

CML in the imatinib era

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Chronic myelogenous leukemia (CML) is a malignant hematopoietic stem cell disorder characterized by the presence of the Philadelphia (Ph) chromosome. The Ph chromosome represents a reciprocal translocation between the long arms of chromosome 9 and 22 t(9; 22)(q34; q11) and the molecular consequence of this translocation resulting a chimeric bcr-abl gene. The BCR-ABL protein shows tyrosine kinase activity and deregulated tyrosine kinase activity results in activation of several downstream signaling pathways, including the Ras/MAPK, PI-3K/AKT, and STAT pathways.

A selective tyrosine kinase inhibitor, imatinib mesylate, was recently developed and blocking the ABL-coded kinase activity provides significant clinical benefit in patients with CML. A phase III randomized study (IRIS study) compared imatinib alone with IFN α + low-dose ara-C in newly diagnosed chronic phase CML patients demonstrated that imatinib was significantly superior to IFN α therapy in cytogenetic response and toxicities. The results of the IRIS study showed that the progression free survival at 18 months was 97% for patients receiving imatinib versus 93% for those given IFN α + ara-C. This was associated with a considerable increase in the proportion of patients achieving major cytogenetic response (CGR) and complete cytogenetic response at 87% and 76% for imatinib versus 34% and 15% for IFN α + ara-C ($P < .001$).

In the IRIS study, it was concluded that imatinib should be considered as the first-line therapy in newly diagnosed chronic-phase CML, and several important issues have also been clarified. Patients who are >65% Ph+ at 12 months have only a 9-14% chance of obtaining a complete CGR at 24 months, while patients who are 1-35% Ph+ at any time point

frequently achieve a complete CGR. As to the molecular response and the prediction of the effect of imatinib, an estimated 39% (imatinib) versus 2% (IFN α) of patients achieved a ≥ 3 log reduction in BCR-ABL levels after 12 months of treatment. Patients who achieved this level of molecular response at 12 months remained progression-free for the subsequent 12 months compared to 95% of patients with < 3 log reduction in BCR-ABL levels and 85% in those patients without complete CGR. Of the patients with ≥ 4 log reduction at 12 months an estimated 100% was still in complete CGR at 24 months versus 97% of those with 3- < 4 log reduction and 88% of those with < 3 log reduction ($p=0.002$).

Despite the encouraging results of the IRIS study, 20-30% of newly diagnosed patients fail to achieve such a good response. With regard to primary resistance, there are several reports that CML progenitors may be suppressed but not eliminated in the course of imatinib treatment. The expression profile of a restricted number of genes which are predominantly related to the degree of myeloid differentiation can define the kinetics of hematopoiesis in chronic phase, and may thereby help to determine optimal treatment for newly diagnosed patients or for patients who respond sub-optimally to initial treatment with imatinib. It is possible that Sokal and/or Euro scores will be found to correlate with outcome of treatment with imatinib, and could be used to distinguish groups of patients at diagnosis. For Sokal low, intermediate and high-risk groups, the complete CGR rates are 84%, 77% and 62%, respectively ($p < 0.001$), and the estimated 24-month PFS 95%, 89% and 85% ($p=0.05$) in the IRIS study. Although the high cytogenetic response rate suggests that patients treated with imatinib could survive longer than with IFN α , little is known

how durable the response to imatinib will be.

In recent surveys in chronic phase patients, the incidence of acquired resistance in early and late chronic phase was 15% and 25% respectively. Point mutations in the kinase region of BCR-ABL are the commonest cause of acquired resistance. Mutations were detected in 33% patients in accelerated phase, 22% in late-chronic phase and 0% in early chronic phase. Mutation in the p-loop may have a particularly poor prognosis.

Furthermore, many questions concerning imatinib remain outstanding. Firstly, although the majority of patients achieve hematologic and cytogenetic remission, a very small proportion (3-6%) achieves RT-PCR negativity for BCR-ABL. This raises the possibility that the effects of imatinib may not be durable.

When a patient does not respond sufficiently to imatinib, the patients must be considered for stem cell transplantation (SCT) or other therapies including IFN α . In a case-matched analysis, survival of 143 such patients, who did not respond to IFN α and were treated with imatinib, with that of 246 historical controls who received conventional treatment were analyzed. Although patients on imatinib who achieved at least some degree of cytogenetic response after 6 months had better survival than controls, those with no cytogenetic response to imatinib had significantly worse survival. These findings suggest that cytogenetic responders obtain benefit from imatinib but patients who show no cytogenetic response should be given alternative treatment without delay.

SCT remains the only treatment with proven curative potential in patients with CML in spite of the immediate morbidity and mortality of allo-SCT. Patients received SCT showed survival of 69% for CML in chronic phase within 1 year of diagnosis, and 57% for patients more than 1 year from diagnosis according to the reports of IBMTR. Until the recent introduction of imatinib, SCT may be recommendable to younger patients who have HLA-matched donor or fail to achieve major cytogenetic response in the IFN α therapy as shown Italian and Japanese studies. The Italian group reported that that a policy of SCT increased survival only in those patients who

were younger or at intermediate or high Sokal risk. And in the Japanese study, unrelated donor SCT may be recommended for younger patients who failed to achieve major CGR in IFN α therapy. The factors influencing the outcome of allo-SCT are well recognized. Age, disease status, disease duration, recipient-donor gender combinations, and the source of the transplant product have all been identified as significantly influencing long-term survival. In recipients of unrelated transplant, cytomegalovirus serostatus is also influential. Young patients with CML in chronic phase within the first year of diagnosis who have HLA-identical donors should continue to be offered allo-SCT. However, by the advent of imatinib therapy, it has been more difficult to make a decision on a newly diagnosed patient who might be eligible for initial treatment by SCT.

Patients who fail to respond or who lose their response in imatinib therapy, even though they remain in chronic phase, should be offered an allogeneic SCT as soon as possible if they are of a suitable age and performance status and have an available donor. However, allo-SCT will be unsuitable for some of these patients and other therapies should be investigated. There are various possibilities including, higher dose of imatinib, adding another agent such as IFN α and ara-C, or changing treatment to one or more of these agents. High-dose imatinib resulted in higher rates of complete cytogenetic and molecular remissions, but was associated with some increase in myelosuppression. The rationale for combining imatinib with IFN α or ara-C is based on in vitro data that demonstrates additive or synergistic activity against CML cell lines. Molecular targets have been investigated, which could eventually lead to a sequential blockade of intra-cellular pathways and multiple new agents are currently being developed in CML. Now, the large clinical randomized trials of imatinib alone, imatinib + IFN α , imatinib+ara-C or higher dose of imatinib are conducted for newly diagnosed CML. Hopefully, the patients with CML will be cured by these strategies.