35 Current Trends in the Management of Chronic Myelogenous Leukemia

Abstract: CML is a hematopoietic stem cell disease which is characterized by the presence of Philadelphia chromosome (Ph-chromosome) resulting from the translocation between chromosomes 9 and 22 [t (9;22)]. This translocation t (9;22) results in the head-to-tail fusion of the breakpoint cluster region gene (BCR) on chromosome 22 and the ABL gene located on chromosome 9. The protein product of the fusion gene (bcr-abl) resulting from the t (9;22) translocation has tyrosine kinase activity and is believed to play a central role in the initial development of CML.

The development of imatinib mesylate, a potent and specific inhibitor of the bcr-abl tyrosine kinase has revolutionized the treatment of CML. Many studies have established the safety, efficacy and excellent survival benefit for imatinib in patients with newly diagnosed CML. Imatinib mesylate is the recommended first-line treatment for newly diagnosed chronic phase CML, at an initial standard dose of 400 mg daily. Higher doses, if tolerated can be administered for patients who are in relapse. Disease monitoring with cytogenetics and quantitative RT-PCR is crucial in CML to assess response to treatment.

Some patients will eventually develop secondary resistance related to the presence of mutation in the BCR-ABL gene, resulting in disease progression on imatinib. Dasatinib, another kinase inhibitor has been found to be active in patients with imatinib resistant or intolerant CML. Dasatinib is a treatment option for those who progress on imatinib therapy. Another kinase inhibitor, Nilotinib has shown encouraging results in imatinib resistant CML.

Allogeneic stem cell transplant (SCT) is the only potentially curative treatment for patients with CML, but the advent of imatinib has challenged the role of transplant as first-line therapy. Allogeneic SCT is essential only for patients who have inadequate or no responses to imatinib therapy, as well as for those who progress on imatinib.

Availability of new, more potent kinase inhibitors has widened the treatment options for CML and the outlook for patients with CML continues to look promising.

INTRODUCTION AND OVERVIEW

Chronic myelogenous leukemia (CML) is the commonest adult leukemia in India, being much more common than chronic lymphatic leukemia as contrasted with data from western countries. The median age of disease onset is at least 10 years younger than in the west (mean age at onset in the US 67 years) in multiple Indian studies.[1]

CML is a hematopoietic stem cell disease and it can occur in three different phases. CML is usually diagnosed in the chronic phase. Untreated CML progresses from a chronic phase to a rapidly fatal blastic phase, generally over 3 to 5 years. The blast phase is often preceded by a transition period, called the accelerated phase, which is marked by the acquisition of new cytogentic abnormalities in 50-80% of patients. Several definitions of the accelerated and blast phase have been published in literature.[2-4]

CML is characterized by identification of a clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22, referred to as the Philadelphia chromosome (Ph1). This translocation t (9;22) results in the head-to-tail fusion of the

breakpoint cluster region gene (BCR) on chromosome 22 at band q11 and the ABL gene (named after the Abelson murine leukaemia virus) located on chromosome 9 at band q24.[2-4]

The product of the fusion gene resulting from the t (9;22) translocation is believed to play a central role in the initial development of CML. The chimeric gene is transcribed into a hybrid BCR-ABL m RNA, producing the bcr-abl fusion protein, p210BCR-ABL. This protein is thought to increase proliferation, affect differentiation and block apoptosis and is the key factor in the pathogenesis of the disease.[2-4]

Disease Monitoring

Disease monitoring is one of the key management strategies of CML to assess the response to therapy and to detect early relapse. The goal of CML therapy is to achieve complete remission, which typically progresses from hematological remission to cytogenetic and molecular remission.

Hematological remission is defined as the normalization of peripheral blood counts and normalization of all signs of the disease like sternal tenderness, splenomegaly, etc.

Cytogenetic remission is determined by bone marrow aspirate and cytogenetic evaluation. Conventional metaphase cytogenetic testing for Ph1 is widely available, relatively quick, and reliable; however, the sensitivity is only about 5% if only 20 metaphases are examined. Cytogenetic remission, based on the absence of the Philadelphia chromosome (Ph^1), can be further evaluated by more sensitive techniques such as fluorescence in situ hybridization (FISH) and RT-PCR (reverse transcriptase polymerase chain reaction)[5-7] (Table 1).

Newer Treatment Options for CML

The conventional treatment options for CML like busulphan, hydroxyl-urea and interferon are no longer used these days. The newer treatment options for the disease include:

1. Tyrosine Kinase Inhibitor Imatinib (Fig. 1)
2. Allogeneic Stem Cell Transplantation
3. Other Tyrosine Kinase Inhibitors like Dasatinib and Nilotinib
4. Newer Tyrosine Kinase Inhibitors (Table 2).

Imatinib in CML

Imatinib mesylate (formerly known as ST1571) is a potent and specific inhibitor of the bcr-abl tyrosine kinase and this class of drugs has revolutionized the treatment of CML.[8,9]

Initial trials with imatinib showed a marked effect as a second line therapy in patients in chronic phase who had failed interferon-based therapy or those with more advanced stage disease (accelerated phase or blast crisis).[9] Newly diagnosed patients were then addressed in the IRIS (International Randomized Study of Interferon and STI571) trial. 1106 patients were randomized to receive initial therapy with either 400 mg of daily imatinib or interferon-alpha plus low-dose cytarabine.[10] Crossover was allowed for treatment failure or intolerance. With a median follow-up of 19 months, the major cytogenetic response rate at 18 months was 87.1% in the imatinib group versus 34.7% in the control group. The estimated rate of complete cytogenetic response was 76.2% with imatinib and 14.5% with interferon ($p<.001$). The estimated rate of freedom from progression to more advanced stage disease was 96.7% in the imatinib arm and 91.5% in the interferon-based arm ($P<.001$). In addition to its significantly greater efficacy, imatinib was also much better tolerated than the combination of interferon plus cytarabine.

Five year follow-up data of the IRIS trial are now available.[11] Median follow-up was 60 months. Cumulative rates of complete cytogenetic response among patients receiving imatinib were 69% at 12 months and 87% at 60 months. 7% of patients had progressed to accelerated-

phase CML or received imatinib as initial treatment. This data confirms the high durable response rates with imatinib in a large proportion of patients.

In May 2001, imatinib mesylate was first approved by the US FDA (Food and Drug Administration) for the advanced stages of CML. In December 2002, based on the results of IRIS study, FDA approved imatinib for the first-line treatment of patients with CML. Today, many generic versions of the drug are available in the Indian market.

Dasatinib

Dasatinib (formerly known as BMS-354825) is an orally available ABL kinase inhibitor, similar to imatinib, but with the added advantage in that it can bind to both the active and inactive conformation of the ABL kinase domain.[12]

In a phase I dose escalation study, dasatinib induced hematological and cytogenetic responses in those patients with CML or Ph-positive ALL that could not tolerate or were resistant to imatinib.[13] This result led to the initiation of several phase II studies in patients with imatinib resistant or intolerant Ph-positive leukemia. Dasatinib was administered at 70 mg twice daily on a continuous basis. In the START-C trial, patients with imatinib-resistant or intolerant chronic phase CML (CP-CML) were treated with dasatinib (70 mg twice daily).[14] An initial result of this study for 186 patients revealed that complete hematological response (CHR) observed in 90% of patients. Dasatinib also induced major cytogenetic response (MCyR) in 52% of the patients; only 2% of patients progressed or died after achieving MCyR. After a follow-up of 8 months, progression free survival rate was 92% (Table 2).

Start-A trial evaluated the safety and efficacy of dasatinib in patients with imatinib resistant or intolerant accelerated phase CML (AP-CML).[15] Results are reported for the first 107 patients enrolled in the study. At 8-month follow-up major hematological response (MaHR) was achieved in 64% of patients and major cytogenetic response (MCyR) was achieved in 33% of the treated population and 76% of patients remained progression-free.

The efficacy of dasatinib in imatinib resistant or intolerant patients with CML in myeloid blast crisis (MBC) or in lymphoid blast crisis (LBC) was evaluated in START-B and START-L trial respectively.[16] In the first 74 patients with MBC-CML, 32% had achieved MaHR at 6-month follow-up which increased to 34% at 8-month follow-up MCyR was achieved in 31% of patients. In the LBC-CML group, out of the first 42 patients evaluated, 31% achieved MaHR at 6-month follow-up, and this rate was maintained at 8-month follow-up. MCyR was achieved in 50% of patients (Table 3).

Dasatinib induced cytogenetic and hematological responses in significant number of patients with imatinib resistant CML (all phases), and was also well tolerated in all of these studies. Non-hematological adverse were manageable with dose modification.

In June 2006, based on the favorable results of the above mentioned four single-arm phase II studies, FDA approved dasatinib for use in patients with CML who are no longer responding to or who can no longer tolerate imatinib. Dasatinib is available in India and is marketed by the Bristol Meyer Squibb under the name of Sprycel.

Nilotinib

Nilotinib (AMN107) is a new orally available, highly selective inhibitor of BCR-ABL tyrosine kinase that is more potent than imatinib, in imatinib resistant (20-50 times more potent) as well as imatinib sensitive (3-7 times more potent) CML cell lines. In phase I study, nilotinib was found to be active in imatinib resistant CML with a favorable safety profile.[17]

Following this study, the safety and efficacy of nilotinib was evaluated in a phase II open label trial in imatinib resistant or intolerant CML-CP patients[18]. Nilotinib was administered at 400 mg twice daily with escalation to 600 mg for those with inadequate responses. 316 patients were

enrolled on this ongoing study. Initial efficacy results from 279 patients with at least 6- month follow-up showed that nilotinib resulted in significant response rates (MCyR was achieved in 74% of patients with no baseline CHR). The most frequent grade 3 or 4 toxicities were thrombocytopenia, neutropenia and asymptomatic lipase elevation (Table 4).

Nilotinib is a promising new agent for the treatment of patients with imatinib resistant CML. On November 01, 2007, the US FDA has approved Nilotinib (Tasigna) for use in patients with CML which has relapsed after or are refractory to imatinib.

CHRONIC PHASE-CML (CP-CML)

Primary Treatment

Most international and national guidelines recommend primary treatment with imatinib mesylate for newly diagnosed patients with Ph1 or BCR-ABL positive chronic phase CML. Most experts believe that interferon should no longer be considered as initial therapy for CML, given the excellent long term results with imatinib. In patients treated with a median survival of more than 10 years; some of these patients may actually be cured. Imatinib mesylate at a standard dose of 400 mg daily is recommended for initial treatment of CML (Fig. 1). In very rare patients who are not able to tolerate imatinib, interferon therapy, participation in a clinical can be considered.

High-dose Imatinib

Most patients retain variable levels of residual molecular disease at the 400 mg dose imatinib. Therefore, higher doses of imatinib, up to 800 mg/day, have also been investigated. In a case series of 114 newly diagnosed patients were treated with 400 mg imatinib twice daily. 96% had a major cytogenetic response and 90% (Ph<35%) had a complete cytogenetic response (Ph 0%).[29] Compared with standard dose imatinib, high dose imatinb was associated with significantly better complete cytogenetic response rate (P=.0005), major molecular response rate (QPCR<0.05%; p=.00001). High dose imatinib was well to tolerated but did result in more frequent myelosuppression; nevertheless, 82% of patients continued to receive 600 mg or more of imatinib daily. With a median follow-up of 15 months, no patient had progressed to accelerated or blastic phase. Similar results were reported in a long term-follow up study which included patients from three sequential trials.[19]

Although resistance to imatinib has developed in patients in late chronic phase initially treated with interferon, little evidence of imatinib resistance has been seen in patients treated at the time of diagnosis.

Some studies on imatinib therapy showed that dose escalation of imatinib might also overcome imatinib-associated resistance.[19] However, further follow-up is clearly warranted in this setting. Several ongoing studies are focusing on dose escalation of imatinib in newly diagnosed patients.

Imatinib Toxicity

Imatinib mesylate is generally well tolerated. Frequently reported grade 3 or 4 toxicities include neutropenia and thrombocytopenia. Most frequently reported adverse events include gastrointestinal disturbances, edema, rash, and musculoskeletal complaints, but none of these led to discontinuation of treatment.[20] Erythropoietin has been shown to be effective in patients who develop imatinib-associated anemia.[21]

Imatinib Monitoring

Data suggest that the number of BCR-ABL transcripts, as measured by QPCR, is associated with progression free survival after treatment with imatinib.

Most patients receiving imatinib as initial treatment for CML will achieve a complete cytogenetic response; therefore, more sensitive testing for residual disease is an important part of monitoring. BCR-ABL transcript levels should be measured every 3 months when the patient appears to be responding to imatinib, and when a complete cytogenetic remission is reached. Cytogenetic evaluation is recommended at 6 and 12 months when the patient appears to be responding to treatment, decreasing to every 12 months when complete cytogenetic response is reached. If the patient is not in a complete cytogenetic remission at 12 months, repeat cytogenetic testing is recommended at 18 months.

Some patients will eventually develop secondary resistance which may be related to mutations in the BCR-ABL fusion mRNA, resulting in conformational changes in the fusion protein that affect the binding site of imatinib on the tyrosine kinase. Identification of mutations supports the diagnosis of imatinib resistance and suggests that the patient should be switched to dasatinib, be considered for allogeneic transplant, or placed on a clinical trial of another tyrosine kinase inhibitor, such as nilotinib.[22,23] However, patients who develop a T3151 mutation usually do not respond to dasatinib or nilotinib, and thus should be considered for transplantation or a clinical trial.

Currently, there are no guidelines for changing therapy based on rising BCR-ABL transcripts as detected by QPCR. A rising BCR-ABL level may be associated with an increased risk of the emergence of an ABL mutation in the future.[22] In such situations, ABL kinase domain (KD) mutational analysis may provide additional information. Thus, a rising BCR-ABL level should prompt a bone marrow aspirate for cytogenetic evaluation, sequencing of the ABL tyrosine kinase domain, and careful monitoring of peripheral blood BCR-ABL. Changes of therapy based solely on a rising BCR-ABL level should be done under the auspices of clinical trial.

Discontinuation of Imatinib

Imatinib has become a standard front- line treatment for patients with CML. Complete cytogenetic responses can be achieved in most patients with CP-CML. However, the disease usually relapses if imatinib therapy is stopped even in patients who achieved complete response.[24] At the present time discontinuation of therapy is not recommended for patients who achieve a molecular remission with imatinib.

Disease Progression While on Imatinib

Disease progression is defined as loss of hematological or cytogenetic response or progression to accelerated phase (AP-CML) or blast crisis (lymphoid or myeloid). A phase II trial was conducted in which patients with imatinib resistant CP-CML were randomized to receive 140 mg of dasatinib or 800 mg of imatinib.[25] Median follow-up was 15 months. Response rates were equivalent for high dose imatinib and dasatinib in patients who had failed treatment with 400 mg of imatinib if they had already failed 600 mg of imatinib. Treatment failure and progression-free survival were favorable for dasatinib, indicating that dasatinib is an effective treatment for CP-CML resistant to conventional imatinib doses.

Nilotinib has also been recently approved for use in patients with disease which is resistant/refractory to imatinib and in patient who have progresses on the drug (Table 4).

Dasatinib, followed by allogeneic transplant, if feasible, is recommended for disease progression following imatinib therapy. Participation in a clinical trial is another option. An ALL-type induction therapy is appropriate for those with a lymphoid blast crisis (LBC), while an AML-type induction therapy is appropriate for those with a myeloid blast crisis.

Allogeneic Stem Cell Transplant

Allogeneic stem cell transplant (SCT) is a potentially curative treatment for patients with CML but the excellent results with imatinib have challenged the role of allogeneic transplant as a first line therapy. The widespread application of hematopoietic stem cell transplant (HSCT) is limited by high costs, donor availability and the high toxicity of the procedure in older patients, which limits the age of eligibility at many centers to younger than 65 years. There is a significant risk of early mortality related to the procedure (15 to 30%) and chances of significant morbidity if GVHD develops in the patient.[26]

Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate human leukocyte antigen (HLA) typing of unrelated donors, and less toxic regimens are broadening the use of HSCT.

Transplants from unrelated matched donors can now be used for many patients with CML in the western countries. The advent of molecular DNA assessment of HLA typing has enabled a rigorous and stringent selection of unrelated matched donors, and this improvement in typing has translated into greatly improved transplant outcomes. Indeed, two studies have shown similar outcomes for transplantation for patients with chronic phase CML using either a full matched related or unrelated donor, with 5-year survival rates greater than 70% for patients age 50 years or younger who receive transplants within a year of diagnosis.[27,28] Matched unrelated donor transplants are not a viable option for patients in India as there are hardly any BM donor registries in our country.

Investigational approaches using non-myeloablative "mini-transplants" have been pioneered to engender a graft-versus-leukemia effect without exposing the toxicity associated with the myeloablative preparative regimen. These studies are still investigational but are quite promising and show that "molecular remissions" may be achieved in patients with CML.[29-31]

Patient age, disease phase and duration, and therapy before transplantation influence the outcome of allogeneic transplant. Age older than 50 years is associated with decreased survival after an unrelated transplant, but an age effect is much less pronounced in the matched-related setting.[27] Most centers show an improved outcome for early transplantation in chronic phase, with transplantation within the first 1 to 2 years from diagnosis producing superior outcomes when compared with transplantation more than 2 years from diagnosis.[27] Outcome is clearly better for patients in chronic phase who receive transplants when compared to patients with advanced disease; 5-year survival rates after matched-related transplants are approximately 75%, 40% and 10% for patients in chronic, accelerated, and blast crisis phases, respectively.[32] There has been concern that previous treatment with imatinib might have a deleterious effect on subsequent transplant outcomes, as previously implicated with busulfan and interferon.[33,34,35] Indeed some studies suggested that previous imatinib treatment might lead to increased regimen-related toxicity after transplant, especially liver toxicity,[36] while other studies have suggested no increase in toxicity.[37] Of note is that these studies include very heterogeneous groups concerning diagnosis (CML and ALL), phase, and transplant regimen. A recent large retrospective study compared the transplant outcomes of 233 patients who had not received imatinib prior to transplant, with 145 who had various exposures to imatinib.[38] There was no significant difference between the two groups regarding death, relapse rate and non-relapse mortality. These data suggest that pre-transplant imatinib does not compromise the outcome of a subsequent allogeneic transplant.

Allogeneic SCT may be recommended for those who are not in remission or in hematological relapse after 3-months following primary treatment with imatinib. Allogeneic SCT can also be considered for those who have no cytogenetic response or those in cytogenetic relapse at 6,12 or 18 months after achieving initial hematological remission, especially those with a T3151 mutation.

Allogeneic SCT as an alternative treatment option for the following patients:

- In patients who do not achieve hematological remission after three months of imatinib therapy

- In patients with no cytogenetic response or those in cytogenetic relapse at 6,12 or 18 months, after achieving initial hematological remission after 3 months of imatinib therapy
- In patients progressing on imatinb to accelerated phase or blast crisis.

Summary and Conclusions

CML is a hematopoietic stem cell disease which is characterized by the presence of Philadelphia chromosome (Ph-chromosome) resulting from the translocation between chromosomes 9 and 22[t(9;22]. The development of imatinib mesylate, a potent and specific inhibitor of the BCR-ABL tyrosine kinase has revolutionized the treatment of CML. The results of the IRIS trial established the safety, efficacy and excellent survival benefit for imatinib in patients with newly diagnosed CML. Imatinib mesylate is the recommended first-line treatment for newly diagnosed chronic phase CML, at an initial standard dose of 400 mg daily. Higher doses, if tolerated can be administered for patients who are in relapse. Disease monitoring with cytogenetics and PCR is crucial in CML to assess response to treatment.

Some patients will eventually develop secondary resistance related to the presence of mutation in the BCR-ABL gene, resulting in disease progression on imatinib. Dasatinib, another kinase inhibitor was found to be active in patients with imatinib resistant or intolerant CML. Dasatinib is a treatment option for those who progress on imatinib therapy. Another kinase inhibitor, Nilotinib has shown encouraging results in imatinib resistant CML.

Allogeneic stem cell transplant (SCT) is the only potentially curative treatment for patients with CML, but the advent of imatinib has challenged the role of transplant as frist-line therapy. Allogeneic SCT is essential only for patients who have inadequate or no responses to imatinib therapy, as well as for those who progress on imatinib.

Treatment options for CML with kinase inhibitors depend on the stage of the disease, the agent's side effect profile and its relative effectiveness against BCR-ABL mutations. Availability of more potent kinase inhibitors has widened the treatment options for CML and the outlook for patients with CML continues to look promising.

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55(1):10-30.
2. Faderl S, Talpaz M, Estrov Z, et al. Chronic myelogenous leukemia: Biology and therapy. Ann Intern Med 1999;131:207-19.
3. Sawyers C. Chronic myeloid leukemia. N Engl J Med. 1999;340:1330-40.
4. Faderl SA, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. N Engl J Med 1999;341: 164-72.
5. Guo JQ, Wang JYG, Arlinghaus RB. Detection of BCR-ABL proteins in blood cells of benign phase chronic myelogenous leukemia patients. Cancer Res 1991;51:3048-51.
6. Muhlmann J, Thaler J, Hilbe W, et al. Fluorescent in situ hybridization (FISH) on peripheral blood smears for monitoring Philadelphia chromosome-positive chronic myeloid leukemia (CML) during interferon treatment: A new strategy for remission assessment. Genes Chromosomes Cancer 1998;21:90-100.
7. Landstrom A, Tefferi A. Fluorescent in situ hybridization in the diagnosis, prognosis, and treatment monitoring of chronic myeloid leukaemia. Leukaemia and Lymphoma. 2006; (3):397-402.
8. Jabbour E, Cortes JE, Giles FJ, O'Brien S, Kantarjian HM. Current and emerging treatment options in chronic myeloid leukaemia. Cancer. 2007; 109(11): 2171-81.
9. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002; 345: 645-52.
10. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic phase chronic myeloid leukemia. N Engl J Med 2003; 348(11):940-1004.
11. Druker BJ, Guilhot F, O'Brien SG, et al. Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. N Engl J Med. 2006; 355(23): 2408-17.
12. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding Imatinib Resistance with a Novel ABl Kinase Inhibitor. Science. 2004; 305(5682):399-401.
13. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib resistant Philadelphia chromosome-positive leukemias. N Eng J Med 2006; 354:2531-41.

14. Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronioc-phase chronic myeloid leukaemia after failure of imatinib therapy. Blood. 2007; 109(6)2303-9.
15. Guilhot F, Apperley J, Kim DW, et al. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or - intolerant chronic myeloid leukaemia in accelerated phase. Blood. 2007; 109(10): 4143-50.
16. Cortes J, Rousselot P, Kim DW, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukaemia in blast crisis Blood. 2007; 109(8): 3207-13.
17. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in Imatinib-resistant CML and Philadelphia Chromosome-Positive ALL. N Engl J Med. 2006: 354(24):2542-51.
18. Rosti G, le Coutre P. Bhalla K, et al. A phase II study of nilotinib administered to imatinib resistant and intolerant patients with chronic myelogenous leukaemia (CML) in chronic phase (CP). J Clin Oncol (Meeting Abstracts). 2007; 25(18 suppl):700.
19. Aoki E, Kantarjian H, O' Brien S, et al. High-Dose (HD) Imatinib Provides Better Responses in Patients with Untreated Early Chronic Phase (CP) CML. ASH Annual Meeting Abstracts. 2006; 108(11):2143.
20. Schiffer CA. BCR-ABL Tyrosine kinase Inhibitors for Chronic Myelogenous Leukemia. N Engl J Med. 2007; 357(3):258-265.
21. Cortes, J, O'Brien S, Quintas A, et al. Erythropoietin is effective in improving the anemia induced by imatinib mesylate therapy in patients with chronic myeloid leukaemia in chronic phase. Cancer 2004; 100(11):2396-2402.
22. Branford S, Rudzki Z, Parkinson I, et al. Real time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. Blood 2004; 104:2926-32.
23. Nardi V, Azam M, Daley GQ. Mechanisms and implications of imatinib resistance mutations in BCR-ABL. Curr Opin Hemato 2003; 11: 35-43.
24. Cortes J, O'Brien S, Kantarjian H. Discontinuation of imatinib therapy after achieving a molecular response Blood. 2004; 104(7) : 2204-5.
25. Kantarjian H, Pasquini R, Hamerschlak N, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukaemia after failure of first-line imatinib: A randomized phase 2 trial Blood. 2007; 108(12): 5143-50.
26. Clift Ra, Storb R. Marrow transplantation for CML: The Seattle experience. Bone Marrow Transplant 1996; 17[suppl 3] : S 1-3.
27. Davies SM, DeFor TE, McGlave PB, et al. Equivalent outcomes in patients with chronic myelogenous leukaemia after early transplantation of phenotypically matched bone marrow from related or unrelated donors. Am J Med 2001; 110: 339-346.
28. Hansen JA, Gooley TA, Martin PJ. et al. Bone marrow transplants from unrelated donors for patients with chronic myeloid leukaemia. N Engl J Med 1998; 338: 962-8.
29. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: Replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood 2001; 97: 3390-400.
30. Shapira M, Resnick I. Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukaemia in first chronic phase. Blood 2003; 101 441-5.
31. Crawley C, Szyldo R, Lalancette M, et al. Outcomes of reduced intensity transplantation for chronic myeloid leukaemia: An analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood 2005; 106: 2969-76.
32. Horowitz MM, Rowlings PA, Passweg JR. Allogeneic bone marrow transplantation for CML: A report from the International Bone Marrow Transplant Registry. Bone Marrow Transplant 1996; 17 [suppl 3]: S5-6.
33. Goldman J, Szydlo R, Horowitz MM, et al. Choice of pretransplant treatment and timing of transplants for chronic myelogenous leukaemia in chronic phase Blood 1993; 82: 2235-8.
34. Beelen DW, Graeven U, Elmaagacli AH, et al. Prolonged administration of interferon-alpha in patients with chronic-phase Philadelphia chromosome-positive chronic myelogenous leukaemia before allogeneic bone marrow transplantation may adversely affect transplant outcome. Blood 1995; 85; 2981-90.
35. Morton AJ, Gooley T, Hansen JA, et al. Association between pretransplant interferon-alpha and outcome after unrelated donor marrow transplantation for chronic myelogenous leukaemia in chronic phase Blood 1998; 92: 394-401.
36. Zander AR, Zabelina T, Renges H, et al. Pretreatment with Glivec increases transplant-related mortality after allogeneic transplant. ASH Annul Meeting Abstracts. Blood 2003; 102(11): Abstract 1708.
37. Deininger M, Schleuning M, Greinix H, et al. The effect of prior exposure to imatinib on transplant-related mortality Haematologica 2006; 91(4): 452-9.
38. Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukaemia. Blood. 2007; 109(4) : 1782-9.

MULTIPLE CHOICE QUESTIONS

MULTIPLE CHOICE QUESTIONS

1. **The commonest Leukemia in adults in India is:**
   A. Acute Lymphoblastic Leukemia
   B. Acute Myeloid Leukemia
   C. Chronic Lymphatic Leukemia
   D. Chronic Myeloid Leukemia
2. **The most sensitive technique for the detection of the BCR/ABL gene copy number is:**
   A. Conventional cytogenetics
   B. Interphase Fluorescence in situ hybridization (FISH)
   C. Metaphase FISH
   D. Quantitative RT-PCR
3. **FISH and RT-PCR testing can be performed in the following sample:**
   A. Only bone marrow
   B. Only peripheral blood
   C. Both of the above
   D. None of the above
4. **The molecular hallmark of CML is:**
   A. RAS amplification
   B. P 53 deletion
   C. BCR/ABL translocation
   D. Deletion of chromosome 13
5. **Recommended first-line treatment for a newly diagnosed patient of CML is:**
   A. Imatinib
   B. Allogeneic bone marrow transplantation
   C. Dasatinib
   D. All of the above
6. **The only curative modality of treatment for patients with CML, to date, is:**
   A. Imatinib
   B. Allogeneic bone marrow transplantation
   C. Dasatinib
   D. All of the above
7. **Recommended treatment for patients of CML who are resistant or intolerant to Imatinib is:**
   A. Dasatinib
   B. Nilotinib
   C. None of the above
   D. Both the above
8. **The duration of treatment of Imatinib for a patient of CML who has achieved complete hematological and molecular remission is:**
   A. Six month after achieving molecular remission
   B. One year after achieving molecular remission
   C. One year after achieving hematological remission
   D. Till hematological/molecular relapse of disease
9. **Best results with allogeneic Bone Marrow Transplantation are achieved when the patient is transplanted in:**
   A. Chronic phase of the disease
   B. Accelerated phase of the disease
   C. Blastic phase of the disease
   D. More than 2 years after diagnosis of the disease
10. **The following statement is false regarding allogeneic bone marrow transplantation for CML:**
    A. Only curative modality available to date
    B. Low rates of procedure-related mortality and morbidity
    C. Applicable only for patients younger that 50 years of age
    D. HLA matched sibling or un-related donor essential for successful outcome