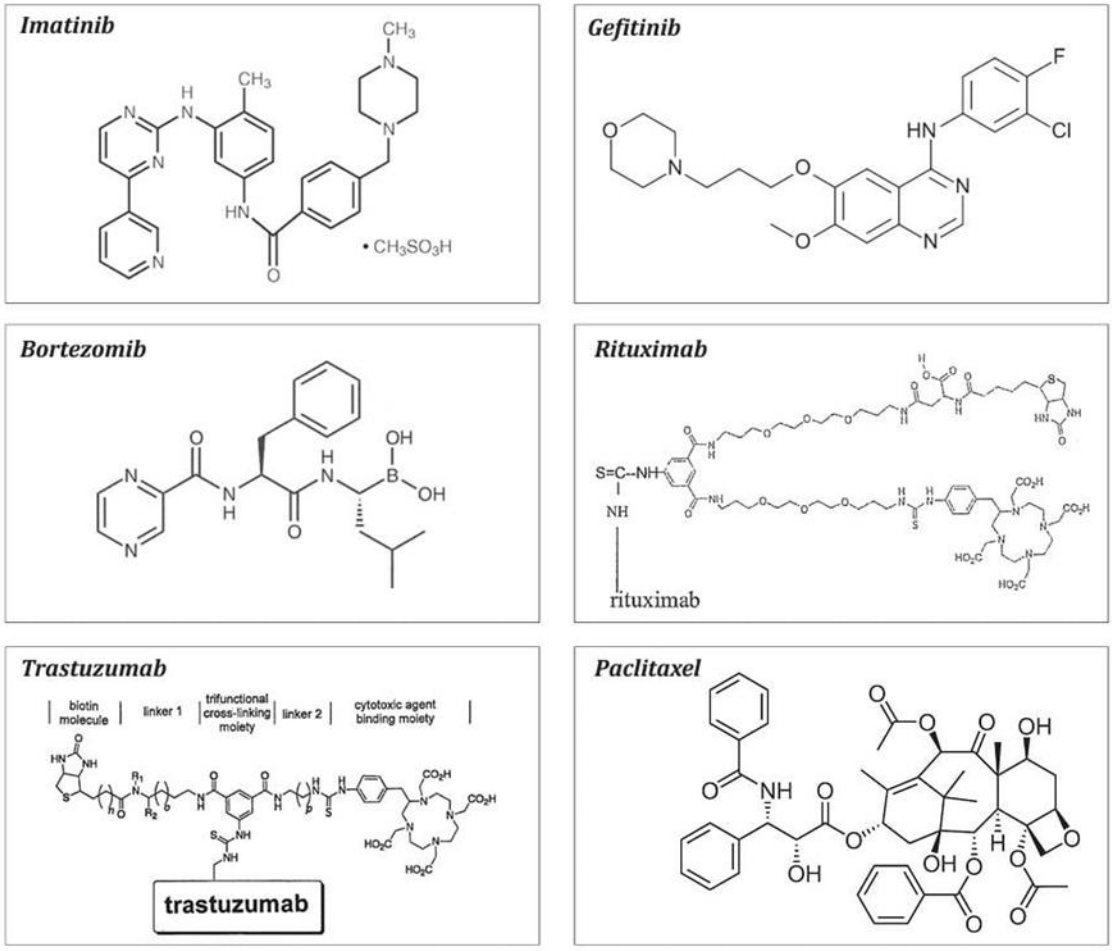

Figure:1: Chemical Structures of The Most Successful Anticancer Drugs Imatinab, Geftin, Bortezomib, Rituximab, Trastuzumab and Paclitaxel

The global market for cancer treatments has seen significant growth. A report from the IMS Institute for Healthcare Informatics in the USA highlighted that worldwide spending on oncology medicines, which covers both therapeutic treatments and supportive care, has surpassed $100 billion. This reflects the increasing investment and advancements in the development of cancer drugs, as well as the growing demand for better treatments and care options globally. In 2012, the global market for anticancer drugs was valued at $80 billion, and it's projected to reach $112 billion by 2020. While the number of commercial anticancer drugs remains limited, many new drugs are awaiting clinical approval. The leading anticancer drugs have generated significant revenue for pharmaceutical companies. For example, in 2013, Avastin (by Genentech/Roche) topped the list with sales of $6.7 billion, followed by $7.02 billion in 2014. Other notable drugs include Rituxan (Roche) with $6.11 billion in 2010 and $7.55 billion in 2014, Herceptin (Roche) at $5.22 billion in 2010, Gleevec (Novartis) at $4.22 billion in 2010, and Neulasta (Amgen) with $3.55 billion in 2010. The high costs associated with research, development, clinical trials, and marketing limit the number of successful anticancer drugs. Interestingly, just 18 anticancer drugs make up about 75% of the global oncology market, and one-third of these drugs are growing

by more than 30% annually. The top three pharmaceutical companies—Hoffmann-La Roche, Novartis, and Celgene Corporation—dominate the market, collectively accounting for approximately 70% of global sales. Other major players include Johnson & Johnson, AstraZeneca, Bristol-Myers Squibb, and Pfizer, along with Merck & Co., GlaxoSmithKline, Eli Lilly, Bayer AG, Amgen, AbbVie, and Sanofi S.A.Pharmaceutical patents typically last 20 years from the date they are filed, but several factors can influence how long a drug's patent remains active. In recent years, the expiration of patents for major cancer drugs like Herceptin, Erbitux, Rituxan, and Avastin is expected to drive the growth of the biosimilars market for cancer drugs by 2020. North America, including the USA, Canada, and Mexico, leads the global anticancer drug market, followed by Europe. In 2013, North America accounted for about 38% of the market share. This is largely due to significant investments by multinational companies in cancer drug research and development, especially in immunotherapies, as well as favorable reimbursement policies and the widespread adoption of these new treatments.The approval process for pharmaceutical drugs has become much more centralized and stringent over the last few decades. Even after a drug is approved and marketed, it continues to be closely monitored through systems designed to track its safety and effectiveness

Anticancer drug research of innovative antitumor mechanisms

The development of cancer drugs has evolved significantly over the years. The first generation of cancer drugs, which emerged in the 1950s, were mostly cytotoxic agents. These drugs worked by damaging DNA, stopping its synthesis, or interfering with cell division. They achieved this by targeting topoisomerases or binding to microtubules. Many of these early drugs were discovered by screening chemical compounds capable of killing cancer cells. One notable class of drugs from this era was DNA-alkylating agents, which were initially based on sulfur and nitrogen mustards. These compounds were later modified to control how quickly they reacted chemically, resulting in drugs like cyclophosphamide and ifosfamide. During this early period of cancer drug development, treatments weren't designed with the genetic and molecular understanding of cancer that we have today. Instead, the goal was simply to damage cancerous cells through DNA destruction. Since the 1950s, the first generation of cancer drugs was primarily made up of cytotoxic agents. These drugs worked by damaging the cancer cell's DNA, blocking its ability to divide, or interfering with the mechanisms that control cell division. They achieved this by targeting topoisomerases or binding to microtubules. Many of these drugs were discovered by screening for chemical compounds that could kill cancer cells. One key group of drugs from this early era was DNA-alkylating agents, which were originally based on sulfur and nitrogen mustards. These compounds were later modified to better control how they reacted chemically, leading to the development of drugs like cyclophosphamide and ifosfamide. At the time, cancer drugs weren't designed with today's understanding of cancer's genetic and molecular foundations. Instead, they were simply intended to damage cancer cells through DNA destruction.In recent years, however, there has been growing optimism among scientists working on new cancer drugs. Researchers are focused on developing innovative treatments with more targeted mechanisms of action. The goal is to discover selective drugs that can specifically target cancer cells, while minimizing the toxic side effects that

are commonly seen with traditional chemotherapy. Much of the research aimed at beating cancer has traditionally focused on understanding the various genetic mutations behind different types of cancer. However, in recent years, there's been a shift towards exploring innovative biochemical mechanisms. A great example of this is a study published in *Cancer Cell* in 2015 by researchers from the University of St. Louis, Missouri, led by Prof. Burris, a professor of pharmacology and physiology. The new approach taken by this research focuses on targeting the unique ways cancer cells satisfy their huge appetite for energy. Since cancer cells grow and divide rapidly, they need a lot of energy, which they often steal from healthy neighboring cells. The idea of disrupting the way cancer cells use energy differently from healthy cells isn't new, but it has recently gained more attention. For their study, the researchers at Saint Louis University focused on how cancer cells attract and utilize energy from surrounding healthy cells to fuel their rapid growth. This new direction in anticancer research holds exciting potential for more effective treatments. When it comes to approving anticancer drugs, different organizations handle the process depending on the region: the European Medicines Agency (EMA) in Europe, the Food and Drug Administration (FDA) in the United States, and the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) in Japan (which has been in operation since 1998). While each agency has its own set of rules and procedures, there is significant collaboration and information-sharing among them, especially between the FDA and EMA. The two agencies have developed a closer working relationship over time, exchanging insights and opinions on anticancer drug approvals. This is crucial because drug companies and their markets are global, making cross-agency cooperation important. Differences in decision-making can arise between the agencies, often due to varying approaches to evaluating the same data or clinical endpoints. There are also differences in how the agencies interact with the pharmaceutical industry and patients, which can influence the approval process. Despite these variations, the agencies are often working in parallel, as international pharmaceutical companies typically submit their approval applications to all three at the same time. A study comparing the approval processes for anticancer drugs in the EU, the USA, and Japan from 2006 to 2011 found that of the 46 applications reviewed, 29 resulted in new cancer drug approvals. Interestingly, the approval rate for cancer drugs in the EU (63%) was lower than for non-cancer drugs (73%). One key factor contributing to this gap was the longer review times in the EU, which were partly due to additional time needed for decision-making by the EU Commission and delays in submitting applications. This led to a median delay of 7.2 months for drugs to reach the market in the EU compared to the USA. In Japan, patients had to wait an additional 25.1 months. The approval process in the EU for anticancer drugs often shows a more modest success rate compared to the USA, where expedited review procedures help speed up access for patients. A separate study comparing drugs approved by both the EMA and the FDA found that, in general, the EMA met its goals for timely reviews. The mean approval times for products approved by both agencies were quite similar. However, some differences did emerge, particularly in the approval of oncology products, but neither the EMA nor the FDA seemed to have a more restrictive approach than the other. To improve patient access to new treatments, there is still a need for greater alignment and harmonization between the regulatory systems of

these agencies. In recent years, the rise of online pharmacies in many countries has led to a troubling increase in counterfeit drugs being sold. In 2012, the FDA discovered counterfeit versions of the expensive injectable anticancer drug bevacizumab (Avastin®) in the U.S. drug supply chain. The investigation revealed that some of these fake drugs came from Egypt. As a result, nearly 1,000 warning letters were sent out by the FDA to doctors and medical practices across 48 states and two U.S. territories, alerting them to the discovery of more counterfeit Avastin batches. Preventing counterfeit medicines from entering the USA is especially difficult, in part because nearly 40% of drugs are made overseas and approximately 80% of the active medicinal components of drugs are imported. Because many of these medicines are expensive, buyers are attracted by lower prices. The rise of Internet pharmacies makes regulation of drug safety more difficult. Detecting counterfeits is often difficult, because many of these goods pass through a long and complicated distribution network, thereby creating opportunities for counterfeits to enter the legitimate supply chain. USA consumers are largely unaware of the dangers of purchasing counterfeit drugs from Internet pharmacies: An estimated 36 million Americans have bought drugs online without a valid prescription Counterfeit medications are also a worldwide problem. The World Health Organization (WHO) estimates that as much as 30% of the medicines sold in parts of Asia, Africa, and Latin America are counterfeit. In 2011, 64% of antimalarial drugs in Nigeria were found to be counterfeit. Worldwide, an estimated 10% of all medicines are counterfeit.62-64 European countries have similar problems with counterfeit drugs, in particular with expensive anticancer pharmaceutical agents. The import of fake medicines in the EU is fuelled by the potential for high profits. Over a two - month period in 2009, European customs officers seized 34 million counterfeit pills, and fake drugs that have entered the legal supply chain in a number of EU countries. Fake Casodex, for instance European policy makers, regulators, health authorities and pharmaceutical companies have started to wage a war against counterfeit medicines. At an EU level, a series of laws to strengthen regulation in this area is currently under discussion, which will seek to ensure that legally produced drugs have a range of recognisable safety features including anti - counterfeiting packaging (barcodes and seals). Oversight of pharmaceutical distributors and legal Internet pharmacies will be tightened. The European Parliament is also pushing for heightened awareness of the dangers of counterfeit drugs as well as stiffer penalties against drug counterfeiters. Pharmaceutical companies are looking to new technologies that can detect tampering and make it easier to verify whether drugs are legitimate Counterfeit medicines are a global public health risk. A recent paper assessed counterfeit reports involving the legitimate supply chain using 2009–2011 data from the Pharmaceutical Security Institute Counterfeit Incident System (PSI CIS) database that uses both open and non - public data sources. Of the 1,510 identified CIS reports involving counterfeits, 27.6% reported China as the source country of the incident/detection. Further, 51.3% were reported as counterfeit but the specific counterfeit subcategory was not known or verifiable. The most prevalent therapeutic category was anti-infectives (21.1%) with most reports originating from health - related government agencies. Geographically, Asian and Latin American regions and, economically, middleincome markets were most represented. A total of 127 (64.8%) of a total of 196 countries had no legitimate supply

chain CIS counterfeit reports. Improvements in surveillance, including detection of security breaches, data collection, analysis, and dissemination are urgently needed to address public health needs to combat the global counterfeit medicines trade

CONCLUSIONS

In the last decades on a global scale, discovery, development, approval and marketing of new anticancer drugs is advancing very rapidly and new antitumour agents for novel treatment therapies are established in the developed countries. Despite vast investment in oncology research and development, the translation of research advances into medicines that substantially improve the treatment of many cancers remains frustratingly slow. It has been noted that although the opportunities are enormous, there are significant challenges to global drug development. Some of the more major threats facing the pharmaceutical industry include the increase in the cost of research and development without an attendant improvement in the number of anticancer medicinal agents approved. The current reality in industry-sponsored clinical trials is that the majority of registration trials are focused on the United States and Europe. Despite the problems, research efforts advanced successful medical methods and drastic antitumour drugs in curing most of the types of malignant neoplasms and prolonged survival rates among cancer patients. Discovery and development of anticancer medicinal agents are the key focus of several pharmaceutical companies as well as non-profit government and non-government organizations all over the world. Major other problems on a global scale is the development of biosimilar anticancer drugs, the high cost of treatment and counterfeit anticancer agents.

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