Chronic Myeloid Leukemia

CML

Current Clinical Practice in the Treatment of Chronic Myeloid Leukemia

Report from the 29th European Group for Blood and Marrow Transplantation (EBMT) Meeting, July 20, 2003, Istanbul, Turkey

Imatinib (Glivec/Gleevec, formerly known as STI571) is a selective inhibitor of adenosine triphosphate (ATP) binding to Bcr-Abl tyrosine kinase. The medication has been demonstrated in a number of trials to result in remission of chronic myeloid leukemia (CML) in the late chronic phase (CP), accelerated and blast phases of the disease (1-3).

By July 2003, imatinib had been used successfully in more than 20,000 patients, including ongoing Phase III and IV trials, and has obviated the need for transplantation in many CML-CP patients. CML-CP patients under the age of 50 years who receive allogeneic stem cell transplantation (allo-SCT) from a histocompatibility locus antigen (HLA)-identical sibling donor have an approximately 70% cure rate. Although there is no long term survival data for imatinib, treatment does result in a very high incidence of complete hematological and cytogenetic responses. To date the studies conducted of imatinib in CML-CP patients who have failed interferon (IFN) treatment have yielded a complete hematological response (CHR) rate of 95% and a major cytogenetic response (MCyR; ≤35% Philadelphia-chromosome [Ph]-positive cells) rate of 49%.

The contribution of Dr John Goldman as guest editor is gratefully acknowledged.

Imatinib Compared with Interferon

These very promising results led to the testing of the efficacy of imatinib as first-line therapy for chronic-phase CML in the International Randomized Study of Interferon + Ara-C vs. STI571 in Chronic Myeloid Leukemia (IRIS). The latest results of the IRIS study were presented recently in Istanbul at the 29th European Group for Blood and Marrow Transplantation (EBMT) meeting (4). IRIS is an open-label, multicentre study of newly diagnosed CML-CP patients randomized to either imatinib 400 mg/day or the combination of subcutaneous (s.c.) interferon (IFN) α at a target dose of 5 MIU/m^2/day and s.c. cytarabine (Ara-C) 20 mg/m^2/day for 10 days/month. At three months the imatinib dose was increased to 600 or 800 mg/day in patients who did not have a CHR. It was also increased at 12 months in patients who had a CHR at three months but not an MCyR at 12 months. Patients were crossed over to the other treatments if they had a lack or loss of response, or if they were intolerant to the first treatment. The primary endpoint of IRIS is time to progression (TTP), defined as death, progression to accelerated or blast phase, rapidly increasing white blood cell (WBC) count in patients without a CHR, or loss of CHR or MCyR at 12 months.

Five hundred fifty-three patients were randomized to each of the imatinib and IFN+Ara-C arms of the trial. At a median of 19 months, 474 people (85.7%) assigned to imatinib were still taking that treatment and 60 (10.8%) who were assigned IFN-Ara-C were still taking the combination. Two hundred eighty-four of the 318 patients switched from IFN+Ara-C to imatinib (89.3%) remained on the imatinib, compared with six of the 11 (54.5%) of those who had switched from imatinib to IFN+Ara-C.

The results of the intention-to-treat (ITT) analysis for progression-free survival are shown in Figure 1, the other efficacy results are summarized in Figure 2.

"Compared to the combination of interferon and cytarabine, imatinib is a significantly superior first-line therapy for CML patients," concluded Dr Niederwieser in presenting these findings at the 29th EBMT Meeting. "Consequently, imatinib should be used as standard first-line therapy for CML."

FIGURE 1
Progression-free survival (intention to treat)

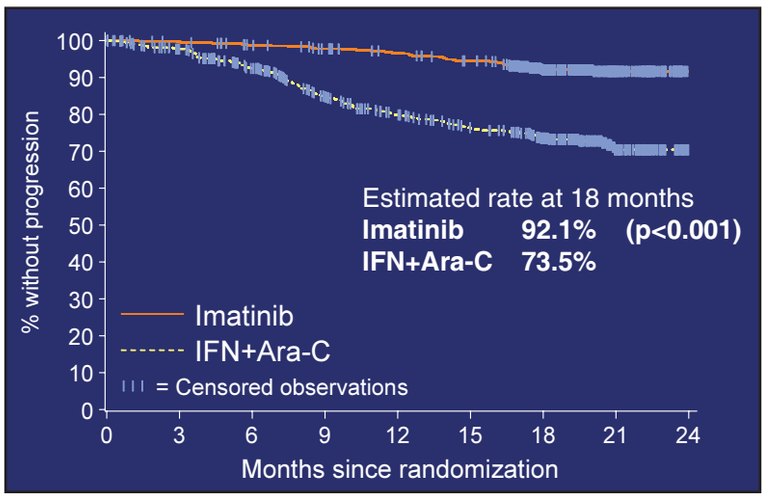
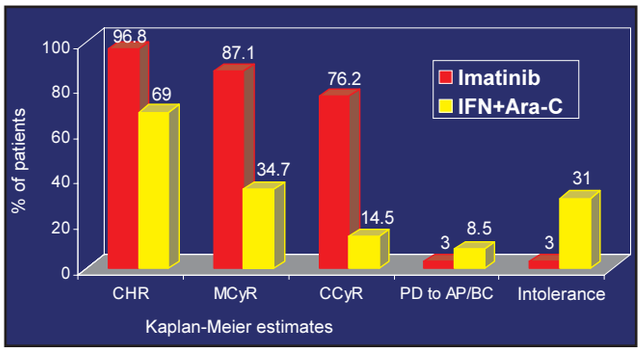


FIGURE 2
Summary of 18 month data



Treating Chronic Myeloid Leukemia in the Late Chronic Phase

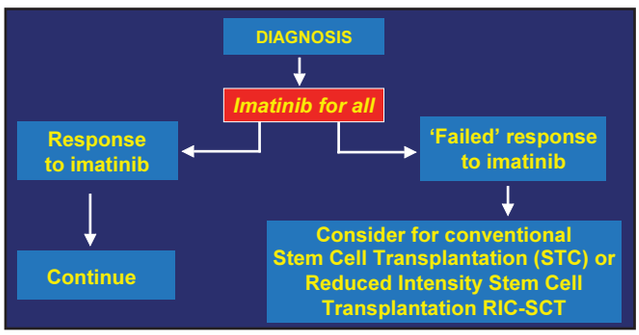
These results underline the fact that serious consideration must be given to the option of using imatinib in newly diagnosed CML-CP patients, observed another speaker at the meeting, Dr John Goldman.

"How then can one advise the younger patient who might, in the pre-imatinib era, have been a candidate for 'up-front' allo-SCT?" he queried attendees. "One must balance the benefits and risks of allogeneic SCT against the estimated likelihood of reasonably long survival with the best available non-transplant therapy."

Dr Goldman said one option is to define a subset of CML patients whose risk of transplant-related mortality (TRM) seems acceptably low, and to offer such patients transplant as the primary treatment. The optimal candidate for an allo-SCT is someone below the age of 30 years who has an HLA-identical male sibling as a donor. Patients with a higher risk of TRM could be offered an initial trial of imatinib, with the intention of using transplantation if the patient fails on imatinib.

A second option is to offer all newly diagnosed CML patients an initial trial of either imatinib or an imatinib-containing combination. After the trial period the patients' response to the medication would be assessed, and those who are responding to imatinib would be continued and those who have failed on this treatment would be considered for SCT (Figure 3). There is currently no evidence that a finite period of treatment with imatinib adversely influences the result of a later transplant, although this is theoretically possible, noted Dr Goldman.

FIGURE 3
Algorithm for treating chronic myeloid leukemia



Dr Goldman said it is currently impossible to determine which of the two options is best in all cases, and that instead clinicians should make their decisions on a case-by-case basis. To illustrate this process, he presented several case studies. One involved a 56-year-old man who was diagnosed with Ph-positive CML in 1999. He was treated initially with IFN but failed and was switched to imatinib in January 2001. A test in January 2002 revealed the patient to be Ph-negative, with a reverse transcriptase polymerase chain reaction (RT-PCR) test in January 2003 confirming a level of BCR-ABL/ABL transcripts in the blood of just 0.04%. The patient now would like to stop taking imatinib because he says he is 'cured'.

"What would you respond?" asked Dr Goldman. "You have six options: to continue him on imatinib 400 mg per day, to start reducing his dose of imatinib, to have him stop taking the drug immediately, to promise to permit him to stop if he becomes completely PCR-negative, to pray for an answer, or to telephone Professor Baccarini [a leading expert on long-term interferon-α trials] to see if there is a trial comparing survival in 'stoppers' with survival in 'non-stoppers.'"

Dr Goldman recommended the latter option, since no definitive data have yet been produced on the discontinuation of imatinib in patients who have succeeded on this therapy. Thus, he was able to demonstrate to meeting attendees that all treatment decisions regarding CML patients must be made carefully, and in a manner that allows as many future options to be preserved as possible.

Allografting in the Imatinib Era

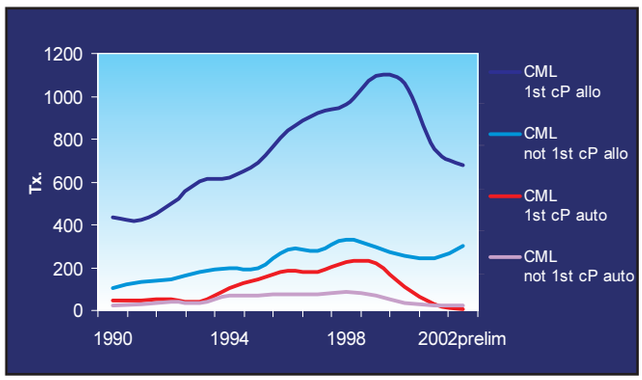
Allografting remains a valuable option in many patients, and thus clinicians should be cognizant of the optimal, risk-adapted strategy for use of this treatment modality, the presenters agreed.

"The pioneering work of Don Thomas and colleagues in Seattle in the 1970s laid the foundations for successful allogeneic stem cell transplantation in the management of CML," pointed out Dr Goldman. "They were able to subject a small number of CML patients fortunate enough to have healthy identical twins to syngeneic bone marrow transplantation and to show impressive short term leukemia-free survival."

Figure 4 shows the overall trends in stage and transplant type of CML between 1990 and 2002. The results indicate that while the most popular option remains allo-SCT after the first exacerbation of chronic-phase CML, allo-SCT after subsequent exacerbations of CML-CP is gradually gaining ground. Auto-SCT of patients experiencing the first and subsequent exacerbations of CML-CP remain relatively infrequently exercised options.

Allo-SCT remains the most powerful antileukemic strategy, although imatinib is the most powerful drug at short-term control of CML, and interferon-α is an established medication for long-term control of CML, pointed out Alois Gratwohl, MD. He and his colleagues made a major contribution to predicting the results of individual transplant procedures for CML by analyzing allo-SCT results in a relatively large group of patients subjected to allo-SCT in centres reporting data to the EBMT (5). The investigators identified five factors that impact favourably on the probability of survival after allo-SCT: age <40 years, having CML-CP, having an

FIGURE 4
EBMT Activity survey on hematopoetic stem cell transplant 1990-2002: changes in CML



HLA-identical sibling donor, short time from diagnosis to transplantation, and avoidance of the combination of female donors for male patients. Integration of these factors into a simple risk score allows clinicians to make a relatively accurate prediction of patient survival for a given transplant procedure.

Another perspective on risk assessment in SCT involves dividing the parameters surrounding the surgery into pre-transplant, peri-transplant, post-transplant and transplant-team factors. All of these factors should be taken into account in determining a patient's probability of developing infections, graft versus host disease (GvHd) or a relapse.

Dr Gratwohl noted that the pre-transplant factors are the most important – including the stage of the disease, time to transplant, the use of conditioning and the resources available to the team of clinicians caring for the patient. For example, a reduced intensity conditioning (RIC) regimen prior to allo- or auto-SCT can significantly increase time to relapse and decrease transplant-related mortality. Furthermore, many studies have demonstrated that patients who are treated in the chronic phase have a significantly improved prognosis compared with those who are not treated until they have advanced CML (Figure 5 and Table 1). Further study will allow investigators to determine the influence

FIGURE 5
Overall survival - disease phase at transplant

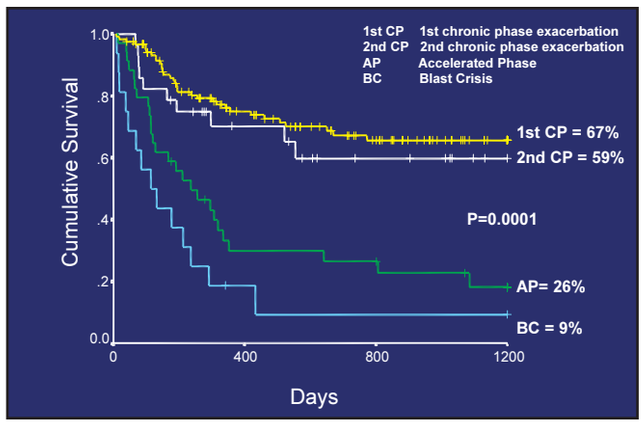


Table 1
Estimated cumulative incidence of relapse and transplant related mortality at 5, 10, 15 years for all CML patients

	N	REL (%) 5	REL (%) 10	REL (%) 15	TRM (%) 5	TRM (%) 10	TRM (%) 15
Total	10206	21	25	27	38	40	43
stage							
CP1	7318	19	24	26	35	37	41
AP	1446	27	30	30	47	49	51
BC	533	36	36	-	52	5	-
donor							
HLA-sib	6717	22	27	28	34	36	39
HLA-nid	721	19	20	26	47	48	50
Twin	79	61	61	-	9	9	-
Unrelated	2355	17	20	-	49	51	-

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on transplant-related morbidity and mortality of imatinib use before, during or after SCT.

The use of various approaches to predict which patients will survive with either transplant or non-transplant therapy is clearly important.

"However, the final decision on whether or when to proceed to a transplant must be made by the patient and his or her family, and not uncommonly this decision is at variance with the clinician's original recommendation," counseled Dr Goldman.

Understanding Resistance

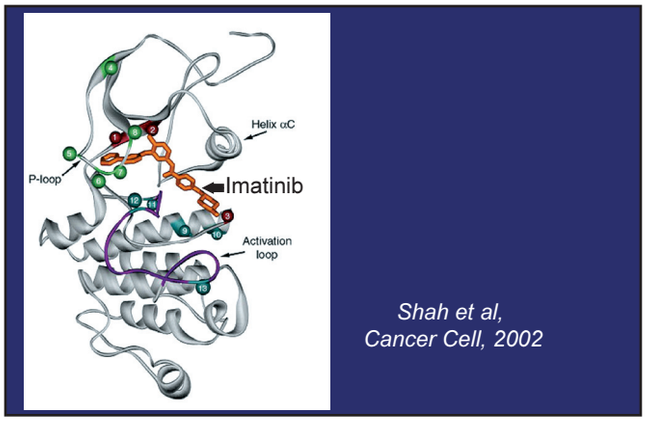
One other factor that will need to be taken into account in future determinations of imatinib efficacy in CML patients is the development of resistance to the medication.

"Fortunately, this issue started to be studied in the research laboratories even before clinical resistance was identified in some patients," pointed out Junia Melo, MD. "Though resistance to imatinib as a single agent seems to be rare in patients treated in the chronic phase, the majority of patients treated in advanced-phase disease do eventually become resistant."

There are three types of resistance to imatinib in CML patients treated in the CP. The first is primary resistance, which develops while the patient is still in the CP and involves hematological or cytogenetic mechanisms. The second is acquired resistance, which also develops during the CP and involves recruitment by CML cells of alternate signal-transduction pathways that bypass imatinib's BCr-Abl inhibitory effect. This resistance mechanism may be common among CML patients with 'innate' resistance, who fail to achieve a complete cytogenetic response during the chronic phase, noted Dr. Melo.

The third type of resistance develops while the patient is progressing to advanced-phase disease. One form of this type of resistance involves amplification and over-expression of the Bcr-Abl gene. Another form is the acquisition of point mutations in the Bcr-Abl tyrosine kinase gene that lead to specific amino acid substitutions which interfere with the binding of imatinib to the enzyme (Figure 6) (6). Other forms

FIGURE 6
Structural map of Abl kinase domain mutations



still likely involve imatinib binding by α-1 acid glycoprotein and other, non-Bcr-Abl-gene-related, mechanisms.

There are several potential approaches to reduce the likelihood of the development of resistance, said Dr Goldman. "These include increasing the dose of imatinib or adding other cytotoxic drugs, adding other kinase- or signal-transduction-inhibitors, stimulating quiescent CML cells to replicate and thus become sensitive to imatinib, or adding some form of immunotherapy," he told attendees. Dr Goldman noted the new STI571 Prospective International Randomised Trial – or SPIRIT – will aid in determining which of these approaches is optimal.

Summary and Conclusions

The prognosis for CML patients at various stages of the disease continues to improve, as the options available for treatment increase. Imatinib is one of the most recent and important new options for CML therapy. The challenge for clinicians today is to determine which patients are candidates for imatinib as first-line therapy, and which should initially be given allo-SCT.

One approach to making this difficult decision is to offer transplantation as first-line treatment to patients who have a low risk of transplant-related morbidity or mortality. The optimal candidate for an allo-SCT is someone below the age of 30 years who has an HLA-identical male sibling as a donor. The pre-transplant factors are the most important in determining the outcome of each patient. Another approach is to offer all newly diagnosed CML patients an initial trial of either imatinib or an imatinib-containing combination. After the trial period the patients' response to the medication can be assessed, and those who are responding to imatinib continued and those who have failed on this treatment considered for SCT. Neither approach is universally acceptable, and thus the clinician must carefully consider the advantages and drawbacks of each approach in each patient, and share these with the patient and their family in order to arrive at a treatment program that is acceptable to all.

Further study will allow investigators to determine the influence on transplant-related morbidity and mortality of imatinib use before, during or after allo-SCT. Research is also ongoing to ensure a limited effect of resistance on the efficacy of the medication, and thus allow patients affected by this devastating disease to have all options available to them in seeking a healthy future.

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Telephone 905-829-4770, fax 905-829-4799, pulsus@pulsus.com, www.pulsus.com