Imatinib mesylate and the management of chronic myeloid leukemia (CML)

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INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of pluripotent hematopoietic stem cells, characterized by increased proliferation, and decreased apoptosis myeloid progenitor cells[1-4]. CML is a malignant disorder of the stem cell due to reciprocal balanced translocation of genetic material between the long arms of chromosomes 9 and 22 t(9;22)(q34;q11). The shortened chromosome 22 can be visualized by standard cytogenetic techniques and was termed Philadelphia chromosome (Figure 1). Fibrosis and abnormalities of cytokine network may be evident during the disease course[5,6]. The cytogenetic hallmark of the disease is the Philadelphia chromosome and the molecular hallmark is the BCR/ABL fusion transcript. Molecular polymerase chain reaction (PCR) techniques can be used to detect the fusion of the BCR-gene located on 22q11 with the translocated ABL-gene, normally situated on 9q34, as well as fluorescent in situ hybridising (FISH) techniques, both techniques with higher sensitivity than cytogenetic visualization. Improvement of sensitivity levels have led to accurate sensitive diagnostic tools, allowing diagnosis of the disease at low tumor burden or in cytogenetic (Philadelphia) negative cases. BCR/ABL is the initiation-causative event of CML[7-9]. CML represents about 7% to 15% of adult leukemias. The formation of BCR/ABL fusion transcripts and their encoded cytoplasmic proteins (P190, P210, P230) are based on the translocation points between ABL and BCR genes (Figure 2). The translocation causes the formation of a new hybrid gene (BCR/ABL) that codes for a 210 kb cytoplasmic protein (P210) that by autophosphorylation activates a number of signalling pathways involved in cell proliferation, maturation, apoptosis and adhesion, leading to the malignant cell transformation (Figure 3). Median age for CML is 45-55 years; 20-30 % of the patients are above 60 years of age[10-12]. The course of the CML goes on through a chronic phase, usually lasting some years, that is characterized by a massive myeloid hyperplasia

İmatinib mesilat ve kronik miyeloid lösemi (KML) tedavisi

Anahtar Kelimeler: Kronik miyeloid lösemi (KML), İmatinib mesilat, BCR-ABL, Sinyal transdüksiyon inhibitör.

Key Words: Chronic myeloid leukemia (CML), Imatinib mesylate, BCR-ABL, Signal transduction inhibitor.

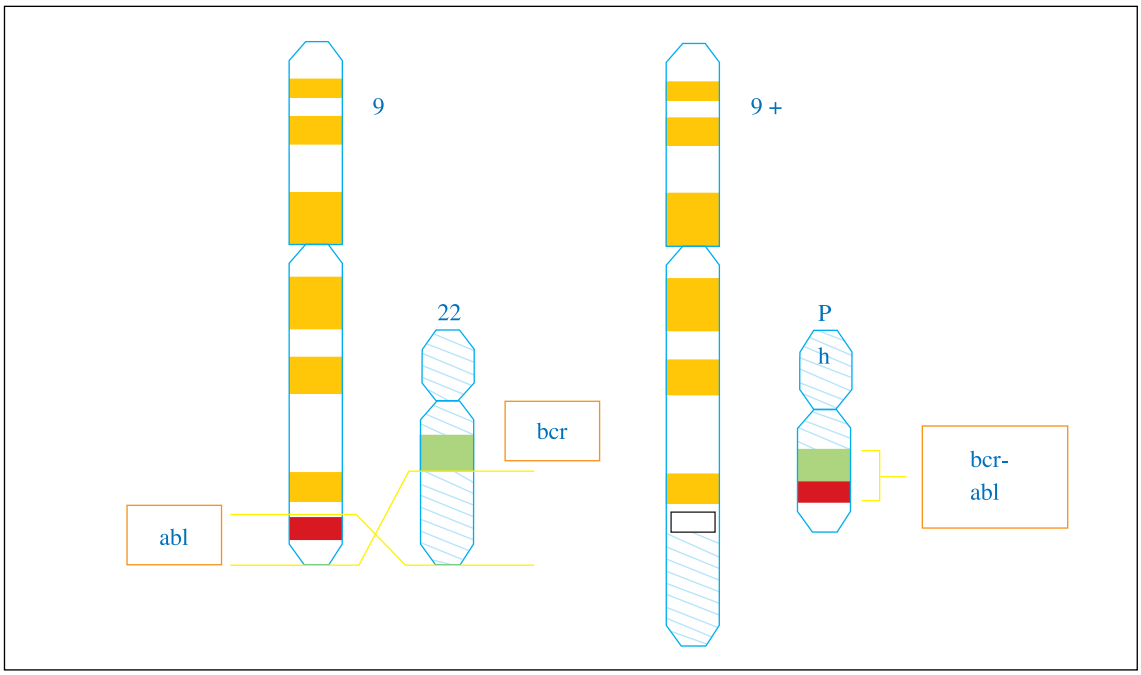

Figure 1. Philadelphia chromosome of chronic myeloid leukemia (CML). The reciprocal balanced translocation of genetic material between the long arms of chromosomes 9 and 22 t(9;22)(q34;q11).

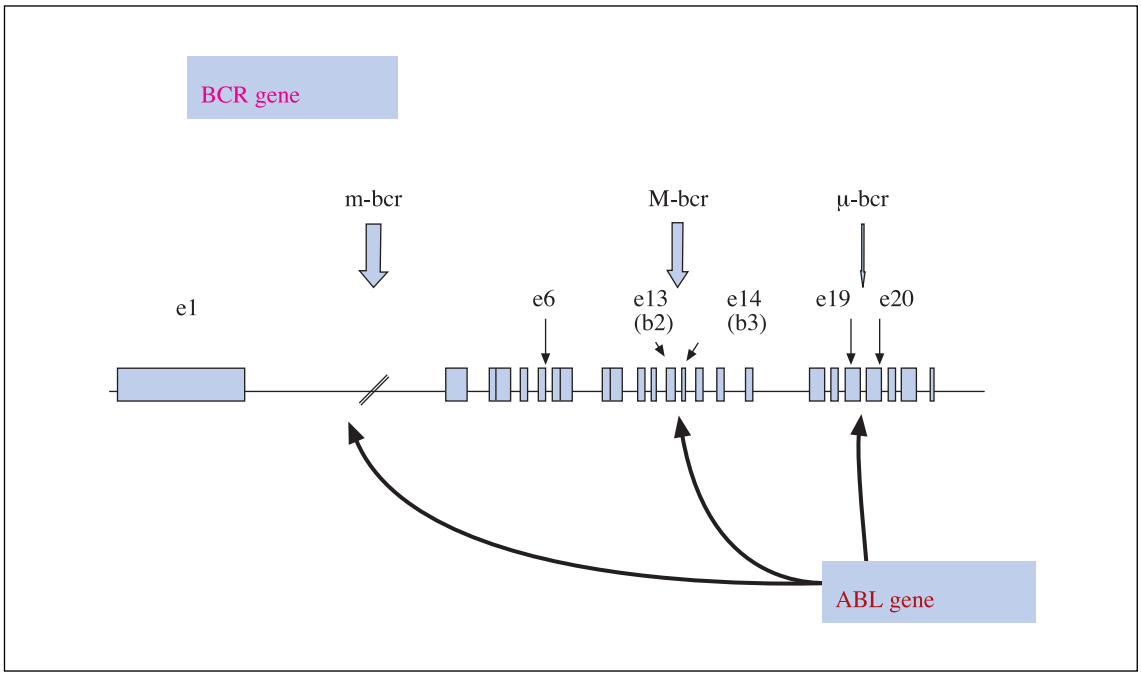

Figure 2. The formation of BCR/ABL fusion transcripts based on the translocation between ABL and BCR genes, and their encoded cytoplasmic proteins (P190, P210, P230).

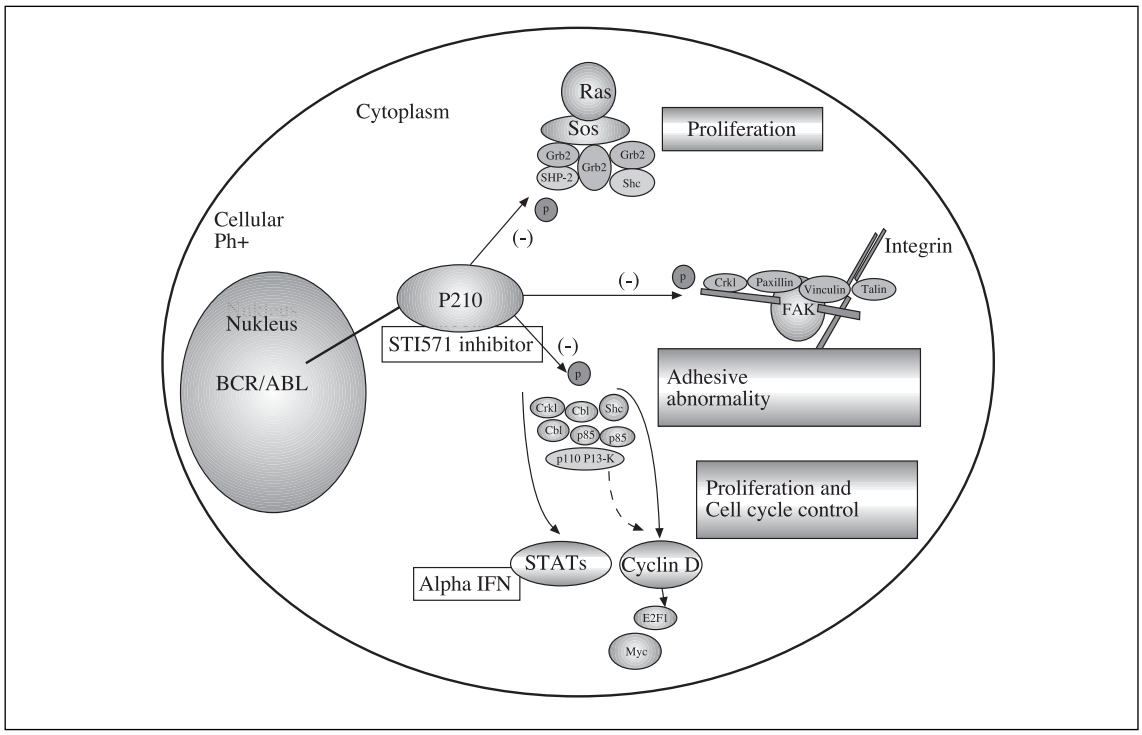

Figure 3. The reciprocal translocation between chromosomes 9 and 22 t(9;22)(q34;q11), causes the formation of a new hybrid gene (BCR/ABL) that codes for a 210 kb cytoplasmic protein (P210) that by autophosphorylation activates a number of signalling pathways involved in cell proliferation, maturation, apoptosis and adhesion, leading to the malignant cell transformation in chronic myeloid leukemia (CML).

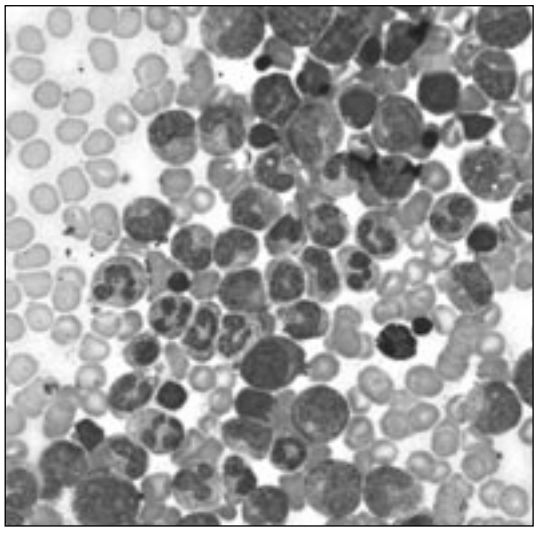

Figure 4. Marked bone marrow myeloid hyperplasia in the chronic phase chronic myeloid leukemia (CML).

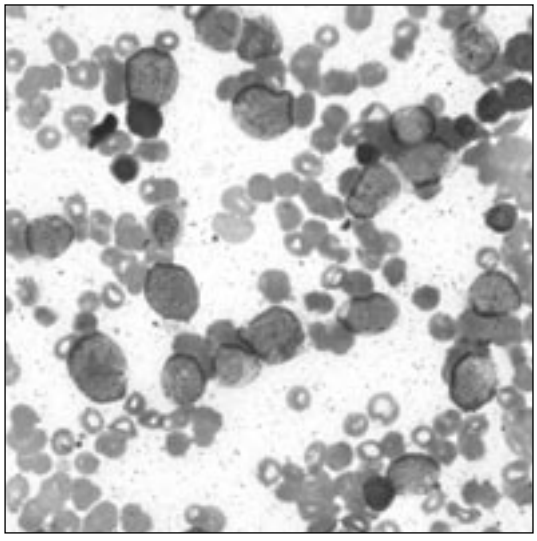

Figure 5. Blastic infiltration of the bone marrow in the blastic transformation phase of chronic myeloid leukemia (CML).

with hyperleukocytosis and splenomegaly (Figure 4). The chronic phase is almost always followed by an accelerated or blastic phase, where the leukemic process transforms to the characteristics of acute leukemia (Figure 5). The blastic aggressive phase usually lasts same months and terminates with the death of the patient[13]. The frequency of CML in western countries ranges between 10 and 15 per million persons (age-standardized). The median age is 55 years[1-4].

The treatment agenda for CML includes conventional cytotoxic chemoterapy, interferon-α (IFN-α), allogeneic hematopoietic stem cell transplantation (allo-SCT), imatinib mesylate and newly developing tyrosine kinase inhibitors such as AMN107 and BMS-354825[7,14-16]. After the introduction of imatinib as a drug (Glivec®) for CML, the management strategies during the clinical course of the disease have radically evolved. Imatinib is a tyrosine-kinase inhibitor which binds to ABL proteins and induces cytogenetic remissions in patients with CML[9,15,17-26]. The aim of this review is to outline current management of CML in the "imatinib era".

Clinical Management of CML

Conventional cytotoxic chemotherapy is based mainly on hydroxyurea and busulfan. Hydroxyurea is a cytotoxic antiproliferative agent that is administered orally, does not require hospitalization, is well tolerated and very cheap. Hydroxyurea controls the chronic phase of the disease in almost 80% of cases, but does not prevent or delay the progression to blastic phase. Currently hydroxyurea is used either to reduce quickly the myeloid hyperplasia to prevent leukostatic complications or to control the disease before allo-SCT or when IFN-α is not tolerated[27,28].

IFN-α based regimes has been the treatment of choice for more than 10 years[1,7,29-37]. Randomized prospective studies disclosed that IFN-α may prolong survival by comparison with conventional chemotherapy. IFN-α induced a complete hematologic response in about 80% of cases and a cytogenetic response in about 50% of cases. In about 30% of cases the cytogenetic response is major (complete or partial, Philadelphia chromosome negative metaphases ≥ 65%). A substantial survival prolongation is obtained only in cytogenetic responders. The probability of obtaining a major cytogenetic response is significantly risk-related and the survival probability among cytogenetic responders remains significantly related with the risk category. Analyzing the results of observational and RCTs of IFN-α in early chronic phase CML patients, a very good correlation is found between the cytogenetic response rates and the Sokal and Euro risk profile (Table 1, 2). Particularly, the Sokal risk profile could influence the survival probability in complete cytogenetic responders. Therefore achieving a major cytogenetic response is a very important short-term target, because it predicts for a long survival but the probability of obtaining a major cytogenetic response and the survival advantage of responders remain significantly related with the Sokal risk profile at the onset of the disease[34,35].

Allo-SCT is a confirmed curative approach to CML with the longest disease free survival periods[38-46]. Hematopoietic SCT carries the burden of increased treatment related mortality (TRM) mainly due to severe graft versus host disease (GVHD) or infectious complications during the time of aplasia after myeloablative conditioning regimens[47]. Improvements of immunosuppression including have shown increased survival and decrease of TRM after transplantation allowing for increased donations of unrelated donors. The use of mismatch donors extends the potential pool for individual patients. Mismatch unrelated donor transplants have been burdened with a higher TRM and increased GVHD[47]. If needed additional donor lymphocyte infusions may be given after transplantation in case of mixed chimerism or disease recurrence[46]. Bone marrow as well as peripheral blood stem cells (PBSC) may be used as stem cell source resulting in similar outcomes with regard to engraftment

Table 1. CML risk-score according to Sokal

Sokal-Score = exp[0.0116 x (age 43.4)	
+ 0.0345 x (spleen size - 7.51)	
+ 0.188 x ([thrombocyte count/700]^2 - 0.563)	
+ 0.0887 x (blasts - 2.1)]	
low risk	: score < 0.8
intermediate risk	: score = 0.8-1.2
high risk	: score > 1.2

Table 2. New European CML risk-score according to Hasford

Hasford-Score = [0.6666 x age(0 if age < 50, else 1)	
+ 0.0420 x spleen size (cm below costal margin)	
+ 0.0584 x blasts (%)	
+ 0.0413 x eosinophiles (%)	
+ 0.2039 x basophils (0 if basophiles < 3%, else 1)	
+ 1.0956 x platelet counts (0 if < 1500 x 10^9/L, else 1)] x 1000	
low risk	: new score ≤ 780
intermediate risk	: new score > 780; ≤ 1480
high risk	: new score > 1480

or frequency of GVHD, although some studies show a higher incidence of chronic GVHD after PBSC[47]. Prognosis of transplantation success depends on several factors, such as the Gratwohl transplantation scoring system in CML patients (Table 3)[38,39,41,42]. The Gratwohl transplantation score combines the effects of several factors: type of transplantation, i.e. related vs. unrelated, disease status, i.e. first chronic phase, acceleration, blastic phase, second or higher chronic phase, age of the patient, i.e. less than 20 years, between 20 and 40 years, above 40 years, gender relation of recipient and donor, time intervall from diagnosis to transplantation, i.e. below and longer than 12 months[38-46]. Long term survival after allogeneic transplantation may reach values of 75% after five years. Data from prospective studies comparing allogeneic transplantation to interferon based therapy is emerging, indicating an overall survival advantage in low risk patients in favor of allo-SCT only after eight years[38-46]. Thus current protocols tend to restrain from allogeneic transplantation in low and intermediate risk groups and recommend an early transplantation only for a high risk group, where even a complete cytogenetic response may not translate into allo-SCT cures a variable proportion of the patients, from 80% to less than 20% depending on disease phase (chronic phase or accelerated-blastic phase), age and donor (HLA-identical sibling or HLA-matched unrelated)[38-46]. TRM is substantial, ranging between 15% and 60% and chronic GVHD is a cause of significant morbidity in about 35% of cured patients[3,27,35,48-50]. TRM is influenced by the intensity of the preparative regimen. Curtailing toxicity by reducing dose intensity (RIC) without jeopardizing the antileukemic effect of conditioning and by the same token en-

Table 3. Gratwohl transplant risk score

Donor	HLA-identical sibling	0
	Unrelated donor	1
Stage of disease	1st chronic phase	0
	Disease progression	1
	Blast crisis or 2./3. chronic phase	2
Age of recipient	< 20 years	0
	20-40 years	1
	> 40 years	2
Gender recipient/donor	All, except	0
	Male recipient/female donor	1
Time elapsed from diagnosis until SCT	< 12 months	0
	> 12 months	1

hancing "graft versus leukemia" effect with donor lymphocytes are primary objectives of non-myeloablative SCT. RIC is particularly useful in the high-risk group of patients older than 45 years of age[39].

Imatinib Mesylate

Imatinib mesylate (formerly STI 571, Glivec®) is a phenylaminopyrimidine derivative with specific property of binding to the ATP-docking site of the P210 oncoprotein, preventing autophosphorylation and all subsequent transforming effects[13,27,31,51-58]. Imatinib has been investigated in phase II studies of CML in ABP and of CML in CP, resistant to or intolerant of IFN-α, and in a phase III study (IRIS trial) where previously untreated patients are randomly assigned to imatinib or to a combination of IFN-α and low-dose Ara-C[13,55-61]. The bulk of evidence of the efficacy of imatinib in CML comes out from the results of clinical trials where imatinib was given alone in CML patients[3,4,13,55-63].

IRIS trial is the most important pioneer randomized clinical trial indicating the efficacy of imatinib in CML[60]. Imatinib, a selective inhibitor of the BCR-ABL tyrosine kinase, produced high response rates in patients with chronic-phase CML who have had no response to IFN-α in IRIS trial. The investigators compared the efficacy of imatinib with that of IFN-α combined with low-dose cytarabine in newly diagnosed chronic-phase CML. They randomly assigned 1106 patients to receive imatinib (553 patients) or IFN-α plus low-dose cytarabine (553 patients). Crossover to the alternative group was allowed if stringent criteria defining treatment failure or intolerance were met. Patients were evaluated for hematologic and cytogenetic responses, toxic effects, and rates of progression. After a median follow-up of 19 months, the estimated rate of a major cytogenetic response (0 to 35 percent of cells in metaphase positive for the Philadelphia chromosome) at 18 months was 87.1 percent in the imatinib group and 34.7 percent in the group given IFN-α plus cytarabine ($p< 0.001$)[60]. The estimated rates of complete cytogenetic response were 76.2 percent and 14.5 percent, respectively ($p< 0.001$) in IRIS. At 18 months, the estimated rate of freedom from progression to accelerated-phase or blast-crisis CML was 96.7 percent in the imatinib group and 91.5 percent in the combination-therapy group ($p< 0.001$). Imatinib was better tolerated than combination therapy[60]. Therefore, in terms of hematologic and cytogenetic responses, tolerability, and the likelihood of progression to accelerated-phase or blast-crisis CML, imatinib has been found to be superior to IFN-α plus low-dose cytarabine as first-line therapy in newly diagnosed chronic-phase CML in IRIS trial[60].

Imatinib Mesylate-Side Effects

Imatinib has generally been well tolerated: although most patients experienced non-hematologic side effects, the events were generally mild to moderate in severity and grade 3 and 4 adverse events were reported in less than 4% of patients[17-19,27,51,54,64-68]. Treatment discontinuation due to drug related side effects occurred in less than 5% of patients. The most commonly reported side effects included musculoskeletal complaints and the development of edema at various sites, most frequently periorbital and at lower limbs. Nausea, vomiting and diarrhea, macupapular skin rash, fatigue and headache were other frequently reported adverse events. Dose-dependent hepatotoxicity and myelosuppression may be observed. Adverse events tend to come on within the first 2-4 weeks of therapy[17-19,27,51,54,64-68]. Fluid retention has been a consistent finding in all studies. This can manifest as subcutaneous edema at any site, including the ankles and periorbital tissues. Some patients have developed pleural effusions and/or ascites, whilst others have had considerable weight gain. A generalized, erythematous, maculopapular, pruritic skin rash has a1so been reported with a positive rechallenge in most patients in whom this was attempted. At present, apart from general supportive measures, no specific treatment can be recommended either as therapy for or as prophylaxis against skin rash, and some patients have permanently discontinued imatinib because of this problem[17-19,27,51,54,64-68]. Abnormalities in liver function tests have been observed, generally consisting of mild elevations in transaminases, though a minority of patients have had elevated levels of bilirubin. The levels generally normalize after withholding therapy for a week or two. Myelosuppression has occurred in a minority of patients and is clearly more prominent in patients with advanced disease presentations. Myelosuppression may represent bone marrow toxicity or may even be a manifestation of the antileukemic activity of the imatinib[17-19,27,51,54,64-68]. Unusual extramedullary relapses may be seen in association with imatinib treatment in CML[69]. In patients with CML in chronic phase, low blood counts generally recover after withholding therapy for a few days or weeks, though recovery has been much slower in the advanced disease settings[17-19,27,51,54,64-68,70].

Critical Points of CML Management in the "Imatinib Era"

A newly diagnosed CML patient's preferred initial standard therapy currently is imatinib based on the evidences obtained from randomized clinical trials[59-62,71-76]. Therapy with imatinib should be initiated at a dose of 400 mg/day. Doses below 300 mg daily do not achieve sufficient intracellular concentrations to be deemed effective and should therefore be avoided. More follow up and further studies are needed to confirm the superior efficacy of higher doses (600 mg or 800 mg) in high-risk chronic phase CML, advanced disease, initially "Imatinib non-responder" patient, and in the "loss of response to Imatinib" or "disease progression under Imatinib"[59-62,71-76].

Current main perspectives for the patient-specific management strategies of CML in the "imatinib era" are;

1. Management of newly diagnosed chronic phase CML patient with imatinib,

2. Management of newly diagnosed "high-risk" chronic phase CML patient with imatinib,

3. Management of "imatinib responder" CML patient,

4. Management of "imatinib non-responder" CML patient, particularly imatinib resistance due to P-loop mutations,

5. Management of CML patient with "imatinib side effects" particularly cytopenias,

6. Management of CML patient with "loss of response to imatinib" or "disease progression under imatinib" due to clonal evolution, overexpression of oncoprotein, expansion of

a Philadelphia positive neoplastic clone, or a point mutation in the kinase domain of BCR-ABL (imatinib resistance),

7. Management of the patients with advanced-stage (accelerated phase/blastic-phase) CML. Since the curative ability and long term survival data of imatinib are under investigation, allo-SCT for CML still remains an important therapeutic tool with decreased disease progression risk and curative potential. However, transplant-related mortality and morbidity, acute and chronic GVHD, and late side effects of the procedure are great challenging problems[10,12,27,29,51,52,54,59-62,71-81].

Thus, critical key decision points at any stage for the management of CML are;

1. Selecting patients likely "to do well with allo-SCT" (such as a "young" patient within the first year of chronic phase, high risk-CML diagnosis with a HLA-identical donor),

2. Selecting patients likely "to do well with imatinib",

3. Definition of "imatinib responder" CML patient,

4. Definition of "loss of imatinib response" and "imatinib non-responder".

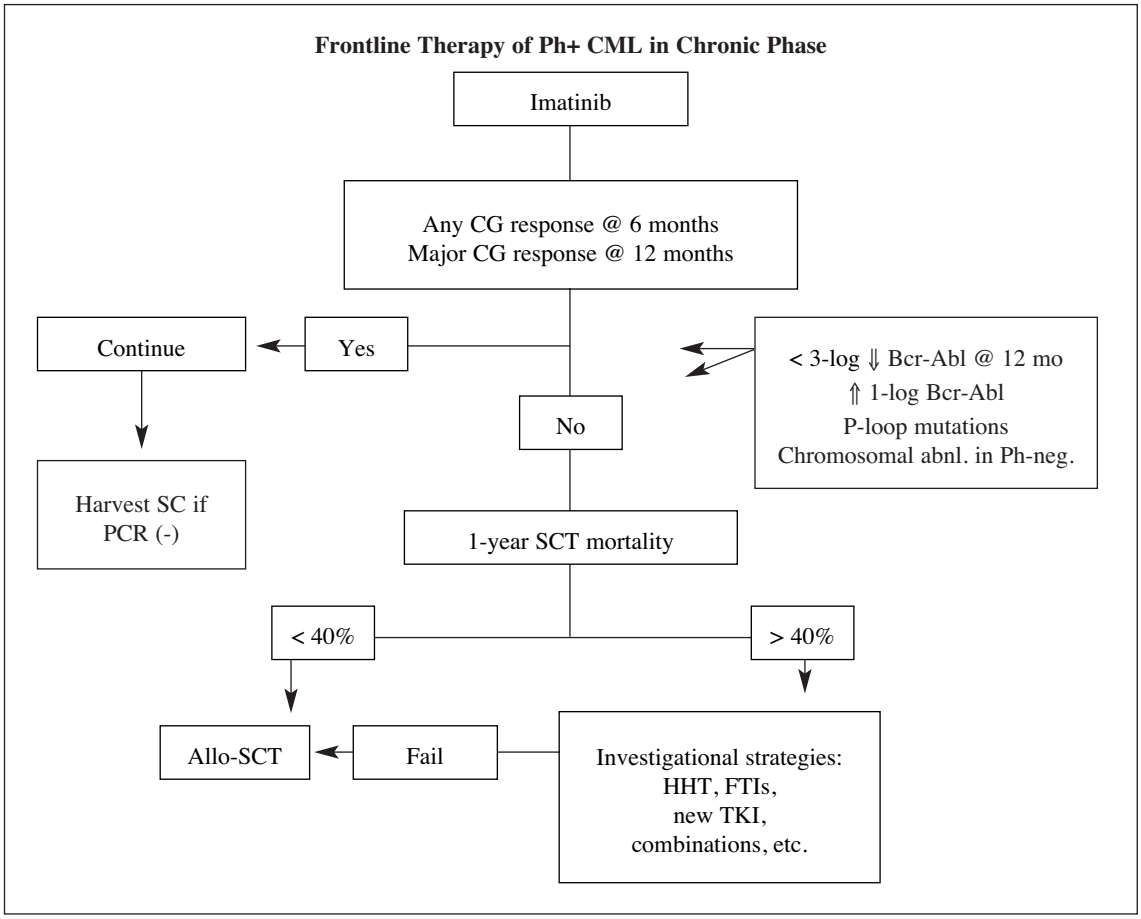

Figure 6. An algorithmic approach to the frontline therapy of Philadelphia positive chronic phase chronic myeloid leukemia (CML) (CG; Cytogenetic, HHT: Homoharringtonin, SCT: Stem cell transplantation, FTI: Farnesyl transferase inhibitors, TKI: Tyrosine kinase inhibitors)

A patient obtaining complete cytogenetic response within the first 12 months of the imatinib treatment is described as "imatinib responder". At least a minor cytogenetic response (> 35% Philadelphia-negative metaphases) after six months treatment or at least a reduction in 30 percentage points in the proportion of Philadelphia positive metaphases at each three month interval are considered as "potential responses". Imatinib and allo-SCT should be combined to optimize management of CML patients[10,12,27,29,51,52,54,59-62,71-81]. An algorithmic approach to the frontline therapy of Philadelphia positive chronic phase CML suggested by Kantarjian is depicted in Figure 6[13,31,55-58,72-76,82,83].

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