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Imatinib and chronic myeloid leukemia: validating the promise of molecularly targeted therapy

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Abstract

The Bcr-Abl tyrosine kinase inhibitor imatinib (Glivec®, formerly STI571, Novartis Pharma AG, Basel, Switzerland) produces complete hematologic and cytogenetic responses in a substantial percentage of chronic myeloid leukemia patients. Imatinib is effective in chronic phase, accelerated phase and blast crisis, with lower response rates in patients with more advanced disease. Although responses have been durable in chronic phase patients, relapses have been common in blast crisis. Relapse has been associated with reactivation of Bcr-Abl kinase activity. The clinical development of imatinib illustrates the effectiveness of targeting molecular pathogenetic events. Hopefully, this example can be extended to other malignancies.

Keywords: Chronic myeloid leukemia; STI571; Imatinib, tyrosine kinase inhibitor, Bcr-Abl; Philadelphia chromosome-positive leukemia

1. Introduction

The Bcr-Abl tyrosine kinase is the molecular abnormality that causes chronic myeloid leukemia (CML) [1,2]. This kinase is the product of the Philadelphia chromosome, which is formed by a reciprocal translocation between the long arms of chromosomes 9 and 22 [3]. The resulting Bcr-Abl fusion protein is a constitutively activated tyrosine kinase and is detected in the vast majority of CML patients. On the basis of animal models, Bcr-Abl alone is sufficient to cause leukemia [4]. Moreover, mutational analyses show that the tyrosine kinase activity is required for its oncogenic activity [5]. Accordingly, inhibition of Bcr-Abl represents an ideal molecular target for drug intervention in CML. Imatinib (Glivec®, formerly STI571, Novartis Pharma AG, Basel, Switzerland) inhibits Abl kinase activity by competing with ATP, preventing binding and thereby inhibiting tyrosine phosphorylation of protein substrates required for the Bcr-Abl transforming function. As a result, imatinib inhibits proliferation and survival of CML cells [6–9].

1.1. Historical perspective

The development of imatinib began in the late 1980s, when investigators at Ciba-Geigy Corporation initiated a protein kinase inhibitor program. At the time, Bcr-Abl was not viewed as the primary molecular target for a kinase inhibitor. Instead, one goal was to identify kinase inhibitors that blocked the platelet-derived growth factor receptor (PDGF-R), in the belief that such agents would be useful for preventing restenosis after coronary angioplasty and possibly for preventing spread of solid tumors. As the activity of test compounds against PDGF-R was optimized, the activity against Bcr-Abl was carried along. In 1993, several lead compounds, including imatinib, were evaluated in CML cells. Importantly, imatinib was shown to be highly cytotoxic to CML cells without harming normal cells. Cellular proliferation of Bcr-Abl-expressing cells and the ability of these cells to induce tumor formation were specifically inhibited by imatinib[6]. Moreover, the formation of Bcr-Abl colonies from peripheral blood or

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bone marrow of CML patients was almost completely prevented by imatinib, whereas colony formation of normal blood cells was unaffected.

At that time, it was evident that imatinib inhibited Bcr-Abl and PDGF-R; therefore, studies were also conducted to define the specificity of this agent. Imatinib did not block other type-3 protein tyrosine kinases, such as Flt-3, c-Fms, or v-Fms, or intracellular tyrosine kinases of the Src family. However, imatinib did inhibit the activity of the stem cell factor (SCF) receptor c-Kit, consistent with the close homology between the kinase domains of PDGF-R and c-Kit [10]. Moreover, the drug concentration producing 50% inhibition (IC_{50}) of c-Kit was approximately 0.1 μM, similar to the IC_{50} values against Bcr-Abl and the PDGF-R. Imatinib was also shown to inhibit SCF-induced intracellular signaling as well as proliferation and survival of leukemic cell lines, including those expressing activated mutant forms of c-Kit [10]. Thus, the preclinical evaluation showed that imatinib is a potent and selective inhibitor of the Bcr-Abl, PDGF-R, and c-Kit tyrosine kinases.

2. Clinical evaluation of imatinib

In planning clinical trials of imatinib in CML, it was our view that continuous inhibition of Bcr-Abl would be necessary and, accordingly, an oral formulation would be preferable. Imatinib was able to be synthesized as a highly bioavailable oral formulation, such that clinical trials were developed using the oral formulation.

2.1. Chronic phase

The phase I trials of imatinib started in June 1998 at the Oregon Health and Science University, University of California at Los Angeles, and M.D. Anderson Cancer Center. Eligible patients had Philadelphia chromosome-positive CML in the chronic phase as defined by less than 15% blasts or basophils in peripheral blood or bone marrow [11]. Patients had previously failed to achieve a complete hematologic or cytogenetic response to interferon-α, or they had relapsed on interferon-α therapy. Other therapies for CML were discontinued before imatinib was started.

The trial used a standard dose-escalation design, in which the safety and tolerability of imatinib were assessed as the primary endpoint [11]. Because imatinib is a molecularly targeted drug, it was hoped that treatment responses would also be evident, but these were considered to be secondary endpoints. Patients were treated at one of 14 dose levels ranging from 25 mg to 1000 mg. Imatinib was administered orally once daily, except the two highest doses (800 and 1000 mg), where the dose was divided and given twice daily. Patients received continuous daily therapy with imatinib unless disease progression or severe toxicity occurred; there was no intrapatient dose escalation. Intracohort escalation was allowed if none of three or one of six patients had grade 3 or 4 nonhematologic toxicity.

Imatinib was generally well tolerated, and a maximum tolerated dose was not identified. The most common adverse events were nausea, muscle cramps and edema, which were reported in 43%, 41% and 39% of patients, respectively, and which tended to be mostly mild (grade 1) to moderate (grade 2) in severity, even at the highest doses. Most adverse events increased in incidence and severity at the highest doses. Grade 3 thrombocytopenia and neutropenia occurred in 16% and 14% of patients, respectively. Many patients were able to tolerate the 1000-mg dose, but this dose is generally associated with lower tolerability than doses in the 400- to 800-mg range. Accordingly, daily doses over 800 mg are generally not recommended.

Evidence of the clinical effectiveness of imatinib became apparent by the fourth dose level (140 mg). All 73 patients who received 140-mg or higher doses achieved a hematologic response, which was defined by a 50% reduction in white blood cell (WBC) counts from baseline that was maintained for at least 2 weeks. Moreover, 53 of 54 patients who received the sixth dose level (300 mg) or higher had a complete hematologic response, defined as normal WBC and platelet counts maintained for at least 4 weeks. White blood cell counts typically declined within 2 weeks of starting imatinib and generally reached normal levels within 4 weeks (Fig. 1). More importantly, WBC counts remained within normal limits throughout the duration of therapy. After a median follow-up of 349 days, 51 of the 53 patients with complete hematologic responses still had WBC counts within normal limits.

Cytogenetic responses were determined from the percentage of bone marrow cells that were positive for the Philadelphia chromosome. Among the 54 patients who received imatinib at doses of 300 mg or above, 29 (53%) patients achieved some degree of cytogenetic response, including 17 (31%) patients with major cytogenetic responses. This latter category included 7 (13%) patients who were Philadelphia chromosome-negative and an additional 10 (18%) patients who had partial responses (1% to 35% marrow cells positive for the Philadelphia chromosome). Major cytogenetic responses were often seen within 5 months of starting imatinib, but some patients achieved these responses with longer durations of therapy. Cytogenetic responses occurred more rapidly than with interferon-α, which often requires 1 to 2 years of treatment. Notably, the cytogenetic responses to imatinib have generally been durable.

2.2. Blast crisis

Over time, the leukemic clone in CML loses its ability to differentiate, and it ultimately progresses to blast crisis [1,2]. In approximately two thirds of patients, the blasts are myeloid, whereas in the other one third, the blasts are lymphoid [2]. Blast crisis is highly refractory

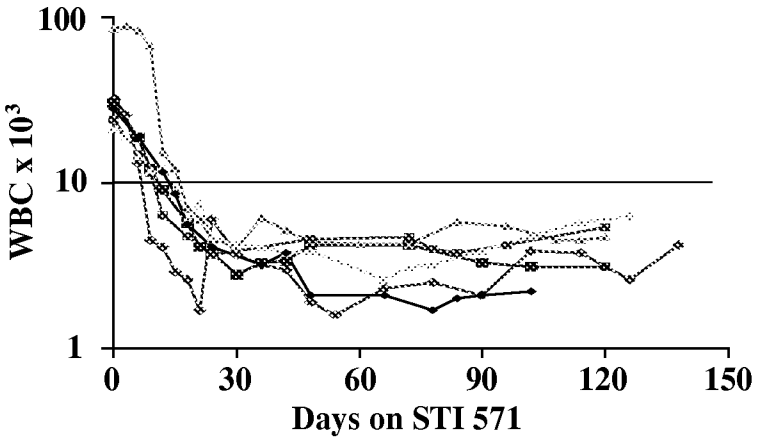

Fig. 1. Hematologic responses in 6 CML patients in chronic phase during treatment with imatinib 500 mg daily. Each line represents the WBC count of an individual patient, with the horizontal line indicating the upper limit of normal. Reprinted with permission from Druker *et al.*, *N Engl J Med* 2001; 344: 1031–1037.

to therapy. Only 10% of patients with myeloid blast crisis achieve complete responses to standard induction therapy [12]. Patients with lymphoid blast crisis achieve higher response rates, but they also remain in remission for short periods. Progression to blast crisis is associated with numerous molecular abnormalities, yet Bcr-Abl is detected in virtually all CML patients in blast crisis [13,14]. A smaller form of Bcr-Abl is found in 50% of adults and 80% of children with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL), and these patients, like CML patients in blast crisis, have a poor prognosis [2]. Cells expressing this smaller Bcr-Abl protein are as sensitive to imatinib in vitro as CML cells expressing full-length Bcr-Abl [8,15].

In April 1999, a second phase I dose-escalation clinical trial of imatinib was initiated in parallel to the chronic phase CML study [12]. This study was based on the rationale that Bcr-Abl kinase activity may still be required for the survival and proliferation of leukemic blasts. Previously treated or untreated CML patients in myeloid or lymphoid blast crisis and patients with relapsed or refractory Philadelphia chromosome(Ph)-positive ALL were eligible. Patients were treated at one of seven dose levels ranging from 300 mg to 1000 mg, with all doses given orally once daily except the 800-mg and 1000-mg doses, which were divided and given twice daily. Imatinib treatment was continued unless disease progression or unacceptable toxicity was seen.

Of the 58 patients in this study, 38 patients were in myeloid blast crisis and 10 patients each were in lymphoid blast crisis or had Ph-positive ALL. An interim analysis of the study showed that imatinib was well tolerated in this patient population [12]. Overall, nausea, vomiting and edema were the most common adverse events, being reported in 55%, 41% and 41% of patients, respectively. Overall, there were 16 deaths due to disease progression in the study, but none were considered to be related to imatinib therapy.

Among the 38 patients in myeloid blast crisis, 21 (55%) patients responded to imatinib as reflected by a reduction in marrow blasts to less than 15% of total cellularity, including 4 (11%) patients with complete hematologic responses and 8 (21%) patients with marrow blasts less than 5% of total cellularity. Among the 20 patients with a lymphoid phenotype, 14 (70%) patients responded to imatinib, including 4 (20%) patients with complete hematologic responses and 7 (35%) patients with reductions in marrow blasts to less than 5% of total cellularity.

Responses in blast crisis can occur rapidly. In one case, a patient with 80% to 90% blasts in peripheral blood showed no evidence of blasts within 10 days of starting treatment, with the bone marrow being completely cleared of blasts. This patient started with an absolute neutrophil count of 2000 cells/mm^3, which improved during therapy, illustrating the specificity of imatinib for leukemic cells. While normal hematopoiesis may recover in some patients during imatinib therapy, it should be noted that myelosuppression has been seen quite frequently in the blast crisis population. Grade 4 neutropenia and thrombocytopenia occurred in 40% and 33% of patients, respectively, in this phase I trial.

Treatment responses have generally not been durable in patients in blast crisis, although 7 of the 21 responding myeloid blast crisis patients continued to be in remission with follow-up between 101 and 349 days (Fig. 2). In comparison, all responding patients with a lymphoid phenotype relapsed within 45 to 120 days after starting therapy. All patients who relapsed remained positive for the Philadelphia chromosome. These results indicate that imatinib has significant single-agent activity in blast crisis, raising the possibility that it may be useful when combined with other agents or as induction therapy before stem cell transplantation. Furthermore, the results suggest that the Bcr-Abl tyrosine kinase remains responsible, at least in part, for the proliferation and survival of the malignant clone.

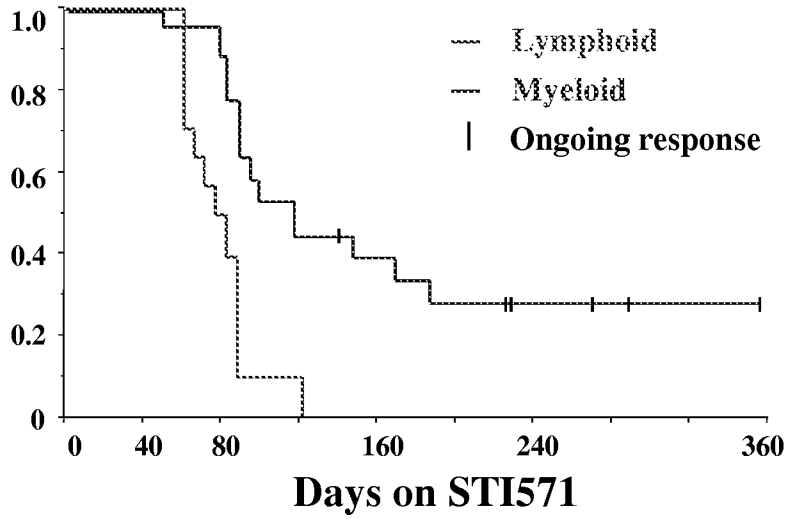

Fig. 2. Time to relapse in patients with myeloid or lymphoid blast crisis who responded to imatinib therapy. The vertical tic marks show patients with ongoing responses. Reprinted with permission from Druker *et al.*, *N Engl J Med* 2001; 344: 1038–1042.

2.3. Phase II trial

After the phase I studies were completed, an international cooperative group was assembled at 30 centers in the United States, Germany, Italy, United Kingdom, France and Switzerland to conduct phase II evaluations of imatinib in CML. More than 1000 CML patients in chronic phase (n=532), accelerated phase (n=235), or blast crisis (n=260) were enrolled within a 6- to 9-month period. Chronic phase patients were treated with imatinib at a daily dose of 400 mg; 91% achieved complete hematologic responses and 36% had complete cytogenetic responses. In the more advanced phases of disease, the response rates declined. Accelerated phase patients received imatinib at 600 mg daily and achieved complete hematologic and cytogenetic response rates of 53% and 17%, respectively. In blast crisis, the 600-mg dose produced complete hematologic and cytogenetic response rates of 26% and 7%, respectively. It is important to recognize that in these more advanced phases of disease, chemotherapy rarely provides any degree of cytogenetic response, thus highlighting the significance of the imatinib responses.

3. Challenges for the future

Several issues remain to be addressed in future studies, including identifying an optimal dose, understanding the mechanisms of relapse and determining how imatinib therapy can be optimized for individual patients. In order to identify an optimal dose, it will be important to maximally inhibit the targeted tyrosine kinase, such as Bcr-Abl in CML, or PDGF-R or c-Kit in other malignancies. In other words, the dose that defines maximal kinase inhibition needs to be determined. The results from the phase I study may provide some insight. At doses of 200 mg, 250 mg and 300 mg or higher, complete hematologic responses occurred in 33%, 57% and 98% of patients, respectively, and major cytogenetic responses occurred in 11%, 14% and 53% of patients, respectively. Thus, the 300-mg dose is believed to be the threshold for treatment responses and, accordingly, doses below this level are rarely if ever recommended. These doses correlated with kinase inhibition, but it is not yet clear whether maximal kinase inhibition has been achieved.

3.1. Understanding relapse after imatinib response

To determine why some patients relapse, it is important to ascertain whether the Bcr-Abl kinase remains inhibited. If inhibition is no longer seen, then various resistance mechanisms may be responsible, such as drug efflux, Bcr-Abl amplification or mutations in the kinase itself [16,17]. If Bcr-Abl is still inhibited by imatinib, then it suggests that additional mutations or other molecular abnormalities may be present.

In 11 patients with advanced Philadelphia chromosome-positive leukemias who relapsed after an initial response to imatinib, Bcr-Abl activity in blood or marrow cells was assessed using a quantitative immunoblot assay for Crkl, a direct substrate of Bcr-Abl [18]. Whereas Crkl phosphorylation decreased by 0.5- to 7-fold in patients responding to imatinib, phosphorylated Crkl reappeared in 11/11 patients at the time of relapse. Relapsed cells remained sensitive to imatinib, but up to 5 times the drug concentration needed at the start of therapy was required. In 3 patients, Bcr-Abl was amplified by approximately 20-fold and in 6 patients a point mutation in the Abl kinase was detected.

In collaboration with Andreas Hochhaus, we have looked at nearly 50 patients who have relapsed after responding to imatinib therapy. Four of these patients had Abl kinase domain mutations, but these were scattered

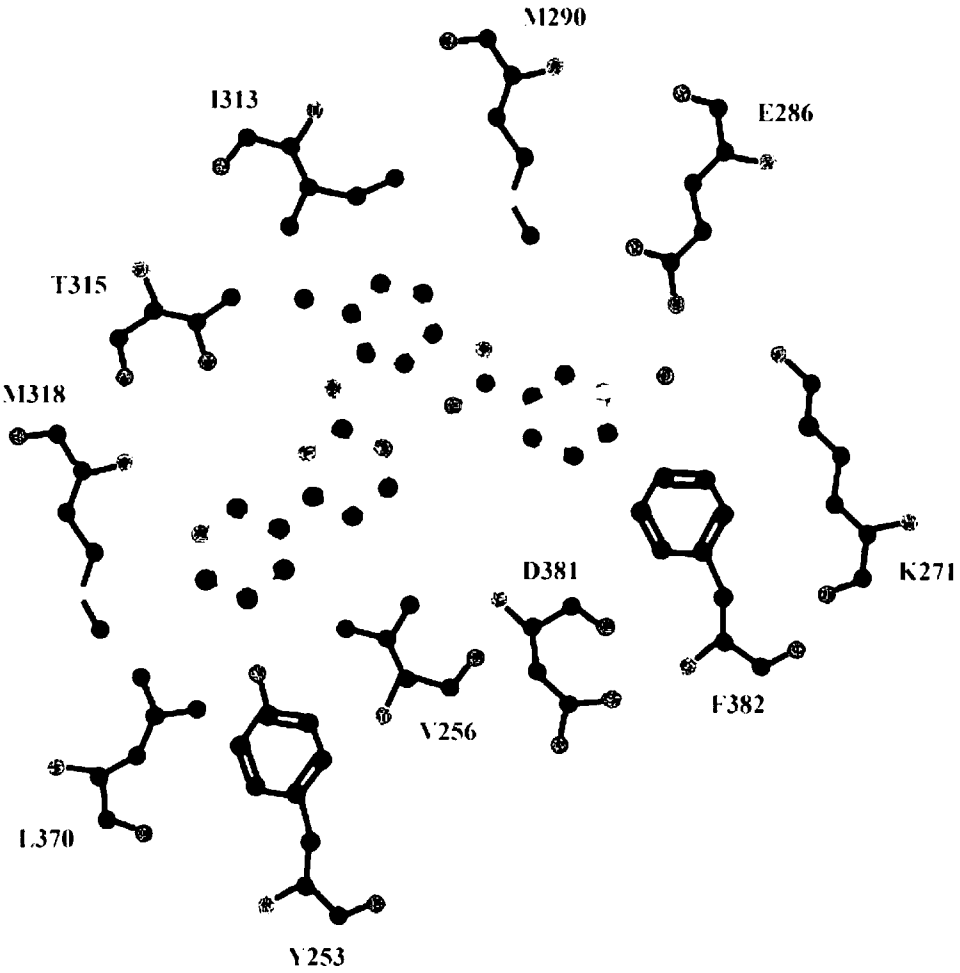

Fig. 3. Schematic drawing of contact points for imatinib in the Abl tyrosine kinase. Hydrogen bonds are shown by the dotted lines, and hydrophobic interactions are shown by surface markings around the contact sites. Reprinted with permission from Schindler *et al.*, *Science*, 289, 1938 (2000), fig 2.

throughout the kinase domain. These findings indicate that relapse appears to be associated with a restoration of Bcr-Abl signaling. Thus Bcr-Abl may still be an appropriate therapeutic target in the relapse setting [19].

X-ray crystallography of the binding of an imatinib variant to the Abl kinase reveals a number of contact points within the nucleotide-binding pocket (Fig. 3) [20]. These contact points include hydrogen bonds as well as hydrophobic interactions between imatinib and the kinase. Many of these contact points are also important for ATP binding.

Table 1
Effect of Abl point mutations on kinase activity based on a model of imatinib binding

Contact site	Mutation	Sensitivity to imatinib
Wild-type	–	IC_{50} = 0.025 μM
K271	R	Kinase inactive
E286	L	Kinase inactive
M290	A	Kinase inactive
I313	G	Kinase inactive
L370	G	Same as wild-type
T315	V	IC_{50} = 0.30 μM

In my laboratory, Amie Corbin has mutated these contact points and then evaluated the impact on kinase activity. Mutations of threonine 315 have been seen in relapsed patients. Mutation of leucine 370 to valine did not affect enzyme activity, whereas mutation of threonine 315 to valine resulted in a 12-fold reduction in the kinase IC_{50}. Mutations at other contact points resulted in a loss of kinase activity (Table 1). Using other prediction models, we have identified mutations at other sites that can also increase the kinase IC_{50}. Many of these point mutations involve amino acids that are adjacent to the contact points and several of these mutations have been described in relapsed patients. Whereas the contact points appear to be absolutely critical for ATP binding, mutations at these adjacent sites may alter the confirmation of the ATP binding site in a more subtle manner, thereby raising the IC_{50} for imatinib.

3.2. Use of imatinib in combination therapy

The rationale for evaluating imatinib in combination therapy is based on the need to prevent resistance and to improve cytogenetic response rates. Imatinib produced

additive antiproliferative effects when combined with interferon-α or daunorubicin and synergistic effects when combined with cytarabine in Bcr-Abl-expressing cell lines, including K562 cells, which were derived from a CML patient in blast crisis [21]. Similarly, in colony-forming assays that used bone marrow or peripheral blood from CML patients in late chronic phase or early accelerated phase, the combination of imatinib with interferon-α, daunorubicin or cytarabine significantly inhibited formation of colony-forming unit-granulocyte-macrophage (CFU-GM) and burst-forming unit erythroid (BFU-E) relative to imatinib alone [21]. Other investigators have also reported additive or synergistic effects when imatinib was combined with various anticancer drugs [22–24]. These in vitro results suggest that imatinib-based combination therapy may provide improved therapeutic outcomes as compared with single-agent therapy. In several ongoing clinical trials, imatinib is being evaluated in combination with either interferon-α or low-dose cytarabine in chronic phase patients and with standard induction therapy in patients in blast crisis or Philadelphia chromosome-positive ALL. As more information is obtained on resistance mechanisms and other disease pathways, it will be possible to design rational drug combinations rather than use combinations based on currently available medications.

The role of imatinib in stem cell transplantation still needs to be defined. Imatinib has been used in advanced CML patients as a bridge to transplant, but it remains to be determined whether it will have an impact on transplant outcomes. In the post-transplant setting, it must be determined whether imatinib prevents relapse in high-risk patients and whether superior outcomes will be achieved if imatinib is used instead of or in combination with donor lymphocyte infusions. Imatinib has re-energized autologous transplants when used as part of a pre- or post-transplant regimen as well as in purging marrow of Philadelphia chromosome-positive cells. Perhaps the most exciting possibility for imatinib in the transplant setting is to use the drug in combination with a minimal conditioning regime to minimize toxicity while maximizing the chance of a cure.

4. Target selection

The clinical development of imatinib illustrates the importance of target selection. In this example, a good molecular target combined with a good drug led to good clinical results. Bcr-Abl is an ideal target, because it is the causative molecular abnormality of CML and the sole oncogenic event occurring early in the disease. In addition, patients who are most likely to respond to imatinib therapy could be easily selected for clinical trials based on the presence of the Philadelphia chromosome. If the Philadelphia chromosome is present, then Bcr-Abl kinase activity is present.

In considering future molecular targets, it is possible to distinguish between general vs. specific ones. General targets, such as those affecting the cell cycle, apoptosis or angiogenesis, are broadly applicable in cancer, because cancer cells need these mechanisms to proliferate and survive. In contrast, molecular pathogenetic targets represent a unique abnormality of the tumor. Drugs affecting pathogenetic targets are likely to have a narrow spectrum of activity. Importantly, expression of the target does not necessarily equate with pathogenesis and, therefore, it is important to analyze for aberrant activity of the target. For example, in gastrointestinal stromal tumor (GIST), imatinib produces high response rates in patients with mutated or constitutively activated c-Kit, but a much lower response rate in those whose tumors express wild-type c-Kit. Myelosuppression has been seen in GIST patients, but it has not been particularly severe. This suggests that c-Kit can be replaced in hematopoietic cells by other mechanisms that promote their growth and survival. In my opinion, imatinib may not be highly effective for indications based solely on c-Kit or PDGF-R expression. Clinical trials in malignancies with c-Kit or PDGF-R expression are nevertheless warranted, but response rates much lower than those seen in CML and GIST should be expected.

5. Translating the success of imatinib to other malignancies

The success of imatinib illustrates the need to identify an appropriate therapeutic target, preferably an early molecular pathogenetic event, and then treat patients at an early stage of disease. In order to translate this approach to various common cancers, such as breast or prostate cancer, extremely reliable techniques will be needed to allow early disease detection. Although these steps have been achieved for imatinib in CML, additional work is needed to further optimize therapy. Ideally, the drug dose will be selected based on an analysis of the molecular target, and combination therapy will be used for patients predicted by molecular analysis to have a poorer prognosis. The success of imatinib in many CML and GIST patients clearly illustrates what can be accomplished when the right drug is given to the right patient with the right molecular target. Hopefully, this example will extend to other malignancies in the future.

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