FRONTLINE THERAPY FOR PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE IN THE YEAR 2004

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Abstract
Treatment options for patients with chronic myeloid leukemia (CML) have evolved significantly over the last 30 years. This process has included the development of the cytoreductive agent hydroxyurea, of complex technologies such as allogeneic stem cell transplantation (alloSCT) and donor lymphocyte infusions, the immunomodulatory agent interferon-alpha (IFN-α), and more recently the small molecule imatinib mesylate (imatinib). In the previous decade, an intense debate centered on whether alloSCT or a trial of IFN-α was the best initial approach for patients with newly diagnosed CML. This debate now seems almost irrelevant in view of the excellent results of imatinib. Whether imatinib or alloSCT should be offered as initial therapy is a question partly answered by the lack of universally available donors for alloSCT, and the fact that most patients want a trial of imatinib as their initial therapy. Here, I discuss the most recent results of imatinib, provide a perspective of the results of alloSCT, and describe our current initial approach for patients with chronic phase CML.

Introduction
Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by the excessive proliferation of a neoplastic stem cell pool. Molecularily, CML is defined by the BCR/ABL gene rearrangement, that is cytogenetically evidenced as the Philadelphia (Ph) chromosome: t(9;22)(q34;q11). The BCR-ABL fusion gene encodes the p210 BCR-ABL oncoprotein that has constitutive tyrosine kinase activity. This aberrant kinase activity induces the abnormal signal transduction cascades characteristic of the CML cell, that result in increased proliferation and failure to undergo apoptosis.

Clinically CML is divided in three phases: chronic, accelerated and blastic. Most patients present in chronic phase. The median survival of patients with CML has improved from 3 to 4 years when treated with busulfan or hydroxyurea to 6 to 8 years in the era of interferon-alpha (IFN-α) therapy. The introduction of newer therapies such as imatinib mesylate (imatinib), a BCR-ABL tyrosine kinase inhibitor, have resulted in significantly better outcomes compared with combination IFN-α therapy for patients with CML. Allogeneic stem cell transplantation (alloSCT) can produce long-term event-free survival rates of 40% to 80%, depending on several factors such as disease stage, patient age, and degree of host-donor matching. These results are offset by the lack of universally available donors, and the excessive mortality and morbidity related to graft-versus-host (GVHD) disease encountered the first few years after transplantation.

At the present time, imatinib and alloSCT are the most frequently offered therapies for patients with newly diagnosed chronic phase CML. In contrast with the IFN-α era and based on the excellent results observed with imatinib, nowadays most centers offer a trial of imatinib to the majority of patients with standard risk CML disease prior to transplantation. The decision to transplant is subsequently made based on the response achieved with imatinib. A criterion for imatinib failure is currently not well defined, but is an area of intense investigation that needs maturation of ongoing studies.

Treatment of chronic myeloid leukemia
Busulfan was the first agent shown to provide effective hematological control in CML. Due to its toxicity, its use should be discouraged outside the setting of preparative regimens for allogeneic SCT. Hydroxyurea is an excellent debulking agent that allows rapid control of peripheral blood counts. Cytogenetic responses are rare, and it should not be considered definitive therapy of CML, even in older patients.

Prior to imatinib, IFN-α was the most active non-transplant therapy in CML. Achieving a complete cytogenetic response was associated with 10-year survival rates of 70% to 80%. IFN-α has been combined with low doses of cytosine arabinoside (ara-C). With IFN-α daily and ara-C 10 mg subcutaneous daily, complete hematological responses (CHR) was achieved in 92% of patients, and a cytogenetic response in 74%. The rates of major cytogenetic responses were higher with IFN-α and daily ara-C, compared with IFN-α and intermittent ara-C, or IFN-α alone. Two randomized trials comparing IFN-α plus ara-C with IFN-α have been reported. In a French multicenter study, IFN-α plus...
IFN-α demonstrated better major cytogenetic response rates than those transplanted during the first 24 months. The timing of transplantation is controversial; most transplant centers recommend transplantation in early chronic phase CML within one year from diagnosis. Several recent updates show little difference in early chronic phase. In chronic phase CML, alloSCT results in 30% to 40% in patients older than 50 years. Large series have reported 5-year survival rates of 30% to 40% in patients older than 30 to 40 years have DFS rates with matched-related alloSCT are 40% to 80% in chronic phase, 15% to 40% in accelerated phase, and 5% to 20% in blastic phase. In chronic phase, patients younger than 30 to 40 years have DFS rates of 60% to 80%, 1-year TRM rates of 5% to 20%, and relapse rates of 20%. Outcome worsens with older age. Large series have reported 5-year survival rates of 30% to 40% in patients older than 20 years. The European Bone Marrow Transplantation Registry reported a TRM of 47% and a 5-year DFS of 25% in patients older than 45 years. The optimal timing of transplantation is controversial, most transplant centers recommend transplantation in early chronic phase CML within one year from diagnosis. Several recent updates show little difference in long-term outcome among patients transplanted in the first 12 months after diagnosis compared with those transplanted during the first 24 months.

Toxicity from preparative regimens is observed in 100% of patients. Acute GVHD occurs in 10% to 60% of patients and is the cause of death in 10% to 15%. Chronic GVHD occurs in 75% of patients and its associated mortality is 10%. The most common causes of death post-transplantation are acute GVHD (2%-13%), chronic GVHD (8% to 10%), terstitial pneumonitis (4%-32%), opportunistic infections (3% to 24%), veno-occlusive disease (1% to 4%), and resistant relapse (5% to 10%). Long-term complications of alloSCT include sterility, cataracts, hip necrosis, secondary cancers (5% to 10%), chronic GVHD complications, and worse quality of life.

One limitation of alloSCT is the availability of related donors. HLA-compatible unrelated donors can be found in 50% of patients. Patients of Caucasian origin have an 85% chance of identification of a perfect match. Median time from donor search to transplant is 3 to 6 months. The use of unrelated donors is associated with higher morbidity and mortality rates. Recent single institutional studies have reported similar outcomes with unrelated SCT compared with related SCT when the transplant is provided by a molecularly perfect matched donor. More than 50% of the mortality associated with unrelated alloSCT is secondary to acute and chronic GVHD.

Non-ablative preparative regimens (mini-transplants, reduced intensity transplants) have attempted to expand the indications of alloSCT to older patients, and to reduce transplant mortality and complications. Preparative regimens rely on immunosuppressive therapy to allow for donor cell engraftment. Early results of non-ablative regimens in patients not eligible for standard transplant show acceptable degrees of engraftment, less mortality, more persistent residual disease, and perhaps similar degrees of GVHD. The improved results from reduced morbidity and mortality may be offset by the higher incidence of persistent or recurrent disease, which could be approached with post SCT maneuvers such as donor lymphocyte infusions (DLI), IFN-α, or imatinib.

Imatinib Mesylate (Gleevec, ST571)

Imatinib has revolutionized the treatment of CML. Following preclinical studies, imatinib entered phase I trials in 1998, and was approved by the FDA in 2001 for the treatment of CML in chronic phase post IFN-α failure, accelerated phase, and blastic phase. Imatinib is a small molecule 2-phenylaminopyrimidine that acts as an ATP mimic thus occupying the binding site for ATP within BCR-ABL which then leads to inhibition of the phosphorylation of tyrosine residues on substrate proteins and BCR-ABL itself. Consequently, imatinib prevents activation of signal transduction pathways that are crucial for CML leukemogenesis.

In a phase I study of patients with late chronic phase and blastic phase CML, including Ph-positive ALL, the dose of imatinib was escalated from 25 mg to 1000 mg orally daily. Common but rarely serious side effects included nausea and vomiting, diarrhea, skin rash, muscle cramps, bone or joint aches, myelosuppression, and weight gain. Less common side effects occurring at higher doses were fluid retention, peripheral and central edema, fever, occasional liver dysfunction, and decreased skin pigmentation.
post IFN-α failure late chronic phase, accelerated phase, and blastic phase were studies of imatinib in IFN-α treated patients treated with imatinib 800 mg daily. The phase II study in chronic phase CML post IFN-α failure included 532 patients. Major cytogenetic responses were observed in 65% of patients, and were complete in 48%. The estimated 24-month transformation rate was 13%; the estimated 24-month survival rate was 92%. A lower incidence of major cytogenetic response was observed in patients with splenomegaly, thrombocytopenia, anemia, longer duration of chronic phase, active disease, clonal evolution, and 100% Ph positivity at the start of therapy.

A multinational study randomized 1106 patients to either imatinib 400 mg orally daily or a combination of IFN-α 5 Mu/m² daily with ara-C 20 mg/m² subcutaneous daily × 10 every month. The median follow-up time is 19 months. After 18 months of therapy, imatinib was associated with significantly higher rates of major cytogenetic responses (83% versus 20%) and complete cytogenetic responses (68% versus 7%), and with lower rates of progression (3% versus 20%), transformation (1.5 versus 9%), and intolerance (1% versus 19%). Survival rates were 97% versus 95% (p = 0.16). However, the median duration of IFN-α plus ara-C therapy was only 8 months, and 89% of patients have either crossed over to imatinib therapy (58%) or elected to be taken off therapy and treated with commercially available imatinib. Therefore a survival advantage of imatinib will not be detectable with this study. Based on these results, imatinib is now considered the frontline standard of care for CML patients in early chronic phase.

The incidence of qualitative or quantitative RT-PCR negativity is currently about 10% in chronic phase post IFN-α failure (median follow-up 3 years), 10% in newly diagnosed patients after 12 months of imatinib 400 mg daily, and 30% or more in similar patients treated with imatinib 800 mg daily.

Choice of initial therapy for patients with chronic phase CML

Patients with newly diagnosed chronic phase CML treated outside the setting of a clinical trial may be offered therapy either with imatinib or alloSCT. The choice of therapy is based on: 1) the benefit: risk ratio of alloSCT versus imatinib, 2) patient risk group, and 3) patient preference. Although the standard of care is still controversial and continuously updated, the treatment algorithm at our center is based on the following principles (fig. 1):

1. Postponing alloSCT for up to 24 months, and pre-transplantation use of imatinib do not influence transplant outcome adversely.
2. The 1-year TRM is age-related and may define what is a reasonably acceptable risk of transplant in exchange for long-term outcome.
3. The median survival with IFN-α based regimens is 6 to 7 years, for good risk patients it is 9 years, for patients who achieve a complete cytogenetic response, the 10-year survival rate is 70% to 80%.
4. Since imatinib induces complete cytogenetic response rates of 60% or more, the median survival in CML may exceed 10 years if the significance of a complete cytogenetic response is similar with imatinib as with IFN-α therapy.

Arguments favoring upfront allogeneic SCT are:

1. It is the only proven curative modality.
2. Delaying alloSCT may worsen patient outcome, and long-term follow up results with imatinib are not yet available, hence: a) it could have a transient benefit, b) it may not have the same association of cytogenetic response with survival, c) it may have unexpected long-term toxicities, and d) it may adversely affect alloSCT results.

Arguments favoring imatinib as frontline CML therapy are:

1. There is the potential of long-term event-free survival outside the setting of alloSCT (10% at 10-years with IFN-α).
2. Comparing imatinib to IFN-α, the complete cytogenetic response rates (68% versus 7%) and major cytogenetic response rates (83% versus 20%), surrogate endpoints for better survival, are much higher with imatinib.

3. Aside from alloSCT mortality (5% to 20% in some series, 10% to 50% in others), there are considerable toxicities associated with alloSCT (catastrophic, second cancers, hip necrosis, decrease quality of life, GVHD).

4. The follow up studies with imatinib have not shown significant unusual or unexpected side effects, or high rates of resistance in chronic phase.

Frontline therapy for patients with newly diagnosed chronic phase CML at MD Anderson Cancer Center

Based on the above discussion, and until the data from imatinib and alloSCT matures further, patients may be offered both options as initial therapies, after detailed discussion of updated results. Our current recommendation for patients with newly diagnosed CML is a trial of imatinib. This is based on several facts including:

1. Lack of data indicating that delaying transplantation for 12 to 24 months results in worse post-transplantation outcomes.

2. Lack of data suggesting that prolonged used imatinib results in unexpected serious side effects (our combined experiences goes back to 1998).

3. Practical considerations including the fact that related donors are only available for a fraction of patients, that there is a delay from initial diagnosis to actual transplantation, and that unrelated transplantation is associated with significantly worse outcomes.

Finally, and more importantly, in my experience patients are electing to receive a trial of imatinib prior to transplantation. This is probably based not only on the activity of imatinib but on the relative excellent toxicity profile of the drug, and the fact that patients do not need to change their life styles significantly as the would if they had received alloSCT.

Also is a trend changing the concept of cure in leukemia were a patient is considered “cured” if he or she does not die from complications of the disease or its treatment, similar to that of other chronic diseases.

Because of these issues, it is crucial at the present time to develop a proper definition of imatinib failure. Such criteria has not been fully developed. Most investigators accept several criteria, including:

1. Lack of complete hematological response at 3 months post-imatinib.

2. Lack of complete cytogenetic response at 12 to 24 months.

3. Loss of cytogenetic response after successful imatinib therapy. This is temptatively defined as reappearance of Ph positive metaphases after achievement of complete cytogenetic response, although strict criteria has not been clearly established.

4. Imatinib associated toxicity that precludes its use above doses of 300 mg even with the use of maximal supportive care including growth factors.

Finally, it should be noted that at the prognostic value of molecular responses, or lack of them, and the fluctuation of BCR-ABL mutational levels has not been established, nor for the presence of BCR-ABL mutations. Therefore data maturation is needed before using these molecular markers to decide on therapy.

Conclusion

At the present time both imatinib and alloSCT are acceptable frontline therapies for patients with newly diagnosed chronic phase CML. The decision to choose one or another is based on donor availability and patient preference. In our center, we consider that providing a trial of imatinib prior to transplantation is the optimal approach for these patients. Although clear criteria for imatinib failure exists, such as failure to achieve a CHR after 3 months of therapy, more refined molecular endpoints are required to define the best time for transplantation.

References


