Transforming Cancer Treatment: The Legacy and Future of Gleevec

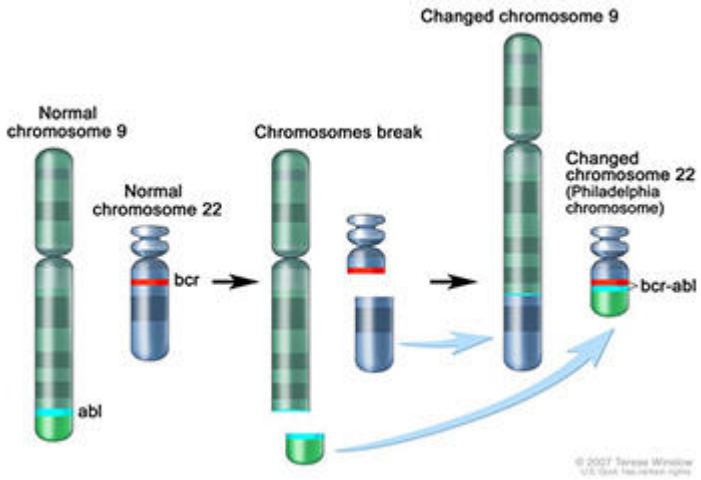
Vedant Shukla

Chronic myeloid leukemia (CML) was once considered a terminal diagnosis for patients. It is a relatively rare cancer as it makes up approximately 15 to 20% of all leukemia cases in the United States with about 9,280 new cases estimated in 2024 (5,330 in men and 3,950 in women) (Kang et al.). As for the UK, CML accounts for less than 1% of all new cancer diagnoses. The disease predominantly affects adults, with the average age of diagnosis being around 64 years, and nearly half of all cases occur in individuals aged 65 or older, the cases of CML in children being extremely rare. In 2024, the United States estimated approximately 1,280 deaths from CML ("Chronic Myeloid Leukaemia (CML) Incidence Statistics"; *Key Statistics for Chronic Myeloid Leukemia*). Before modern therapies were available, patients often endured the full progression of the disease, which typically resulted in a fatal outcome. However, the development of Gleevec (imatinib) during the early 2000s revolutionized CML treatment and marked the beginning of a new era in targeted therapy. This paper will explore Gleevec's development, mechanism of action, and initial application to CML and similar working diseases. Moreover, Gleevec's success has extended beyond just CML. It has proven effective in other cancers driven by similar molecular mechanisms, such as gastrointestinal stromal tumors (GIST), and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). The purpose of this paper is to discuss and explore Gleevec's broader impact in treating these diseases, highlighting its role in advancing targeted cancer therapies.

CML is a type of cancer that affects the bone marrow, where blood cells and blood plasma are produced. The disease originates from an anomaly that occurs in a hematopoietic stem cell (HSC): during homeostasis, HSCs give rise to various types of blood cells (*How Gleevec Transformed Leukemia Treatment - NCI*; *Gleevec: The Breakthrough in Cancer Treatment | Learn Science at Scitable*). CML is characterized by the uncontrolled production of myeloid cells, a type of white blood cell that normally helps the body fight infections. Chronic Myeloid Leukemia progresses through three different phases: chronic phase, accelerated phase, and blast crisis phase. Between 90% and 95% of patients will be diagnosed in the accelerated phase of the disease. Historically, within an average of 4 to 6 years, the disease transformed through an accelerated phase to variably fatal acute leukemia, also known as blast crisis (*Translation of the Philadelphia Chromosome into Therapy for CML | Blood | American Society of Hematology*). The first phase is also the longest-lasting one. During this initial phase, the leukemia continuously progresses slowly, and the bone marrow produces an overabundance of mature myeloid cells. These myeloid cells function normally, which is why many patients experience few or no symptoms. The next phase is the accelerated phase. This phase is also considered to be the transition phase between the chronic and blast crisis phases. CML in this phase starts to cultivate genetic mutations causing unstable behavior of the cancer. These changes can include an increase in the number of immature white blood cells in the blood or bone marrow, elevated basophil counts, and difficulty controlling white blood cell levels despite treatment. Due to this, patients may experience worsening fatigue, unexplained weight loss, fever, and splenomegaly (enlarged spleen) As the symptoms start to worsen, the blast crisis phase initiates. Out of the three phases, it is considered the most advanced and aggressive stage of the disease. It occurs when immature white blood cells called blasts

dominate the bone marrow and blood. By definition, the blast phase is characterized by 20% or more blasts in the blood or bone marrow. At this stage, the cancer resembles acute leukemia, which can be myeloid or lymphoid leukemia depending on the type of blasts involved. In the blast crisis phase, leukemia cells start to lose the ability to function normally, leading to a huge number of dysfunctional cells. This disrupts the production of normal blood cells, causing severe symptoms such as anemia, thrombocytopenia (increased bleeding and bruising), and neutropenia (increased risk of infections). Additionally, patients may experience bone pain, fever, significant weight loss, and a dramatically enlarged spleen.

Historically, CML was almost always fatal, with invasive treatments like stem cell transplantation offering limited success. The discovery of the Philadelphia chromosome in 1960 by Drs. Peter Nowell and David Hungerford was a landmark event. They observed that one of the 46 chromosomes was abnormally short. Though they had no clues as to how the short chromosome was created, or what its function was, the genetic alteration piqued their interest (*How Gleevec Transformed Leukemia Treatment - NCI*). It was an unusually short chromosome 22 in CML patients, which was identified as the result of a translocation between chromosomes 9 and 22. This translocation fuses the BCR and ABL genes, producing the BCR-ABL fusion protein.



(*How Gleevec Transformed Leukemia Treatment - NCI*)

It was later discovered that it was an active tyrosine kinase that drives unregulated cell growth and survival. The discovery of the BCR-ABL fusion protein demonstrated for the first time that cancer could be caused by a specific genetic mutation, fundamentally changing the understanding of cancer biology. By the late 20th century, scientists had identified the BCR-ABL protein as a critical target for CML treatment. Dr. Brian Druker and his colleagues hypothesized that selectively inhibiting this protein could halt the progression of the disease without affecting normal cells. Their groundbreaking work led to the development of a molecule called STI-571 later known as Gleevec (Imatinib), a tyrosine kinase inhibitor. After preclinical studies demonstrated its efficacy, human clinical trials began in 1998, with promising results that

dramatically altered the cancer treatment landscape. The FDA's approval of Gleevec transformed CML from a fatal disease into a manageable chronic condition for many patients. Gleevec not only revolutionized CML treatment but also validated the concept of targeted therapy, guiding in a new era of precision medicine that has since transformed the treatment of many cancers (*How Gleevec Transformed Leukemia Treatment - NCI*; *Gleevec: The Breakthrough in Cancer Treatment | Learn Science at Scitable*; *Past, Present, and Future of Bcr-Abl Inhibitors: From Chemical Development to Clinical Efficacy | Journal of Hematology & Oncology | Full Text*).

Gleevec, when used as a monotherapy, has proven to be highly effective, particularly for patients in the chronic phase of CML, providing long-term survival benefits and high response rates. Monotherapy with Gleevec is also associated with fewer side effects compared to traditional chemotherapy, making it a preferable option for many patients. Despite its remarkable success, Gleevec is not without issues. Some patients develop resistance due to mutations in the BCR-ABL gene, such as the T315I mutation, which limits the drug's ability to inhibit the BCR-ABL protein. However, in cases where Gleevec alone does not yield sufficient results or when resistance to the drug develops, especially in the later phases of CML, combination therapy, or "cocktail" treatment, is utilized. In these instances, Gleevec is often combined with chemotherapy or other tyrosine kinase inhibitors to enhance its efficacy and improve patient outcomes (*Efficacy Evaluation of Imatinib for the Treatment of Melanoma: Evidence From a Retrospective Study - PMC*; *Frontiers | Combination Therapies in Chronic Myeloid Leukemia for Potential Treatment-Free Remission: Focus on Leukemia Stem Cells and Immune Modulation*; *Past, Present, and Future of Bcr-Abl Inhibitors: From Chemical Development to Clinical Efficacy | Journal of Hematology & Oncology | Full Text*).

Nonetheless, Gleevec's discovery not only emphasized the importance of targeted cancer therapies but also opened the door to new treatments for a range of malignancies, offering hope for future advancements. One of the cancers for which Gleevec is used as a treatment is Gastrointestinal Stromal Tumors (GIST). GISTs are rare cancer masses that develop in various parts of the gastrointestinal (GI) tract: stomach (60%), small intestine (30%), and other areas (10%). The cancer originates from the interstitial cells of Cajal (ICCs), specialized cells located in the walls of the GI tract that act as the "pacemaker cells" of the digestive system (*Gastrointestinal Stromal Tumour (GIST)*; *Gastrointestinal Stromal Tumors Treatment - NCI*). These cells control the contractions of the smooth muscle, a process known as peristalsis. This ensures the proper movement of food and waste through the digestive tract. Although these tumors account for less than 1% of GI cancers, they are the most common mesenchymal tumors of the GI tract (*Gastrointestinal Stromal Tumour (GIST)*). Most cases of this disease are driven by mutations in the KIT or PDGFRA genes, leading to a continuous activation of tyrosine kinase pathways and uncontrolled tumor growth. Approximately 80% of GISTs have KIT mutations, while about 5 to 10% involve PDGFRA mutations (*Gastrointestinal Stromal Tumour (GIST)*; *Gastrointestinal Stromal Tumors Treatment - NCI*).

GISTs can occur at any age; however, most are diagnosed over the age of 50. The median age of the diagnosis is between 65-69 years old. Cases in children and young adults are extremely rare and are often linked to genetic predispositions (*Gastrointestinal Stromal Tumour (GIST)*). There have been seen to be no distinctions with gender as both biological men and

women are equally affected by GIST. Additionally in the United States, the condition is more frequently diagnosed in Black and Asian or Pacific Islander populations compared to White individuals.

Early-stage GIST patients are often asymptomatic and may discover the disease incidentally during imaging or surgery. However, when symptoms do occur, they can include abdominal pain, swelling, nausea, vomiting, loss of appetite, or gastrointestinal bleeding, leading to anemia and other complications. Diagnosis for the condition typically involves imaging such as CT, MRI, or PET scans, followed by a biopsy to confirm the tumor's molecular characteristics. Immunohistochemical markers, particularly CD117 (KIT) and DOG1 are crucial for accurate diagnosis (*Gastrointestinal Stromal Tumors Treatment - NCI*; *Gastrointestinal Stromal Tumour (GIST)*). Treatment usually begins with surgery, which can be helpful for localized tumors if complete resection is possible. For unresectable, metastatic, or recurrent GISTs, targeted therapy with tyrosine kinase inhibitors (TKIs) such as Gleevec has become part of the standard treatment regimen. Approved by the FDA for the treatment of GISTs on February 1, 2002, Gleevec has revolutionized GIST treatment for patients with this tumor by targeting the tyrosine kinase activity of mutated KIT and PDGFRA proteins, blocking tumor proliferation. GIST treatment can include Gleevec in combination with surgical intervention or can be used as a first-line therapy for advanced cases. It is utilized pre-surgery to shrink tumors and improve surgical outcomes. Post-operation is used to reduce recurrence risk. Over 80% of patients respond positively to Gleevec, achieving tumor shrinkage or disease stabilization. Resistance can develop due to secondary mutations, but alternative TKIs like sunitinib and regorafenib provide additional options. By dramatically improving survival rates and transforming GIST into a manageable chronic condition, Gleevec exemplifies the success of targeted cancer therapies.

Another Cancer Gleevec has had a tremendous impact on is acute lymphoblastic leukemia (ALL). This is a rare form of cancer which represents less than 1% of all cancers in the United States. Among its ALL subdivisions, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) is quite aggressive, accounting for about 25% of adult ALL cases and 2 to 5% of cases in children. This high-risk leukemia is driven by the translocation that forms the BCR-ABL1 fusion gene, which encodes an excited tyrosine kinase. This abnormal enzyme fuels the expansion of leukemic cells, leading to rapid disease progression. Unlike CML, which affects myeloid cells, Ph+ ALL targets lymphoid cells specifically B-cell precursors that are essential for immune responses. The disease often exhibits symptoms such as fatigue, fever, frequent infections, easy bruising or bleeding, bone pain, weight loss, and swollen lymph nodes. It is more common in younger individuals and progresses quickly, therefore needing immediate and aggressive treatment. Historically, treatment for Ph+ ALL involved intensive chemotherapy combined with allogeneic stem cell transplantation (SCT) during the first remission to improve survival. However, these approaches yielded suboptimal results, with long-term survival rates ranging from just 10% to 35%. The introduction of Gleevec (imatinib), a first-generation tyrosine kinase inhibitor (TKI), revolutionized the treatment landscape for this disease. Gleevec specifically targets the BCR-ABL1 tyrosine kinase, inhibiting the carcinogenic driver of Ph+ ALL. When used in combination with chemotherapy, Gleevec significantly improved patient outcomes, achieving complete remission (CR) rates as high as 93% and five-year overall survival (OS) rates of 43%. This combination therapy has enhanced survival prospects by increasing the likelihood of achieving remission deep enough to proceed to SCT.

However, the intensified treatment approach also comes with an increased risk of side effects and complications compared to chemotherapy alone. Gleevec's impact marked a turning point in managing Ph+ ALL, laying the groundwork for the development of even more effective therapies. Newer-generation TKIs, such as dasatinib and ponatinib, have since shown superior efficacy by achieving higher rates of molecular remission and overall survival, often in chemotherapy-free regimens. Nevertheless, Gleevec established targeted therapy as a cornerstone in treating this aggressive leukemia, transforming what was once an extremely poor prognosis into a more manageable condition with significantly improved outcomes(*Past, Present, and Future of Bcr-Abl Inhibitors: From Chemical Development to Clinical Efficacy | Journal of Hematology & Oncology | Full Text*; *Frontiers | Combination Therapies in Chronic Myeloid Leukemia for Potential Treatment-Free Remission: Focus on Leukemia Stem Cells and Immune Modulation*).

The future of Gleevec and similar drugs holds promising advancements in the field of precision medicine. While Gleevec revolutionized cancer treatment by targeting the specific molecular pathway of BCR-ABL in CML, newer drugs like dasatinib, nilotinib, and bosutinib have been developed to address Gleevec-resistant forms of the disease. The challenge, however, lies in access to these life-saving treatments, as high costs and availability remain significant issues. Proposing solutions such as global drug pricing reforms, expanded generic drug production, and partnerships with governments could help make these therapies more accessible worldwide. Beyond CML, the potential for Gleevec to treat other conditions is being explored. Research is ongoing into its possible application in autoimmune diseases like rheumatoid arthritis, lupus, and multiple sclerosis, as well as in fibrotic conditions such as pulmonary fibrosis and scleroderma. Additionally, early studies suggest that Gleevec may have a role in treating neurodegenerative diseases like Alzheimer's, although more research is needed to confirm its effectiveness. As precision medicine evolves, the development of more tyrosine kinase inhibitors for a broader range of cancers and rare diseases is likely to continue, offering hope for more targeted and effective treatments (*Past, Present, and Future of Bcr-Abl Inhibitors: From Chemical Development to Clinical Efficacy | Journal of Hematology & Oncology | Full Text*).

Despite its groundbreaking success, access to Gleevec remains a significant challenge for many patients due to its high costs. Initially priced at approximately $100,000 per year, the drug's expense has remained substantial, even with the introduction of generic versions following patent expiration (Fitzsimmons). While competition from generics has lowered prices in some regions, the cost reductions are uneven, particularly in developing countries where access to Gleevec is further limited by inadequate healthcare infrastructure, insufficient funding, and availability issues. In addition, insurance coverage and reimbursement policies vary widely between countries, with some providing only limited support for Gleevec and related second-line treatments. These accessibility barriers hinder many patients from receiving life-saving treatment, especially in low-resource settings.

Aside from accessibility issues, some patients develop resistance to the drug over time. This resistance is often driven by mutations in the BCR-ABL gene, which alter the structure of the protein and reduce Gleevec's ability to bind and inhibit tyrosine kinase activity. To address these cases, next-generation drugs like ponatinib have been developed to target resistant forms of CML, including those with the particularly challenging T315I mutation. As resistance remains

a concern, ongoing research is focused on the development of more potent inhibitors and the potential use of combination therapies. Combining Gleevec with other drugs may enhance its efficacy, prevent resistance, and offer new strategies for long-term disease management in CML patients (*Past, Present, and Future of Bcr-Abl Inhibitors: From Chemical Development to Clinical Efficacy | Journal of Hematology & Oncology | Full Text*; *Frontiers | Combination Therapies in Chronic Myeloid Leukemia for Potential Treatment-Free Remission: Focus on Leukemia Stem Cells and Immune Modulation*).

The discovery of Gleevec (imatinib) marked a groundbreaking shift in cancer treatment, transforming chronic myeloid leukemia (CML) from a terminal diagnosis to a manageable chronic condition. Beyond its remarkable success in targeting the BCR-ABL tyrosine kinase in CML, Gleevec has revolutionized treatment paradigms for other cancers driven by similar mechanisms, such as gastrointestinal stromal tumors (GIST) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Gleevec has established precision medicine as a cornerstone in oncology by pioneering targeted therapy. Despite its profound impact, challenges remain. Resistance due to mutations in the BCR-ABL gene, such as the T315I mutation, and accessibility issues due to high costs underscore the need for continuous advancements. Second- and third-generation tyrosine kinase inhibitors (TKIs) like dasatinib, nilotinib, and ponatinib have shown promise in addressing resistance, offering options for patients who no longer respond to Gleevec. The future of targeted therapy is bright. The development of fourth-generation inhibitors and novel combination therapies holds the potential to overcome resistance more effectively. Furthermore, expanding TKIs into other disease areas, such as autoimmune disorders and neurodegenerative diseases, represents an exciting frontier. Additionally, leveraging cutting-edge technologies like AI-driven drug design, personalized genomic profiling, and enhanced global access strategies could further democratize the benefits of these therapies. In summary, while Gleevec's legacy in cancer treatment is unparalleled, ongoing innovation and collaboration will be key to addressing current limitations and unlocking its full potential in diverse therapeutic landscapes (*Past, Present, and Future of Bcr-Abl Inhibitors: From Chemical Development to Clinical Efficacy | Journal of Hematology & Oncology | Full Text*; *Frontiers | Combination Therapies in Chronic Myeloid Leukemia for Potential Treatment-Free Remission: Focus on Leukemia Stem Cells and Immune Modulation*).

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