3. Imatinib Therapy in Chronic Myelogenous Leukemia

Itsuro Jinnai

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Introduction

Chronic myelogenous leukemia (CML) is a clonal proliferative disease originating from a pluripotential stem cell in which a 9:22 translocation, Philadelphia (Ph) chromosome, results in the production of BCR-ABL fusion protein that has constitutive tyrosine kinase activity and deregulates signal transduction pathways, thus causing leukemia. The natural course of CML is usually triphasic (chronic, accelerated and blast-crisis phases). The blast-crisis phase is refractory to standard chemotherapy.

The introduction of imatinib, a selective inhibitor of the BCR-ABL tyrosine kinase, has caused rapid change in the treatment protocols for patients with CML. The great efficacy of imatinib in achieving a cytogenetic response has been demonstrated in many trials, but long-term clinical data regarding imatinib are not yet available.

Imatinib Therapy in the Chronic Phase of CML

The phase III International Randomized Interferon vs STI 571 (IRIS) study was undertaken to compare imatinib monotherapy to a combination of interferon plus cytarabine as initial therapy for newly diagnosed chronic phase CML (1). This trial investigated whether the high rate of cytogenetic response in advanced chronic phase patients noted in the phase II trial translated to disease-free and overall survival benefits. The results at the 18-month follow-up showed that imatinib monotherapy was superior in providing a higher cytogenetic response, slower progression to the advanced phase, and better tolerability to the interferon-based regimen (Table 1). Further follow-up of IRIS study (42 months) demonstrated that responses to first-line imatinib are continuing to improve with 84% of patients achieving complete cytogenetic response (CCyR, Ph chromosome = 0%) and that rates of progression-free survival and survival without an accelerated or blast-crisis phase in first-line imatinib were 84% and 94%, respectively (Fig. 1) (2). Imatinib is now approved as a first-line agent for CML.

Resistance to Imatinib

One of the biggest problems in the treatment with imatinib is emergence of imatinib resistance (3). Imatinib resistance appears within a short duration in patients with the blastic crisis phase, or in patients with Ph chromosome-positive ALL. The mechanism of imatinib resistance is classified into BCR-ABL dependency and non-dependency, and mutation of the BCR-ABL kinase domain is the most frequent. Structural changes in the BCR-ABL protein due to the mutation make it impossible to combine imatinib with BCR-ABL protein. It has been reported that leukemia cells with a mutation in the BCR-ABL gene had already existed before treatment with imatinib. In patients in whom an imatinib-resistant clone has not been generated, reduction of leukemia cells may lead to a decreased emergence of a resistant clone.

Monitoring of Minimal Residual Disease

The monitoring of minimal residual disease (MRD) by measuring the BCR-ABL chimera mRNA using the RT-PCR method is useful to assess the effect of treatment in patients with CCyR. In the IRIS study, 39% of patients treated with imatinib were estimated to have a 3 log reduction after 12 months of therapy (4). A 3 log or greater reduction in BCR-ABL levels after 12 months was associated with 98% progression-free survival at 42 months (2). Branford et al reported that it appears reasonable to conclude that even relatively small increases in the level of BCR-ABL transcript (>2 fold) are an indication that resistance may be developing and in such case, it is necessary to examine mutation of the BCR-ABL kinase domain (5).

High-dose Imatinib Therapy

The recommended dosage is 400 mg/day for chronic phase CML and 600 mg/day for the accelerated or blastic-crisis phase CML. At MD Anderson Cancer Center, however, high-dose IM (800 mg/day) therapy for chronic phase
Table 1. Imatinib vs IFN+Ara-C for Newly Diagnosed CML in Chronic Phase: Summary of 18 months Data of IRIS Study

<table>
<thead>
<tr>
<th></th>
<th>Imatinib (n=553)</th>
<th>IFN/Ara-C (553)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematologic response</td>
<td>96.8%</td>
<td>69.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cytogenetic response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major cytogenetic response</td>
<td>87.1%</td>
<td>34.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete cytogenetic response</td>
<td>76.2%</td>
<td>14.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to AC/BC</td>
<td>3.3%</td>
<td>8.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall survival</td>
<td>97.2%</td>
<td>95.1%</td>
<td>0.16</td>
</tr>
<tr>
<td>Treatment intolerance</td>
<td>2.9%</td>
<td>30.6%</td>
<td></td>
</tr>
</tbody>
</table>

Kaplan-Meier estimates (ref. 1)

Figure 1. Progression-free survival and survival without accelerated or blastic crisis phase on Imatinib therapy for patients with newly diagnosed chronic phase CML: IRIS study. (ref. 2).

CML is performed. In their pilot study in newly diagnosed CML, the high-dose regimen compared to standard-dose imatinib, produced higher rates of CCyR and undetectable BCR-ABL transcript, and better progression-free survival (6).

Allogeneic Hematopoietic Stem cell Transplantation

In the pre-imatinib era, chronic phase patients under 50 years who had an HLA-matched sibling donor were recommended to have rapid allo-hematopoietic stem cell transplantation (HSCT). However, the role of allo-HSCT requires reassessment in the imatinib era (7). Early outcomes of imatinib therapy for patients with newly diagnosed chronic phase CML show a very high incidence of CCyR, suggesting that responding patients may survive significantly longer than they would have survived with any alternative non-transplant therapy. Patients with no hematological response after 3 months of imatinib therapy, Ph-positivity of greater than 95% after 3 months, more than 65% after 6 months or more than 35% after 12 months could be offered allo-HSCT. The role of allo-HSCT for CML would be facilitated to some degree by further follow-up of patients treated with imatinib.

New BCR-ABL Tyrosine Kinase Inhibitors

Clinical trials of new BCR-ABL tyrosine kinase inhibitors, BMS 354825 and AMN107 are underway. BMS 354825 is a dual inhibitor of ABL/SRC. AMN107 is an inhibitor of ABL and preclinical studies have shown 10 to 30 times more potent than imatinib against BCR-ABL positive cells. It is noteworthy that both are active against most of imatinib-resistant BCR-ABL mutants except T315I. The results of Phase I studies in patients with CML resistant to imatinib were reported, respectively in American Society of Hematology in 2004 (8, 9). The initial results both studies are encouraging.

Perspective

The introduction of imatinib has brought a new era in the treatment of CML. However, long-term and true effects of imatinib for CML are still unknown. To define the relative roles of imatinib and allo-HSCT, longer follow-up is needed. Early cytogenetic response would be related to prognosis and monitoring cytogenetic response and MRD is important to assess the effect of imatinib. In order to optimize therapy, maintain responses and minimize the emergence of resistant clones, the dose of imatinib therapy and its use in combination must be studied further.

References

1. O’Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-


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