DAVID A. KARNOFSKY MEMORIAL AWARD LECTURE

Imatinib As a Paradigm of Targeted Therapies

By Brian J. Druker

The expanding knowledge of signaling pathways regulating cell growth, cell cycle progression, and programmed cell death has led to a dramatic improvement in our understanding of the molecular events involved in cancer. This knowledge has allowed the identification of numerous targets for anticancer agents. As we move forward into an era of molecularly targeted therapeutics, it is worth reviewing some of the lessons learned from the development of one of the prototype drugs of this class, imatinib (Gleevec, Glivec, formerly STI571; Novartis, Basel, Switzerland). However, it is also worth noting that the concept of specific targeting of cancer is certainly not new and in fact, was the basis for one of the drugs developed by Dr David Karnofsky, l-asparaginase. What differs is our ability to target specific pathways that are critical to the pathogenesis of cancer based on the knowledge gained over the past several decades.

Historical Aspects of CML

At the core of translational research is the description of a clinical entity, followed by an understanding of its molecular pathogenesis, and then development of a specific therapy based on the molecular pathogenesis. In the case of chronic myeloid leukemia (CML) and imatinib, this process took over 160 years (Fig 1A). It began with the first description of cases of CML by two pathologists, Dr Robert Virchow and Dr John Hughes Bennett in 1845. Although a debate ensued as to whose description was first, Virchow publicly acknowledged that Bennett’s case report had predated his. These first accounts of CML occurred before staining methods for blood, which were not developed until the late 1800s.

Historically, therapy for CML was empirically based. Thus, during the late 1800s, the mainstay of therapy for CML was Fowler’s solution, which was developed by Dr. Thomas Fowler in the mid 1700s. We now know that the active ingredient in Fowler’s solution is arsenic trioxide, and today, the knowledge gained over the past several decades.

The development of imatinib could not have occurred were it not for a long history of scientific discoveries that led to an unraveling of the molecular pathogenesis of CML. One thread of this began in 1960 with the identification of an abnormal chromosome in the blood and bone marrow of patients with CML. In their seminal article, Peter Nowell and David Hungerford stated, “The findings suggest a causal relationship between the chromosomal abnormality observed and chronic granulocytic leukemia.” In 1973, Dr Janet Rowley determined that the shortened chromosome 22, the so-called Philadelphia chromosome, was the product of a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9:22)(q34;q11). In 1982, by mapping oncogenes to specific chromosomal locations, it was recognized that the c-ABL tyrosine kinase, which normally resides on chromosome 9, had been translocated to chromosome 22 in CML patients. Shortly thereafter, Eli Canaani et al showed that a chimeric mRNA called BCR-ABL was present in patients with CML that was larger than the normal c-ABL mRNA. One year later, Owen Witte and David Baltimore demonstrated that a chimeric, BCR-ABL protein was made and that it possessed tyrosine kinase activity. Lastly, in 1990, John Groffen’s laboratory and George Daley in David Baltimore’s laboratory put BCR-ABL into animal models and demonstrated that BCR-ABL, as the sole oncogenic event induced leukemia, thus establishing BCR-ABL as a leukemic oncogene.

Each of the discoveries in the previous paragraph can be linked to various other scientific discoveries. For example, the discovery of tyrosine kinases can be traced to the identification of the Rous Sarcoma Virus by Peyton Rous in 1911. His crucial discovery was that a cell-free filtrate from a tumor was capable of inducing tumors in animals. Although this finding was met with enormous skepticism, by the 1950s, this finding, along with the development of routine methods for cell culture, led to the birth of the field of tumor virology. From this came the discovery of the transforming principal of the Rous sarcoma virus, termed v-SRC. In 1976, Michael Bishop and Harold Varmus reported their seminal finding, that the v-SRC oncogene hybridized to normal cellular DNA. From this came the recognition that the SRC oncogene had been transduced from normal cellular DNA, and thus, the field of oncogenes was born. By 1979, Tony Hunter and Jonathan Cooper recognized a novel, intracellular phosphorylation event—tyrosine phosphorylation—

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and SRC became the founding member of the family of tyrosine kinases. In the background of this, the v-ABL retrovirus was identified and in 1980, the ABL gene was cloned and recognized to be a tyrosine kinase.

When you put all of this together, from the first description of CML to a specific therapy, you realize that the understanding of the molecular pathogenesis of CML has relied on numerous fields and their convergence (Fig 1B). A thread tied to tumor virology led to the identification of the SRC and ABL oncogenes. A thread from chromosomal banding and gene mapping led to the recognition of BCR-ABL arising from the (9:22) chromosomal translocation. In addition, there is the entire field of protein phosphorylation, from serine-threonine kinases to tyrosine kinases, linking to oncogenes, and ultimately leading to the development of tyrosine kinase inhibitors.

**Development of Imatinib**

In reviewing BCR-ABL as a target for CML, it is the product of the (9;22) translocation that is present in 95% of patients with CML and defines the disease. We know from animal work that BCR-ABL is a leukemic oncogene. BCR-ABL functions as a constitutively activated tyrosine kinase, and its kinase activity is absolutely essential for all the transforming functions of the protein. Tyrosine kinases bind adenosine triphosphate (ATP) and transfer phosphate from ATP to tyrosine residues on specific proteins and these tyrosine phosphorylated proteins lead to all of

### Table: The Core of Translational Research as Exemplified by Chronic Myeloid Leukemia (CML)

<table>
<thead>
<tr>
<th>Year</th>
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<tr>
<td>1845</td>
<td>First description of CML</td>
<td>1985</td>
<td>Bcr-Abl</td>
<td>2001</td>
<td>Specific therapy for CML</td>
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**Diagram:**

- **Rous Sarcoma Virus**
  - Tumor Virology
    - v-srC
    - v-abl 1970
  - Oncogenes 1976
  - CML

- **Protein phosphorylation**
  - 1933
  - Tyrosine kinases 1979
  - Bcr-Abl 1985
  - Gene mapping
  - Chromosome banding
  - Specific Therapy

*Fig 1. The core of translational research as exemplified by chronic myeloid leukemia (CML): from the description of a clinical entity to an understanding of the molecular pathogenesis to the design of a specific therapy based on the molecular pathogenesis (A). Summary of the significant events leading to an understanding of the molecular pathogenesis of CML and to specific therapy for this disease (B).*

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the pathological defects observed in CML. Thus, if you could block binding of ATP to this specific tyrosine kinase, you would have an effective and selective therapy for this disease (Fig 2).

Beginning in 1993, we began testing various tyrosine kinase inhibitors that had been synthesized by Nicholas Lydon’s group at Novartis Pharmaceuticals. From our testing, STI571 (Gleevec, Glivec, imatinib) emerged as the best compound capable of specifically killing CML cells.15 Our preclinical data showed imatinib to be a potent and selective inhibitor of the ABL, platelet-derived growth factor receptor (PDGFR), and KIT tyrosine kinases.16 We showed that it selectively kills BCR-ABL-expressing cells both in vitro and in vivo, and it was highly bioavailable as an oral formulation.

Clinical Trials of Imatinib in CML

In the initial phase I clinical trials of imatinib in CML, which began in 1998, once doses of 300 mg and above were obtained, significant therapeutic benefits were observed while side effects were relatively minimal. The common side effects included occasional nausea, periorbital edema, and muscle cramps. In chronic phase patients who had failed therapy with IFN-α, 53 of 54 (98%) patients treated at 300 mg and above, achieved a complete hematologic response and with 1 year of follow-up, only one of these patients relapsed.17

This remarkable phase I data led to very rapidly accruing phase II clinical trials that were initiated at 30 sites in six countries. In chronic phase patients who had failed IFN-α therapy, 95% of patients achieved a complete hematologic response and 60% a major cytogenetic response, defined as a reduction in the percentage of Philadelphia chromosome positive metaphases to less than 35. With median follow-up of 29 months, only 13% of these patients have relapsed.18 In accelerated phase and blast crisis patients, the response rates were also quite high, but relapses have been much more common, with the majority of blast crisis patients relapsing during the first year of therapy (Fig 3).19,20

The next clinical trial performed was a phase III study in newly diagnosed chronic phase patients, comparing imatinib to standard therapy with IFN-α plus cytarabine (Ara-C). This study was opened at 177 centers in sixteen countries and accrued over 1,000 patients in a 7-month period. Five hundred fifty-three patients were randomized to each of the two treatments, imatinib at 400 mg per day or IFN-α plus Ara-C. There were no significant differences in prognostic features on the two arms. With a median follow-up of 19 months, patients randomized to imatinib had significantly better results than patients treated with IFN-α plus Ara-C in all parameters measured, including rates of complete hematologic response, (97% v 56%, P < .001), major and complete cytogenetic responses (85% and 74% v 22% and 8%, P < .001), discontinuation of assigned therapy due to intolerance (3% v 31%), and progression to accelerated phase or blast crisis (3% v 8%, P < .001) (Table 1).21 Responses to imatinib are rapid with most patients on imatinib achieving complete hematologic responses within the first 4 to 6 weeks of therapy. In addition, over 50% of patients obtain a complete cytogenetic response in 3 months.

![Fig 2. The constitutively active BCR-ABL tyrosine kinase functions by transferring phosphate from adenosine triphosphate (ATP) to tyrosine residues on various substrates to cause excess proliferation of myeloid cells characteristic of chronic myeloid leukemia (CML). (A), STI571 (imatinib) blocks the binding of ATP to the BCR-ABL tyrosine kinase, thus inhibiting kinase activity (B). ADP, adenosine diphosphate. TYR, tyrosine.](image1)

![Fig 3. Phase II and III results of imatinib for chronic myeloid leukemia (CML). The results shown are for newly diagnosed chronic phase patients with a median follow-up of 18 months. For the phase II studies in chronic-phase patients for whom IFN-α therapy failed, accelerated-phase patients, and blast-crisis patients, results are with a median follow-up of up to 30 months, and the rate of disease progression is at 24 months. Complete response (CR) and partial response (PR) for cytogenetic responses include patients with Ph chromosome positive metaphases of less than or equal to 35%.](image2)

<table>
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<tr>
<th>Table 1. Phase III Results of Imatinib Versus IFN-α Plus Cytarabine for Newly Diagnosed Chronic-Phase Patients With CML21</th>
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<tr>
<td><strong>Imatinib 400 mg/day</strong> (n = 553)</td>
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<td>CHR, % patients</td>
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<td>MCR, % patients</td>
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<tr>
<td>CCR, % patients</td>
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<tr>
<td>Intolerance,* % patients</td>
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<tr>
<td>Progressive disease, † % patients</td>
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*NOTE. Results are with a median follow-up of 18 months. All differences are highly statistically significant, with P < .001. Abbreviations: IFN-α, interferon alpha; CML, chronic myeloid leukemia; Ara-C, cytarabine; CHR, complete hematologic response; MCR, major cytogenetic response; CCR, complete cytogenetic response.‡Intolerance leading to discontinuation of first-line therapy. †Progressive disease to accelerated phase or blast crisis. |
Remaining questions in chronic phase patients include the durability of responses and how to integrate imatinib therapy with allogeneic stem-cell transplantation. Whether it will be possible and whether it is necessary to improve on these results is currently being investigated. However, for advanced phase patients, the more pressing question is why do they relapse?

Mechanisms of Relapse

One of the most useful categorizations of relapse mechanisms has been to separate patients into two categories, those with persistent inhibition of the BCR-ABL kinase and those with reactivation of the BCR-ABL kinase at relapse (Fig 4). Patients with persistent inhibition of the BCR-ABL kinase would be predicted to have additional molecular abnormalities besides BCR-ABL driving the growth and survival of the malignant clone. In contrast, patients with persistent BCR-ABL kinase activity or reactivation of the kinase would be postulated to have resistance mechanisms that either prevent imatinib from reaching the target or render the target insensitive to imatinib. In the former category are mechanisms such as drug efflux or protein binding of imatinib. In the latter category would be mutations of the BCR-ABL kinase that render BCR-ABL insensitive to imatinib or amplification of the BCR-ABL protein.

To examine BCR-ABL kinase activity, an assay has been developed that looks at the major tyrosine phosphorylated protein in CML patient samples, CRKL. Using this assay, it has been determined that the majority of patients who respond to imatinib and then relapse have reactivation of the BCR-ABL tyrosine kinase. In these studies, greater than 50% and perhaps as many as 90% of patients have BCR-ABL point mutations in at least 13 different amino acids scattered throughout the ABL kinase domain (Fig 5). Other patients have amplification of BCR-ABL at the genomic or transcript level. In contrast, in patients with primary resistance, that is, patients who do not respond to imatinib therapy, BCR-ABL-independent mechanisms are most common.

Analysis of the ability of imatinib to inhibit the kinase activity of the BCR-ABL kinase domain mutations found in relapsed patients has shown that some might be sensitive to dose escalation, but that most are highly resistant to imatinib. ABL kinase inhibitors with specificity that differs from imatinib have already been synthetized and one of these compounds, PD180970, is capable of inhibiting some, but not all of the common BCR-ABL kinase mutations. These data suggest that it may be possible to treat patients with several different ABL kinase inhibitors to circumvent resistance.

Imatinib and Gastrointestinal Stromal Tumor

In addition to its activity in CML, imatinib is also a highly active agent for the treatment of gastrointestinal stromal tumors (GISTs). GISTs are mesenchymal neoplasms that can arise from any organ in the gastrointestinal tract or from the mesentery or omentum with an annual incidence of approximately 5,000 cases in the US. Although GISTs morphologically resemble leiomyosarcomas and nerve sheath tumors, they are a distinct entity. The majority of GISTs express KIT, and in 90% of cases, KIT activation is linked to somatic mutations, usually involving exons 9 or 11. Published data suggest that the response rate of GISTs to single- or multiagent chemotherapy is less than 5%. Given the sensitivity of KIT to imatinib, GISTs were another rational tumor for clinical trials of this agent. In these clinical trials, the objective response rate to imatinib as a single agent in patients with advanced GIST was 53% to 65% with another 19% to 36% of patients having disease stabilization. These clinical trials have served as the basis for further exploration of the utility of imatinib in GIST, including the adjuvant and neoadjuvant, since the recurrence rate of GISTs after surgery is quite high.

Extending the Imatinib Paradigm: Target Expression Versus Response

In thinking about extending the imatinib paradigm to other tumors, the first issue to address is target expression versus response. If we look in two advanced malignancies where imatinib has been tested, CML blast crisis and GIST, the partial response rate was 50% to 65% with another 19% to 36% of patients having disease stabilization. In both of these cases, the target for imatinib, either BCR-ABL in CML or KIT in GIST is expressed in 90% to 100% of tumors. This is quite similar to
historical data for responses to tamoxifen in estrogen receptor–positive metastatic breast cancer, in an era when tamoxifen was not routinely used in the adjuvant setting. In contrast, responses to tamoxifen in estrogen receptor–negative patients are uncommon. So in these simple cases, expression of a molecular target correlates with response to an agent directed against that target.

However, in GISTs, the situation is more complicated. In these studies, the majority of patients had activating KIT mutations in exon 11 and these patients had a partial response rate of close to 80%. In contrast, patients whose tumors expressed wild-type KIT, with no mutation, the response rate was only 18%. Thus, KIT mutational status correlated with response. But more importantly, expression of a target doesn’t necessarily equate with a response to an agent directed against that target, nor does it equate with a critical role for the target in the growth or survival of a tumor.

From the foregoing examples, we can begin to evaluate what it means if the response rate to a molecularly targeted agent is low. In this paradigm, you would first want to ensure that the target against which an agent is directed is expressed. In some cases, expression may not be sufficient; rather, some measure of activation, mutations, overexpression, or aberrant expression may also be necessary. Regardless, it is critical to determine whether the agent being tested modulates the target. If the target is expressed and modulated by the agent being tested, and the response rate is low, then you have to question whether the target is critical to the growth and survival of the cancer. Of course, it may be possible that combinations with other agents or alternative end points could alter the interpretation of the results. Lastly, one must consider that there may be a subset of patients who respond well, even when response rates are low.

Going back to GIST patients with wild-type KIT expression, the response rate was 18%. Examination of tumors from these patients showed that one-third of these tumors had activating mutations of the PDGFRA. These mutations occurred in two different exons. One set of mutations was imatinib-sensitive and this accounted for responses observed in patients whose tumors expressed wild-type KIT. Thus, careful evaluations of subsets of responding patients can yield important insights into disease pathogenesis and the mechanism of response to a targeted agent.

**Activity of Imatinib in Other Diseases**

There are several other diseases where imatinib has shown clinical benefits that are based on an understanding of the molecular pathogenesis of the disease (Table 2). This includes patients with acute lymphoblastic leukemia who are Philadelphia chromosome and BCR-ABL-positive, patients with chronic myelomonocytic leukemia (CMML) who have (5;12) translocations that fuse the EV7 (TEL) and PDGFRB genes, resulting in the activation of the PDGFRB, and patients with dermatofibrosarcoma protubersans (DFSP). Several patients with CMML containing the (5;12)(q33;p13) translocation were treated with imatinib and all achieved complete hematologic remissions. DFSP is a low-grade sarcoma of the dermis that often recurs after surgical excision. These tumors are characterized by a (17;22) translocation involving the COL1A1 and PDGF-B genes, which results in over-production of fusion COL1A1-PDGFB ligand and consequent hyperactivation of PDGFRB. Thus, making this disease a rational choice for treatment with imatinib.

Both KIT and the PDGF receptors are expressed in many common tumors and have been reported to be activated by both autocrine and paracrine mechanisms. In most of these tumors, it is unclear whether monotherapy with imatinib would be useful. Most likely, KIT and PDGFR activation have a supportive rather than a pathogenetic role in these tumors. Although imatinib may have a role in the treatment of such cancers, clinical trials in these indications would be far more empiric than those with CML and GIST. In these latter cases, meaningful conclusions will only be derived from carefully designed clinical trials that incorporate end points as discussed.

That being said, an example where empiric clinical trials of imatinib have resulted in the definition of a molecular pathogenic event is the hypereosinophilic syndrome (HES). The dramatic empiric results of imatinib in this disease prompted investigations of the molecular basis for imatinib’s activity in this disease. Two groups independently arrived at the conclusion that an intrachromosomal deletion on chromosome 4 resulted in a fusion between a gene of unknown function, FIP1L1, and a truncated PDGFRB in a large percentage of patients with this disorder. The resulting FIP1L1-PDGFRA fusion protein is a constitutively activated tyrosine kinase that is imatinib sensitive, thus accounting for the responsiveness of this disease to imatinib.

**Lessons Learned From Clinical Trials of Imatinib**

Perhaps the most important lesson learned from the clinical trials of imatinib is that defining the appropriate target is the most critical component of a successful clinical trial. Of course, BCR-ABL was an ideal target based on the fact that it the causative molecular abnormality of CML and that it may be the sole oncogenic event early in the disease. As we were testing an ABL inhibitor, enrollment was limited to patients with activated ABL driving their cancer, and these patients could be identified easily as they had the Philadelphia chromosome. In addition, we learned an old lesson for oncologists, and that is, the earlier that...
you treat in the course of a disease, the better the response. This is quite apparent from an examination of response in CML patients in the chronic, accelerated or blast phases, where responses were significantly higher and more durable in chronic phase patients (Fig 3).

Thus, to translate the success of imatinib to other malignancies, we need to identify the appropriate therapeutic targets. Ideally, these targets would be early molecular pathogenetic events. To maximize clinical benefits, we need to treat early in the course of the disease. To treat early in the course of the disease, we need to develop extremely reliable techniques for early detection. Lastly, we need to match the right patient with the drug based on specific knowledge of the critical lesions in a person’s tumor.

In the 21st century, as we endeavor to improve the therapeutic outcome for cancer patients, a broad based approach to cancer therapeutics will be required. Certainly, we need many more specific therapies like imatinib for all other cancers. However, if we borrow a lesson from infectious disease, it is clear that more than antibiotics are needed in an effective strategy to eradicate infections. For cancer, this would include preventative measures, early diagnostic techniques, and immune–based therapies along with additional molecularly targeted therapies.

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