Chronic myeloid leukemia: Standard treatment options

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Purpose. Treatment options for chronic myeloid leukemia (CML) are discussed. Summary. In the 1980s busulfan and hydroxyurea were the standards of care. These were subsequently replaced by interferon α (IFN α) based therapy. Currently, bone marrow transplant survival has improved, making this also a viable option. Five-year progression-free survival averaged above 70% for chemotherapeutic options. Transplant survival at 56 months was approximately 60%; however, these survivors were generally cured of disease. The recognition of the role for BCR-ABL in CML has led to the development of specific kinase inhibitors such as imatinib. Clinical trial evidence has demonstrated a clear superiority of imatinib over interferon plus cytarabine, making this the new standard of care in first-line treatment of CML. Resistance to imatinib has been observed, in addition to relapse. The data suggest that the probability of response may be estimated as early as six months after initiation of imatinib therapy. Although combinations of imatinib with IFN α show small improvements compared to imatinib therapy alone, the biggest improvements were seen when imatinib doses were doubled. Unfortunately, not all patients can tolerate this increase in dose. The most common mechanism for imatinib resistance is the presence of a mutated BCR-ABL kinase. Several of these mutants have been cloned and characterized. Conclusion. Molecular-targeted BCR-ABL kinase inhibitors, such as imatinib, are now first-line treatment for CML. Allogeneic stem cell transplant is still the only proven curable treatment for CML in patients with an appropriate donor. Next generation BCR-ABL kinase inhibitors hold promise for patients with mutated BCR-ABL kinase that confer resistance to imatinib.

Index terms: Antineoplastic agents; Busulfan; Combined therapy; Cytarabine; Dosage; Hydroxyurea; Imatinib; Interferon alfa; Leukemia; Mechanism of action; Resistance; Site of action; Toxicity; Transplantation Am J Health-Syst Pharm. 2006; 63(Suppl 8):S10-4

Although we have now moved to targeted kinase inhibitors, it is still quite useful to consider historical treatment options. Combinations of these older chemotherapeutic strategies with the newer targeted kinase inhibitors are beginning to be used. Initially, the therapy of choice was hydroxyurea or busulfan. Hydroxyurea, introduced in 1972, eventually was shown to provide better survival than busulfan and became the first-line treatment option. Hydroxyurea is quite effective at producing a hematologic response (HR) but has no ability to produce a cytogenetic response (CR), even at high doses. In 1983, interferon α (IFN α) was introduced. IFN α was found to be superior to hydroxyurea with an average HR of 60–70% and a CR of 13–27%. However, the responses often were of short duration. In addition, the side effects of IFN α treatment are significant, including flulike symptoms, arthralgia, myalgia, neutropenia, and depression. Perhaps the biggest difference between hydroxyurea and IFN α is that when patients who had achieved a CR went off IFN α, approximately 50% of that group remained in CR. This was virtually never observed with the previous chemotherapeutic treatments and, for that matter, has not been seen with the targeted kinase inhibitors used today.

Earlier work with cytarabine demonstrated its efficacy in treating chronic myeloid leukemia (CML). This led to the combination of IFN α with cytarabine being investigated. In one trial, 721 patients who had undergone HR under hydroxyurea therapy were randomized to receive IFN α in the absence or presence of cytarabine. Overall 3-year survival was 86% with cytarabine and 79% without cytarabine. Major cytogenetic response (MCR) at 12 months was 41% as opposed to 24% for IFN α.
α alone. A second study, considering the same treatment groups, recruited 538 patients who had chronic phase (CP) CML but who had not undergone any treatment yet. Surprisingly, this study showed no statistical difference for the two groups. One thought as to the discrepancy between the two studies is that the first population, having responded to hydroxyurea, may be predispositioned to respond to cytarabine. Nonetheless, IFN α plus cytarabine became the standard of care for a time.

During this period, allogeneic transplants were coming of age with treatment-related mortalities and infection decreased to 20–30%. As CML is a disease of the bone marrow, it was an attractive candidate for hematopoietic stem cell transplantation (SCT). A retrospective study was performed comparing IFN α and hydroxyurea treatment to allogeneic SCT. The chemotherapeutic data were derived from the study of Hehlmann et al. This was compared to 548 patients with CP CML aged 15 through 55. The mortality risk was significantly greater for the transplant group but only for the first 18 months. For the next 38 months the mortality risks for all the groups were approximately equal. Finally, after this 56-month period, the mortality risk of the nontransplant groups began to exceed that of the transplant group. After that period, patient survival was quite good, and importantly, the patient was generally disease-free. Seven-year survival for the busulfan/hydroxyurea group was 32%, whereas for the transplant group it was 58%. Additionally, transplant within a year from diagnosis was found to increase survival odds.

Hematopoietic SCT, similar to other transplants, requires that the various HLAs of donor and recipient be matched to some extent. In terms of HLA matches in matched unrelated donor transplants, it appears that some matches are more important than others. A recent study compared HLA-DRB1, HLA-DQA1, HLA-DQB1, HLA-DPA1, and HLA-DPB1 in terms of their importance for survival. Of these, HLA-DRB1 matched donors had a small but significant increase (i.e., 1.29) in survival as compared to other matches. This 15–20% increase in survival also is seen in matched related donor transplants.

**BCR-ABL kinase inhibition**

Many tyrosine kinases seem to play important roles in various cancer-related processes, such as proliferation, differentiation, and programmed cell death, making these molecules excellent therapeutic targets in cancer therapy. However, the realization that all protein kinases must use adenosine triphosphate (ATP) as a source of the donor phosphate group suggested that the ATP binding site (the P loop) would be a particularly nonspecific target. Surprisingly, this was disproved by Yaish et al. when they reported on the synthesis of the first synthetic tyrosine kinase inhibitor (TKI) targeting the epidermal growth factor receptor. A second group independently searched for TKIs by screening small molecule libraries. They identified a member of the 2-phenylaminopyrimidine class and subsequently optimized one compound, STI571 (now known as imatinib), for binding to the platelet derived growth factor receptor. Subsequently, they found STI571 inhibited BCR-ABL. Imatinib functions by binding to the ATP binding site of BCR-ABL kinase, thus blocking ATP binding and inhibiting downstream messages, leading to a decrease in cell proliferation.

The International Randomized IFN versus STI571 trial was initiated involving 1106 newly diagnosed patients with CP CML. The study compared imatinib to IFN α plus cytarabine with crossover permitted between the two groups if treatment failure criteria were met. Comparing the imatinib and IFN α groups respectively after an average of 19 months, the complete hematologic response (CHR) was 97% versus 69%. The MCR was 87% versus 35%. The complete cytogenetic response (CCR) was 76% versus 14%. Finally, progression free survival was 97% versus 92%. In another study of 532 patients who had failed IFN α therapy, imatinib treatment induced an MCR in approximately 60% of patients and a CHR in 95% of the patients. Clearly imatinib was superior and the side effects were far less than those of IFN α.

An early CHR is a very common response to imatinib therapy. How well do these results hold up over time? Recently, the 4.5-year follow-up of patients treated with imatinib was published. The percentage of patients with CP CML without relapse had stabilized at approximately 70% for many months. It should be noted that for patients who presented in advanced stages of CML (accelerated phase [AP] or blast crisis [BC]) the results were not as good. Approximately 40% of patients with AP CML and only 5% of patients with BC remained without relapse by the endpoint of the study. Nevertheless, because the vast majority of patients are diagnosed in CP, the results were promising. Recent data from M. D. Anderson Cancer Center indicate that if the dose of imatinib is doubled from 400 mg to 800 mg, there is a 15% improvement in initial response for patients diagnosed in AP. Long-term data for these patients are not available yet.

There are perhaps three distinct categories of response to imatinib therapy as measured by residual bcr-abl mRNA polymerase chain reaction (Figure 1). One group of patients undergoes a 2-log molecular response (MR) by 6 months and stabilizes at that level. Another group undergoes a 3-log MR by 6 months but then after approximately 12 months their bcr-abl mRNA begins to increase rapidly. Finally, the third
group undergoes a 2-log MR by 6 months and this number continues to drop until a complete molecular response (CMR) is reached. The second group, obviously, is the most troubling. Their disease often returns in AP or BC and the prognosis is poor. How can one predict which group a patient will fall into? The 4.5-year follow-up study shows that if a patient achieves an MCR within the first 12 months, the chance for progression-free survival at 4.5 years is 94%. If the patient does not achieve an MCR, the probability falls to 81%. Looking at bcr-abl mRNA data, if a patient achieves a major molecular response (MMR, i.e., >3-log reduction), then the probability of progression-free survival at four years rises to 98%. Patients with less than a 3-log reduction in bcr-abl mRNA but a CCR have a 90% probability of progression-free survival. For patients who do not achieve a CCR the probability drops to 75%. These data indicate that it is possible to begin to get a sense of the patient’s response by 12 months. What is the possibility of prediction by six months? A small amount of data have suggested that the relationship between the degree of reduction of bcr-abl mRNA at six months can predict the probability of achieving a CCR. If there are 1–35% Philadelphia chromosome positive (Ph+) cells at six months, it places the patient into a group that has an 80% chance of achieving a CCR. If there are 36–66% Ph+ cells, it leads to a 50% chance of achieving a CCR. Unfortunately, if there are 67–95% Ph+ cells at six months, it predicts a similar chance of CCR, which makes it difficult to interpret when a decision to switch from imatinib in this setting may be beneficial. Finally, a minimal response (i.e., >95% Ph+ cells) places the patient in a group that shows only a 15% chance of achieving a CCR. If there are 36–66% Ph+ cells, it leads to a 50% chance of achieving a CCR. If there are 1–35% Philadelphia chromosome positive cells (Ph+) at six months fall into a group who only have a 15% chance of progression-free survival at 24 months. These data suggest it may be possible to begin to predict patient outcome at six months; however, more research needs to be done in this area.

Options for suboptimal responses to imatinib

Some clinical investigators have tried combining IFN α or cytarabine with imatinib. The results of these trials are shown in Table 1.18 IFN α is of special interest because, as mentioned previously, it can result in a long-term cessation of disease progression. One likely mechanism is that IFN α activates the immune system to recognize and eradicate Ph+ cells. There is an increase in the percentage of patients achieving a CMR; however, there also is a large increase in the number of patients experiencing neutropenia. High dose imatinib is another option. Early data on patients starting on an 800-mg dose show significant increases in MMR and CMR with a smaller increase in side effects, such as neutropenia or thrombocytopenia. Nevertheless, there will be a larger patient population who cannot tolerate this imatinib dose as compared to the 400-mg dose.

Allogeneic transplant remains an option in some patients but is limited by age, performance status, and finding a matched donor. As described before, the risks associated with this option are substantial. The chances of survival are higher for the younger patient with a matched sibling. As described earlier, we are beginning to be able to predict prognosis earlier in the treatment phase, and patients with a poorer prognosis are candidates for transplant. Sokal scores, used as prognostic indicators for IFN α plus cytarabine response, may or may not be useful for patients treated with imatinib. The data are not available yet.

The most attractive emerging options for many suboptimal respond-
ers are some of the new BCR-ABL kinase inhibitors being developed. These will be discussed in detail in the next article.

**Disease progression in the presence of imatinib**

The most common means for disease to progress is for imatinib resistant *bcr-abl* mutants to arise. It is estimated that 50–90% of relapses are the result of the outgrowth of *bcr-abl* kinase domain mutations.\(^1\) Imatinib binds tightly to the kinase domain through a series of hydrogen bonds with side chains from certain amino acids found within that domain. Moreover, the kinase domain of BCR-ABL (like many other enzymatic active sites) can assume one of several conformations. Imatinib binds to BCR-ABL in the closed conformation. Mutations that disrupt those hydrogen bonds disrupt imatinib binding and result in an imatinib resistant clone. The first mutation to be discovered in a cohort of imatinib resistant patients was T315I.\(^2\) Other BCR-ABL mutations are shown in Figure 2.\(^3\) In some cases it is assumed that these mutations were present before treatment began because they have been identified in newly diagnosed patients.\(^4\) Imatinib therapy may be inhibiting the wild type BCR-ABL expressing stem cells but the mutant *bcr-abl* stem cells may begin to expand in their place. It is important to note that currently only one BCR-ABL mutant, T315I, has been identified as truly resistant to imatinib. The other mutations simply decrease the affinity of imatinib for the kinase. A second mechanism leading to imatinib resistance is *bcr-abl* gene amplification.\(^5\) In

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**Table 1.** Response Rate in Patients with Chronic Phase Chronic Myeloid Leukemia\(^,\)\(^b,c\)

<table>
<thead>
<tr>
<th>Response</th>
<th>IM + Low-dose Cytarabine</th>
<th>IM + High-dose Cytarabine</th>
<th>IM + Pegylated IFN</th>
<th>High-dose IM</th>
<th>Standard-dose IM</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>30</td>
<td>127</td>
<td>76</td>
<td>114</td>
<td>553</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>12</td>
<td>18</td>
<td>12</td>
<td>12</td>
<td>18</td>
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<td>CHR, %</td>
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<td>NR</td>
<td>97</td>
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<tr>
<td>MCR, %</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>96(^c)</td>
<td>87</td>
</tr>
<tr>
<td>CCR, %</td>
<td>70</td>
<td>67</td>
<td>70</td>
<td>95</td>
<td>76</td>
</tr>
<tr>
<td>MMR, %</td>
<td>NR</td>
<td>51</td>
<td>47</td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>CMR, %</td>
<td>NR</td>
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<td>14</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Grade 3/4 neutropenia, %</td>
<td>27</td>
<td>NR</td>
<td>63</td>
<td>36</td>
<td>14</td>
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<tr>
<td>Grade 3/4 thrombocytopenia, %</td>
<td>37</td>
<td>NR</td>
<td>28</td>
<td>25</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\)CCR = complete cytogenic response, CHR = complete hematologic response, CMR = complete molecular response, IFN = interferon, IM = imatinib, MCR = major cytogenic response, MMR = major molecular response, NR = no response.

\(^b\)At 18 months of follow-up.

\(^c\)Reprinted with permission from reference 18.

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**Figure 2.** Common BCR-ABL Mutants Observed in Imatinib Resistant and Relapsing Chronic Myeloid Leukemia. A = activation domain, C = catalytic domain, IB = imatinib-binding region, P = adenosine triphosphate-binding domain (P loop). Adapted with permission from reference 21.
this scenario, rare leukemic clones in which the bcr-abl gene has been amplified generate enough BCR-ABL protein that the 400-mg dose of imatinib is insufficient to block activity. Other relevant hypotheses include the ability of the leukemic stem cell to hide within the bone marrow microenvironment or for the leukemic stem cell to overexpress a molecular pump, such as hOCT1, which can use imatinib as a substrate, removing it from the cell. Additionally, other translocations may have occurred in addition to the t(9;22) translocation that created bcr-abl, such that BCR-ABL kinase activity is no longer required for the transformed phenotype. One such translocation that has been identified in several leukemias is the nup98 gene of chromosome 11p15.5 which, in the specific context of CML, has been found fused to the gene ddx10.

The presence of drug resistant mutations to imatinib has spurred research into the generation of new kinase inhibitors. Several have been developed and are in clinical trials which will be discussed in the next article.

Conclusion

Chronic myeloid leukemia treatment strategies have undergone a tremendous advance during the past three decades. Hydroxyurea and IFN α have been replaced by BCR-ABL kinase specific inhibitors, such as imatinib. In addition, improvements in SCT have made this an option for patients, especially those who are younger, have matched siblings, and have imatinib-resistant CML. Imatinib has been found to halt disease progression in many cases, sometimes reducing the level of bcr-abl mRNA to undetectable levels. However, in all cases discontinuation of therapy results in the return of disease, indicating that imatinib does not eradicate all Ph+ stem cells. It has also become apparent that bcr-abl mutants can exist that are resistant to imatinib action. New kinase inhibitors with activity against some, but not all, of these mutations are in clinical development. Thus, although the fate of the patient with CML is vastly improved from previous decades, there is clearly still more to do to control this disease.

References