Review Article

Chronic myelogenous leukaemia (CML): An update

LALIT KUMAR

ABSTRACT

The management of chronic myelogenous leukaemia (CML) has undergone a major change over the past 5 years. All newly diagnosed patients of CML are candidates for imatinib mesylate therapy. Almost 95% of patients with early chronic phase CML achieve complete haematological remission (CHR) and nearly 80% achieve complete cytogenetic response (CGR; 0% Philadelphia [Ph] chromosome–positive metaphases). These responses are stable in most patients with a risk of relapse of 4%–6% per year. For patients with advanced CML (accelerated phase and blast crisis), achievement of CHR and major (complete and partial) CGR occurs in 25%–37% and 10%–30% of patients, respectively. Most investigators agree that patients who fail to achieve CHR by 12 weeks, have partial cytogenetic response (<35% Ph–positive metaphases) at 12 months, have CGR by 18 months, who relapse after initial response to imatinib, and those with a high Sokal score or in an advanced phase of CML should be considered for allogeneic stem cell transplantation (SCT). Despite Ph negativity with imatinib treatment, most patients continue to remain BCR–ABL positive on molecular studies, and require treatment indefinitely. Identification of patients at high risk for relapse and understanding the mechanisms to unravel resistance to imatinib are current areas of active research.

Natl Med J India 2006;**19**:255–63

INTRODUCTION

Chronic myelogenous leukaemia (CML) is a clonal myeloproliferative disorder of the pluripotent stem cell. Its incidence is 1 per 100 000 population in the West.[1] The true incidence of CML in India is not available. According to 6 population-based cancer registries (covering <0.3% of the total population), the incidence of CML in India varies from 0.8 to 2.2 per 100 000 population for men and from 0.6 to 1.6 per 100 000 population for women.[2] Hospital-based studies have reported a higher frequency of CML ranging from 40% to 82% of all cases of leukaemia among adults.[3]

The disease is usually characterized by an insidious onset of symptoms, progressive splenomegaly, marrow hypercellularity, anaemia, leucocytosis and cytogenetically by the presence of Philadelphia (Ph) chromosome t(9;22)(q34;q11) in 90%–95% of patients. The disease follows a biphasic or triphasic course. There is an initial chronic phase which after an average of 5–5.5 years may progress to an intermediate phase called accelerated phase followed by blastic transformation or blast crisis. At the time of presentation 90%–95% of patients are in the chronic phase while the remaining may have features of advanced disease.[4]

CLINICAL AND HAEMATOLOGICAL FEATURES

The median age of onset is 38–40 years in India[3] compared to 50 years in the West. There is a slight male preponderance. With routine screening tests, 5%–15% of patients are diagnosed in the asymptomatic stage. The presenting symptoms are usually malaise, fatigue, abdominal fullness, fever, weight loss, abdominal pain and occasionally easy bruising or bleeding. Splenomegaly is present in 90% of patients and in one-third of them it is >10 cm in size. Nearly 25% of patients have hepatomegaly (>2 cm) but lymphadenopathy is uncommon (<10%) in the chronic phase (CP) and is confined to 1–2 regions with small lymph nodes. Initial haematological investigations show a normal haemoglobin, total leucocyte count (WBC) of 100–300×10^9/L and platelet count of 200–400×10^9/L. Differential count shows the myeloid series of cells in all stages of maturation with <10% myeloblasts and promyelocytes and a predominance of myelocytes. Basophils are increased but only 10%–15% of patients have ≥7% basophils in the peripheral blood. Frequently, eosinophils are mildly increased. The bone marrow (BM) is hypercellular and devoid of fat. There is myeloid hyperplasia with a myeloid-to-erythroid ratio of 10–30:1. Evidence of focal fibrosis may be seen on reticulin stain in 25%–28% of patients in the chronic phase but increases with disease progression. The biochemical abnormalities include low leucocyte alkaline phosphatase (LAP) score, and marked elevation of serum B_{12} and B_{12} binding protein transcobalamine-I.

Hyperuricaemia related to increased cell turnover may occur prior to therapy and may be exacerbated by treatment. The LAP score may increase with infection, clinical remission or onset of blast crisis.[4] Though earlier studies (prior to the 1970s) reported the clinical and laboratory features of CML patients at diagnosis, only few studies have reported this aspect in the past 3 decades. We analysed the clinical and laboratory features of 437 patients seen at our institute between 1987 and 2000[5] and compared them with two other Indian studies (from AIIMS, New Delhi [1975–1983][6] and from the Cancer Institute, Chennai [1975–1985][7]), two European studies (from Hammersmith Hospital, London [1973–1995][8] and the German CML Study Group [1983–1991][9]) and a study from North America[10] (Table I).

Department of Medical Oncology, Dr B.R. Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India *lalitaiims@yahoo.com*

TABLE I. Clinical and laboratory features of patients with chronic myelogenous leukaemia in different studies

Characteristic	Kumar *et al*.[5]	Prabhu *et al*.[6]	Kumar *et al*.[7]	Savage *et al*.[8]	Hehlmann *et al*.[9]	Kantarjian *et al*.*[10]
Period of study	1989–2000	1975–83	1975–85	1973–95	1983–91	1999–2000
No. of patients	437	152	160	430	513	454
Chronic/accelerated phase, blast crisis (%)	88.5/11.5	93.4/6.6	–	93.3/6.7	–	94/6
M:F	1.6:1	1.4:1	1.7:1	1.4:1	1.4:1	1.5:1
Median (range) age in years	35 (8–75)	36.5 (12–65)	38 (11–75)	34 (5–62)	47.6 (17–85)	57 (18–81)
Median (range) duration of symptoms in months	4 (3–120)	nr	3 (1–36)	3 (0–36)	nr	nr
Asymptomatic (%)	5.3	3.9	7.5	20.3	nr	nr
Symptoms (%)						
Weakness, malaise, fatigue	61.7	60	56.3	33.5	62.8	nr
Abdominal mass	53.7	54	52.5	14.8	33.7	
Fever	54.5	31	30.6	0.9	18.3	
Weight loss	24.2	–	27	20	20.5	
Bleeding	6.3	8	17	21.3	–	
Signs						
Splenomegaly (%)	95.2	91.4	89.4	75.8	71.3	17.7
>10 cm (%)	32.8	38.2	46.2	8.0	–	2
Hepatomegaly (%)	55.3	88.8	48.1	2.2	49.3	8.4
Lymphadenopathy (%)	16.2	–	16.3	<1.0	19.1	0
Laboratory parameters						
Haemoglobin (g/dl)	10	–	9	10.3	12	12.5
Median (range)	(3–16.7)	–	(4.5–11.3)	(4.9-16.6)	(4.2–17.2)	(7.3–17.2)
White cell count ($\times 10^9$/L)	145	–	180	174	166	15.0
Median (range)	(1800–980)	–	(25–500)	(5–850)	(12–600)	(2–260)
Platelet count ($\times 10^9$/L)	280	–	250	430	497	303
Median (range)	(20–1631)	–	(50–3182)	(17–3182)	(10–3400)	(100–2081)

* This study included patients in late chronic phase nr not reported

ACCELERATED PHASE/BLAST CRISIS

With conventional treatment CP progresses to an accelerated phase (AP) that lasts for 1–1.5 years and is followed by a blast crisis (BC). In 20%–25% of patients, the transition to BC may be without an intermediate AP. The criteria used to define AP are presence of 10%–19% blasts in the peripheral blood (PB) and/or bone marrow (BM), ≥20% basophils in the PB or BM, platelet count <100 000/cmm unrelated to therapy, or platelet count >1 000 000 unresponsive to therapy, cytogenetic evolution with new abnormalities in addition to the Philadelphia chromosome (double Ph chromosome, isochromosome 17 and trisomy of chromosomes 8, 19 or 21), and *p53* mutations or deletions, increasing splenomegaly or WBC count, unresponsive to therapy.[11] BC is a terminal event in 70% of patients and is characterized by the above features as well as >30% blasts in the PB/BM.[4,11]

Occasionally, extramedullary blastic infiltrates in the lymph nodes, bone or skin may precede BC in the BM. Phenotypically, blasts are mainly myeloblastic (60%), lymphoblastic (20%) and undifferentiated (10%–15%). Rarely, there may be erythroblastic, megakaryocytic or mixed transformation.[4,11] Focal myelofibrosis may be seen in up to 30% of patients at presentation. Increasing myelofibrosis on serial BM biopsies may be associated with AP/BC.[12]

MOLECULAR BIOLOGY

The Ph chromosome results from reciprocal translocation between the long arm of chromosomes 9 and 22.[13] Cell synchronization and high resolution banding techniques have identified the chromosome breakpoints as t(9;22)(q34.1:11.2).[14] The Ph chromosome is also found in 20%–25% of adults and 5% of children with acute lymphoblastic leukaemia (ALL) and in 1%–2% of patients with acute myeloblastic leukaemia.[15] In the formation of the Ph chromosome, the ABL proto-oncogene is translocated from chromosome 9 (q34.1) to the BCR gene in chromosome 22 (q11.2). The resultant fusion gene *BCR–ABL* transcribes a chimeric 8.5 mRNA which in turn is translated into a novel protein of p210 kDa termed as p210. The latter, presumably through increased tyrosine kinase activity changes normal haematopoietic cells into CML cells *in vitro* and *in vivo*.[16,17] The activation of multiple signal transduction pathways in BCR–ABL transformed cells leads to increased proliferation, reduced growth factor dependence and apoptosis, and perturbed interaction with the extracellular matrix and stroma.[18]

Approximately, 3%–10% of CML patients have cytogenetically normal leukaemic cells (Ph-negative). A proportion of these patients (30%–80%) have re-arrangements of the *BCR–ABL* gene with the production of an 8.5 kb mRNA and p210 kDa BCR–ABL protein similar to that in patients with Ph-positive CML. The clinical outcome of patients who are Ph-negative but *BCR–ABL* positive is similar to that of patients with Ph-positive, re-arranged *BCR–ABL*, suggesting that they represent a single disease. Ph-negative patients with absence of *BCR–ABL* re-arrangement have a distinct clinical course despite their early resemblance to classical CML. They eventually develop BM failure (anaemia, thrombocytopenia) accompanied by a markedly increased leukaemia burden with increased WBC count, organomegaly and extramedullary disease. Blast transformation generally does not occur. These are probably cases of myelodysplastic syndrome/chronic myelomonocytic leukaemia. WHO has defined this subgroup as 'myeloproliferative syndrome, unclassifiable'.[11]

WORK-UP

The investigations to be done in a newly suspected case of CML are

1. Blood: Haemoglobin, total and differential count, platelet count
2. Liver and renal function tests, serum uric acid
3. Urine examination
4. Chest X-ray
5. Bone marrow aspiration and biopsy, and cytogenetics for Ph chromosome
6. Reverse transcriptase polymerase chain reaction (RT-PCR) for the *BCR–ABL* gene

Bone marrow (BM) cytogenetic studies must be done for all patients with CML before initiation of treatment. Marrow cytogenetics help to identify any unusual translocation or additional cytogenetic abnormalities. RT-PCR for *BCR–ABL* at diagnosis will identify whether the commonly observed e13a2(b2a2) or e14a2(b3a2) transcripts are present, or one of the less common fusion transcripts that are not amplified by the standard primer sets. If BM examination is not feasible, fluorescence *in situ* hybridization (FISH) on a PB specimen using dual probes for the *BCR* and *ABL* gene is a useful but secondary method of confirming the diagnosis. This may detect cytogenetically silent *BCR–ABL* gene re-arrangements and deletions in the derivatives 9q+. FISH is considerably less sensitive than RT-PCR and should not replace it.[19,20]

TREATMENT

Though CML was described more than 100 years ago, Fowler solution[21] (arsenic trioxide in potassium bicarbonate) and splenic radiation[22] were the only treatment options available till the 1950s. Busulphan, an alkylating agent, was introduced in 1954 and was effective in controlling leucocytosis. However, in view of its toxicity—bone marrow aplasia (1%–3%), hyperpigmentation and pulmonary fibrosis, and inferior survival compared to hydroxyurea—it is used only as part of high dose chemotherapy along with cyclophosphamide in the setting of haemopoietic stem cell transplantation (SCT).[23] Hydroxyurea, introduced in the late 1960s, has a favourable toxicity profile and is effective in controlling the white cell count. Recombinant interferon-α (IFN-α) became available in the early 1990s and was superior to both busulphan and hydroxyurea in attaining complete haematological remission (CHR), complete cytogenetic response (CGR) and prolonging survival. Over the past 25 years, experience with allogeneic haemopoietic SCT from an HLA-matched sibling or an unrelated donor suggests that it is the only potentially curative treatment for CML. Its limitations are the availability of a matched sibling donor in less than one-third of patients and the potential morbidity (acute and chronic graft-versus-host disease) and mortality (5%–15%). Imatinib mesylate (STI-571 or Gleevec) was approved for use in May 2001 and has revolutionized the management of CML.[24] A comparison of hydroxyurea, IFN-α and imatinib mesylate is given in Table II.

Hydroxyurea

It is an S phase agent and acts by inhibiting DNA synthesis. The drug has a rapid onset and short duration of action. Therefore, it controls the white cell count without marked or prolonged myelosuppression. It is usually given in doses of 0.5–2.0 g per day in 2 divided doses. This drug has a special role in patients with a very high white cell count when rapid cytoreduction is essential. In a newly diagnosed patient of CP-CML (white cell count ≥50 000/cmm), hydroxyurea should be started in a dose of 2–3 g day along with imatinib mesylate. Once the count is ≤20 000/cmm hydroxyurea may be stopped.[25] In many countries where imatinib is still not easily available, hydroxyurea is used in intermittent dose schedules with monitoring of the white cell count.

Interferon alpha (IFN-α)

A number of non-randomized[26–33] and randomized studies[34–37] have shown the effectiveness of IFN-α in CP-CML (Tables III and IV). A CHR rate of 60%–80% and a CGR rate of 40%–60% (including complete CGR in about 10%) is achieved. Five randomized trials compared the outcome of patients treated with IFN-α and those treated with hydroxyurea or busulphan. Subsequently, a meta-analysis of all the randomized trials provided conclusive evidence that IFN-α significantly prolonged survival in comparison to hydroxyurea.[38,39] The duration of response was significantly longer in patients with complete CGR. The results are better if IFN-α is used in early CP (within 1 year of diagnosis) compared with late CP and in AP/BC (Ph suppression <10%). The dose of IFN-α varies from 2 to 5 mIU/m^2 daily subcutaneously.[40] A study comparing 3 mIU of IFN-α three times a week with 5 mIU daily indicated that the low dose was as effective as and better tolerated than the high dose.[41] Elderly patients (>60 years) tolerate IFN-α poorly compared with younger patients. The response criteria[42] are given in Table V.

To improve the response rate and survival, IFN-α has been combined with low dose cytosine arabinoside (Ara-C), homoharringtonine. Two randomized trials by the French[43] and Italian Groups[44] compared low dose Ara-C and IFN-α with IFN-α alone in CP-CML. The French study showed that the combination was better than IFN-α alone, both in terms of cytogenetic response (35% *v.* 21%) and 5-year survival (70% *v.* 62%). However, the Italian study failed to demonstrate a survival benefit (68% *v.* 65%) despite better cytogenetic response (21% *v.* 13%) in the combination arm. Only an occasional patient achieves molecular remission with IFN-α therapy.

The early side-effects of IFN-α include fever, chills and anorexia. These can be managed symptomatically by giving

TABLE II. Comparison of hydroxyurea, interferon-α and imatinib mesylate

Factor	Hydroxyurea	Interferon-α	Imatinib mesylate
Mechanism of action	Ribonucleotide reductase inhibitor	Unknown	Selective inhibitor of BCR–ABL
Haematological response	Yes	Yes	Yes
Rapidity	Yes	No	Yes
Cytogenetic response	No	Yes	Yes
Activity in blastic phase	No	No	Yes
Survival benefit	No	Yes	Yes
Impact on allogeneic bone marrow transplant	No	Perhaps	Unknown
Daily dose	0.5–2 g	3–5 mU/m^2	CP 400 mg/day AP/BC 600 mg/day
Major toxicity	No	Yes	No
Oral administration	Yes	No	Yes
Cost	Low	High	Very high

AP accelerated phase BC blast crisis CP chronic phase

TABLE III. Results of interferon (IFN)-α treatment in patients with chronic myelogenous leukaemia

Author (year)	*n*	IFN-α dose	Haematological response (%)		Cytogenetic response (%)		Median survival (%)
			Complete	Partial	Complete	Partial	
Ozer *et al*. (1993)[26]	107	5 mU/m² daily	59	36.4	13	16	52 at 5 years (66 months)
Alimena *et al*. (1990)[27]	74	2 *v*. 5 mU/m² daily	41.6	–	22.2	na	na
Kloke *et al*. (1993)[28]	71	4 mU/m² daily	na	na	13	13	55 at 5 years
Thaler *et al*. (1993)[29]	80*	3.5 mU daily	39	35	5	5	na
Mahon *et al*. (1994)[30]	52	5 mU/m² daily	80.7	17.3	42.5 (20/47)	6.9 (3/47)	na
Schofield *et al*. (1994)[31]	27	2 mU/m² thrice a week	70	7	15	–	79 at 2 years,73 at 3 years
Kantarjian *et al*. (1995)[32]	274	5 mU/m² daily	80	7	26	12	63 at 5 years (89 months)
Kumar *et al*. (2005)[33]	114	5 mU daily	31.6	25.4	1.8	28	–

na not available * 74 evaluable for response

TABLE IV. Results of randomized trials of interferon (IFN)-α versus hydroxyurea (HU) /busulphan (Bu)

Author (year)	IFN-α	HU/Bu	Dose of IFN-α	Major cytogenetic response (%)		5-year overall survival (%)	
				IFN-α	HU/Bu	IFN-α	HU/Bu
Italian Study Group (1994)[34]	218	94/10	5 mU/m²	19	1	60	45
Hehlmann *et al*. (1994)[9]	133	194/186	5 mU/m²	6	1/1	58	48/33
Allan *et al*. (1995)[35]	293	142/152	5 mU/m²	10	2	50	32
Ohnishi *et al*. (1995)[36]	85	0/85	5 mU/m²	15	5	63	37
Benelux Study Group (1998)[37]	100	95/0	3 mU (total)	16	2	54	54
Hasford *et al*. (1996)[38]	640	286/345	–	nr	nr	57	46/34

nr not reported

IFN-α at bed time and paracetamol one hour prior to IFN-α. Tachyphylaxis develops within 1–2 weeks. The late side-effects are dose-related and include persistent fatigue, weight loss, neurotoxicity and occasionally immune-related complications. IFN-α should be discontinued in patients with severe suicidal tendencies, parkinsonism, autoimmune haemolytic anaemia, or severe pulmonary or cardiac toxicity. Dose modification is indicated in patients with severe central nervous system toxicity, e.g memory changes, concentration problems and grades II–III fatigue. The pegylated form of IFN-α given once a week has been reported to have a similar efficacy and less toxicity in initial studies.[45]

Imatinib mesylate (STI-571, Gleevec)

Imatinib mesylate is a 2-phenylaminopyrimidine derivative and is a BCR–ABL tyrosine kinase signal transduction inhibitor 571 (STI-571). It acts as a competitive inhibitor of the ATP binding site on the protein and prevents its phosphorylation (and thus its activity).[46] The initial landmark studies by Druker *et al*. showed high response rates to imtainib mesylate in patients with advanced CML[47] and those pre-treated with IFN-α.[24,47] Recently, O'Brien *et al*. (IRIS Group) have reported the results of a randomized study of 1106 CP-CML patients.[48] Patients received imatinib (*n*=553) or IFN-α and low dose Ara-C (*n*=553). At a median follow up of 18 months, the estimated major CGR rate was 87% compared with 34.7% in the IFN-α group. The estimated CGR rate was 76% in the imatinib group compared to 14.5% in the IFN-α group. This randomized study confirmed that in terms of CHR, major cytogenetic response, CGR and the likelihood of progression to AP/BC, imatinib was superior to IFN-α and low dose Ara-C as first-line therapy in newly diagnosed CP-CML patients.[48] In addition, patients on imatinib had a better quality of life.[49] An update on the IRIS study published recently showed that at a median follow up of 42 months, 98% of the patients were in CHR and 84% had CGR; 75% of the patients were still on imatinib, 9% had progressed to AP/BC, 6% developed significant toxicity and 9% stopped imatinib due to other reasons.[42]

Two studies have been reported from India (Table VI).[50,51] The CHR rates in both these studies were similar to those reported by the IRIS study and from other centres[52–54] but the CGR rates were inferior to those reported by the IRIS trial. The possible reasons for the low CGR rates in the studies from India could be inclusion of a large number of patients in late CP and with advanced disease, and of those pre-treated with IFN-α. There appears to be a correlation between plasma levels of imatinib and achievement of CGR.[55]

TABLE V. Criteria for assessing response in patients with chronic myeloid leukaemia (adapted from references 20, 42)

Haematological response

Complete

1. Total leucocyte count <10 000/cmm, platelets counts <450 000/cmm
2. Normalization of differential count with no immature forms (myelocytes, metamyelocytes, promyelocytes and blasts)
3. Disappearance of all clinical signs and symptoms including splenomegaly
4. No evidence of extramedullary disease

Partial

1. More than 50% decrease in total leucocyte count from pre-treatment levels to <20 000/cmm
2. Persistence of immature forms on the differential count
3. Persistent splenomegaly

Cytogenetic response (Ph-positive metaphases in bone marrow)*

Complete†	0%
Partial†	1%–35%
Minor	36%–65%
Minimal	66%–95%
No	100%

Molecular response

Major	≥3 log reduction of *BCR–ABL* mRNA
Complete	Negative by RT-PCR

* based on the analysis of at least 20 metaphases

† major cytogenetic response includes complete and partial response

Dose. Patients in CP-CML should receive imatinib 400 mg or 250 mg/m^2 as a single daily dose. However, in those with advanced disease a higher dose (600 mg daily) is used. Kantarjian *et al*. treated 114 newly diagnosed CP-CML patients using higher doses of imatinib—400 mg twice daily compared to 400 mg daily in the standard arm. At a median follow up of 15 months, 96% (109/114) achieved major cytogenetic response with 90% CGR. In 63% of patients, BCR–ABL transcripts decreased to <0.05% by quantitative PCR and were undetectable in 28% of them.[56] An update on this study was presented recently;[57] among 171 evaluable patients, the CGR rate was 90% compared with 78% in the standard arm (p<0.03). At 12 months, major molecular response was noted in 54% compared with 24% in the standard arm (p<0.001); 25 patients (4%) progressed compared with 8% in the standard arm (p<0.05). However, the overall survival was similar in both arms, 99% *v*. 98% (p=0.24). High doses of imatinib were associated with more frequent grades III–IV myelosuppression and 39% of patients required dose reduction.[56,57] Phase I–II studies have explored combinations of imatinib and low dose Ara-C[58] or imatinib and pegylated IFN[59] in an attempt to achieve higher response rates. Recent data of two new drugs—BMS 354825 (dasatinib) and AMN107 (nilotinib) with potent ABL kinase inhibitor activity are promising[60,61] and combining either of them with imatinib may prove to be superior than imatinib alone.[62]

Toxicity. In the IRIS trial, the common late side-effects (at 18 months) were neutropenia (3.8%), thrombocytopenia (2.1%), anaemia (1%) and other drug-related grades III–IV toxicities in 5.8% of patients. Common non-haematological toxicities of imatinib are weight gain (median time 4–5 months), hypopigmentation of exposed parts[63] and skin toxicity. Transient reversible elevation of liver enzymes may occur in 10%–20% of patients. Occasionally, tumour lysis syndrome[64] and bone marrow aplasia[65] have been reported.

Monitoring treatment. Weekly blood counts for the first 4 weeks, twice weekly during the second month, then at 2–4-week intervals are recommended. This helps to identify non-responders as well as those who develop major toxicities requiring dose adjustment and/or granulocyte colony stimulating factor (G-CSF) support. Renal and liver function tests must be done initially 2-weekly for 1–2 months and then monthly.[42]

Monitoring response. Bone marrow cytogenetics is the gold standard for monitoring response. It has been suggested that circulating BCR–ABL transcript numbers should be measured by RT-PCR. For monitoring cytogenetic response, bone marrow cytogenetic studies must be done at 3, 6, 9 and 12 months (Table VII). In patients who achieve significant response, quantitative PCR studies to monitor BCR–ABL transcripts may be done from PB. Almost all patients (>95%) achieve CHR by 12 weeks of imatinib therapy. More than 80% of patients achieve CGR after 12 months of imatinib therapy. Response rates are lower in patients previously treated with IFN-α. Patients who achieve some degree of CGR at 3 or 6 months are more likely to achieve CGR at 12 months. About 5%–15% of patients on imatinib achieve complete molecular remission. As patients who achieve CGR or major molecular remission become Ph-positive or BCR–ABL positive after stopping imatinib, it is recommended that in responders imatinib should be continued indefinitely.[42]

Despite achieving high CGR rates with imatinib, why patients remain positive for BCR–ABL is not entirely clear. It has been suggested that imatinib primarily inhibits proliferation of BCR–ABL positive primitive progenitor cells without induction of apoptosis. Hence, imatinib may be able to prevent stem cell proliferation but unable to eliminate quiescent cells.[66]

Imatinib resistance. Primary haematological resistance (defined as failure to obtain CHR) is seen in <5% of early CP-CML patients (disease duration ≤6 months).[67] Primary cytogenetic resistance (failure to achieve major CGR) after 6 months of treatment or CGR after 12 months of therapy is more common and is seen in about 15% of CP-CML patients. In the IRIS study, 16% of patients developed secondary resistance (defined as loss of haematological or cytogenetic response) at 42 months of follow up. This was low compared with 26% in the IFN-α and low dose Ara-C group at 48 months of follow up.[42,68] The frequency of resistance is higher in patients with AP (73%) and BC (95%). The common mechanisms of secondary resistance include mutations in the *BCR–ABL* kinase domain (50%–90%), overexpression of *BCR–ABL* (10%) typically through gene amplification,[69,70] or acquisition of additional Ph chromosomes. Strategies to overcome imatinib resistance include (i) dose escalation[56,57] (higher doses of imatinib can overcome resistance in a subset of patients but these responses are not durable); (ii) combining it with conventional cytotoxic drugs with established activity in CML (Ara-C,[58] homoharringtonine, interferon-α[59]) has been studied in phase I–II trials; (iii) treatment

TABLE VI. Comparison of results of imatinib mesylate in patients with chronic myelogenous leukaemia

Item	Arora *et al*. (2005)[50]	Deshmukh *et al*. (2005)[51]	Lahaye *et al*. (2005)[54]	O'Brien *et al*. (2003)[48]
n	110	174	300	553
Median age (range) in years	CP 38 (11–65) AP/BC 36 (13–60)	38 (4–79)	CP 56(18.5–77)	50 (18–70)
Sex (M:F)	84:34	122:52	78:61	341:212
Median (range) interval from diagnosis to starting imatinib in months	CP 25 (2–204) AP/BC 37 (6.5–120)	36	31 (2–312)	2.1
Disease status CP/AP/BC	79/23/16	97/47/30	139/80/81	553
Complete haematological response (%)	CP 95.8 AP+BC 35	Early CP 100 Late CP 89 AP 55.5 BC 36.7	CP 97 AP 61 BC 18	95.3
Median time for CHR	21 days (7–122)	nr	nr	1 month
Complete/major cytogenetic response (%)	CP 24.5/30 AP+BC 6.7/13.4	Early CP 20.8/41.7 Late CP 19/27 AP 6.4/15 BC 13/10	CP 49/61 AP 26/31 BC 8/12	73.8/85.2

CP chronic phase AP accelerated phase BC blast crisis nr not reported

TABLE VII. Guidelines for monitoring response to imatinib (adapted from references 19, 42)

Investigation	Interval
Blood counts	Weekly during first 4 weeks, 2-weekly for next 8 weeks, then 2–4-weekly
Bone marrow cytogenetics	At baseline, then at 3, 6, 9 and 12 months, then every 12 months in responders
BCR–ABL transcripts numbers	At diagnosis, and can be done at 3-month intervals in complete cytogenetic responders
Fluorescent *in situ* hybridization	From peripheral blood at diagnosis if bone marrow collection is not feasible. Less sensitive compared to RT-PCR in complete cytogenetic response

RT-PCR reverse transcriptase polymerase chain reaction

with ABL kinase inhibitors, e.g. dasatinib (BMS-354825) and nilotinib (AMN 107) (Table VIII).[60,61]

These data indicate that both agents have significant activity in patients with CML resistant or intolerant to imatinib. Whether a combination of imatinib with dasatinib or nilotinib would be more effective in the primary treatment of CML needs to be studied.

Allogeneic bone marrow/blood stem cell transplantation

Allogeneic haemopoietic SCT is a potentially curative treatment for CML and results in sustained molecular remission (RT-PCR negative) in a majority of patients. Such cures presumably result from the combined effects of high dose chemotherapy and the graft-versus-leukaemia effect mediated by donor-derived T lymphocytes.[70] Gratwohl *et al*. for the European Bone Marrow Transplant Registry (EBMTR) have reported a risk-based scoring system (called EURO score) based on 5 principal prognostic factors (donor type, stage of CML, recipient's age, donor–recipient sex combination and interval from diagnosis). Each factor was scored 0, 1 or 2 (0=most favourable, 2=least favourable). The aggregate score calculated in this manner correlated well with the actual survival.[76] This approach appears useful for a clinician to make recommendations and for the patient to decide whether or not to undergo allogeneic SCT.[76] This has been validated in a large number of patients in a recent study by the EBMTR (Table IX).[77]

About 50% of CP-CML patients achieve long term leukaemia-free survival (LFS) following transplant; LFS is higher for young patients and those with a EURO risk score of 0–1 (60%–70%). The outcome of HLA-matched sibling transplants is superior compared to matched unrelated donor transplants. For patients with AP and BC allogeneic SCT results in a disease-free survival rate of 15%–25% and <15%, respectively.

CML is highly susceptible to a graft-versus-leukaemia effect. Patients who relapse after allogeneic SCT can be treated successfully using donor lymphocyte infusion (DLI) without pre-transplant conditioning. For patients with molecular or cytogenetic relapse of CML, the complete remission rate is 85%–90%, and most responses are sustained.[82–84] These observations have led to the use of non-myeloablative or less intensive allotransplants, especially for patients above 45–50 years of age. Patients may engraft with mixed chimerism which gradually converts to full donor chimerism with the use of DLI.[85]

Excellent and rapid responses achieved with imatinib have led to a dilemma for patients and physicians: whether to delay allogeneic SCT (in view of its potential morbidity and mortality). Imatinib results in complete CGR in 75%–80% of CP patients but

TABLE VIII. Studies on the treatment of patients with imatinib resistance using dasatinib and nilotinib

Author	CML phase	*n*	Response		Grade III–IV toxicity
			Haematological	Cytogenetic	
Dasatinib					
Talpaz *et al*.[60]	CP AP/BC Ph+ve, ALL	40 44	Complete 37/40 Major 31/44	(45) (25)	Neutropenia, pleural effusion, oedema, headache
Talpaz *et al*.[71] START-A study	AP	107 evaluable	Major 63/107 (59) Complete 35 (33) No evidence of leukaemia 28 (26)	Major 33 (32) Complete 23 (22) Partial 10 (10)	Thrombocytopenia (79), neutropenia (69), diarrhoea (46), peripheral oedema (27), pleural effusion (16), rashes (8), gastrointestinal bleed (7)
Coutre *et al*.[72] START-L study	L-BC Ph+ve ALL	42 36	Major (31) Complete (26) Major (42) Complete (31)	Major (50) Major (58)	Thrombocytopenia (82), neutropenia (76), diarrhoea (30), nausea (23), fatigue (19); rash (17), pleural effusion (13)
Estrov *et al*.[73]	Nilotinib failed CML	CP 1 AP 5 BC 5 2nd CP 1	Complete 1/1 Complete 4/5 CP 1, BMCR 1	Not given	Not given
Cortes *et al*.[74] START-B study	Myeloid BC	74	HR 39 (53) Major 24 (32) Complete 18 (24) No leukaemia 6 (8)	Major 22 (32) Complete 20 (27)	Diarrhoea (7), pleural effusion (9), nausea (4), peripheral oedema (14), rash (11)
Nilotinib					
Kantarjian *et al*.[61]	BC/AP/CP	33/46/12	13/33; 33/46; 11/12	9/33; 22/46	Neutropenia, diarrhoea, thrombocytopenia
Le Coutre *et al*.[75]	AP	22	HR 14 (64) Complete 10 (45) No leukaemia 3 (14) CP-1	Complete 1 Partial 1 Minimal 3 Minor 1	Thrombocytopenia (27), neutropenia (18)

Values in parentheses are percentages CP chronic phase AP accelerated phase BC blast crisis L–BC lymphoid blast crisis HR haematological response

molecular CR in only 5%–15%. Further, the depth of molecular CR is inferior compared with those achieved after allogeneic SCT.[42] Other limitations of imatinib include prolonged treatment (currently lifelong); in 6%–9% patients the disease progresses even after an excellent response, sometimes without early warning;[42] and the high cost of the drug. Many investigators are of the opinion that for young patients (<30–35 years) with an HLA-identical sibling donor and a low risk EURO score (0–2) allogeneic SCT may be offered as the primary treatment. For those in a higher age group or who do not have an HLA-identical match, imatinib should be used. Patients who achieve CHR by 12 weeks and major cytogenetic response by 12 months or CGR by 18 months of imatinib therapy should be continued on imatinib.[19,20] Patients who fail to achieve these milestones or have evidence of loss of response or imatinib resistance after an initial response, should be considered for allogeneic SCT. Patients with a high Sokal score should be considered for SCT in the beginning. Similarly, children regardless of Sokal score should be considered for allogeneic SCT. Since the results of imatinib therapy in advanced stages of CML are poor, such patients should be considered for allogeneic SCT at the earliest (Fig. 1).[42]

CML vaccine

The junctional region of p210 *bcr–abl* contains amino acid sequences that are not expressed in a normal cell. From these amino acid sequences peptides can be synthesized which can elicit HLA class I restricted cytotoxic T lymphocytes and class II responses.

Recently, Bocchia *et al*. in a phase II multicentric trial have shown that a vaccine targeting the BCR–ABL derived p210 fusion protein can further reduce persistent residual disease in patients on conventional treatment for CML and elicits a tumour-specific immune response.[86] These findings need confirmation in a larger number of patients. The dose (of peptide) and schedule of administration of the vaccine also need to be worked out.[87]

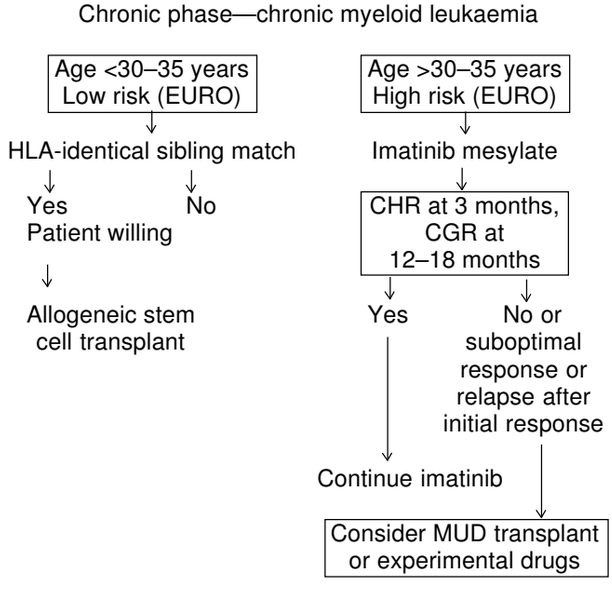

FIG 1. Algorithm for the management of CML EURO score is based on stage of CML, age of recipient, donor type (sibling *v*. matched unrelated donor [MUD]), donor–recipient sex combination, and interval from diagnosis. Each factor is scored 0, 1 or 2. An aggregate score of 0–2 is associated with good outcome following transplant and is considered low risk. A score of 3–5 is associated with poor outcome and is considered high risk (Gratwohl *et al*.[76]). CHR complete haematological response CGR complete cytogenetic response

TABLE IX. Results of allogeneic stem cell transplantation in chronic phase—chronic myeloid leukaemia

Study	*n*	Follow up (years)	Survival (%)	Relapse (%)
HLA matched sibling donor				
CIBMTR[78]	3372	18	50	25
EBMTR[79]	2628	2	41	19
Seattle[80]	351	10	70	20
Matched unrelated donor				
IBMTR[79]	331	3	38	na
Seattle[81]	196	5	75	na

CIBMTR Center for International Blood and Marrow Transplant Registry
EBMTR European Blood and Marrow Transplant Registry na not available

CONCLUSION

The introduction of imatinib mesylate has revolutionized the management of CML. Imatinib treatment is associated with higher haematological and cytogenetic response rates. While most of these responses are stable, resistance to treatment after an initial response can occur, more so in patients in advanced stages of the disease. Most patients continue to be positive for *BCR–ABL* by RT-PCR, indicating persistence of disease. The option of allogeneic SCT must be considered carefully after evaluating the response to imatinib at important time points and taking patient preference into account.[42]

REFERENCES

1 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55:**74–108.
2 National Cancer Registry Programme. *Two year report of the population based cancer registries 1999–2000.* New Delhi:Indian Council of Medical Research; 2005.
3 Bhutani M, Vora A, Kumar L, Kochupillai V. Lympho-hemopoietic malignancies in India. *Med Oncol* 2002;**19:**141–50.
4 Sawyers CL. Chronic myeloid leukemia. *N Engl J Med* 1999;**340:**1330–40.
5 Kumar L, Kumari M, Kumar S, Kochupillai V, Singh R. Clinical and laboratory features at diagnsis in 437 patients with chronic myelogenous leukemia: An experience of a tertiary care center. In: Kumar L (ed). *Progress in haematologic oncology.* New York:The Advanced Research Foundation, 2003:83–98.
6 Prabhu M, Kochupillai V, Sharma S, Ramachandran P, Sundaram KR, Bijlani L, *et al.* Prognostic assessment of various parameters in chronic myeloid leukemia. *Cancer* 1986;**58:**1357–60.
7 Kumar L, Sagar TG, Maitreyan V, Majhi U, Shanta V. Chronic granulocytic leukaemia: A study of 160 cases. *J Assoc Physicians India* 1990;**38:**899–902.
8 Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. *Br J Haematol* 1997;**96:**111–16.
9 Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, *et al.* Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. *Blood* 1994;**84:**4064–77.
10 Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, *et al.* Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002;**346:**645–52.
11 Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood* 2002;**100:**2292–302.
12 Kantarjian HM, Bueso-Ramos CE, Talpaz M, O'Brien S, Giles F, Faderl S, *et al.* Significance of myelofibrosis in early chronic-phase, chronic myelogenous leukemia on imatinib mesylate therapy. *Cancer* 2005;**104:**777–80.
13 Nowell P, Hungerford D. A minute chromosome in human chronic granulocytic leukemia. *Science* 1960;**132:**1497.
14 Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 1973;**243:**290–3.
15 Kurzrock R, Gutterman JU, Talpaz M. The molecular genetics of Philadelphia chromosome-positive leukemias. *N Engl J Med* 1988;**319:**990–8.

16 Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the *P210bcr/abl* gene of the Philadelphia chromosome. *Science* 1990;**247:**824–30.

17 Lugo TG, Pendergast AM, Muller AJ, Witte ON. Tyrosine kinase activity and transformation potency of *bcr–abl* oncogene products. *Science* 1990;**247:**1079–82.

18 Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. *Blood* 2000;**96:**3343–56.

19 Hughes T, Deininger M, Hochhaus A, Branford S, Radich J, Kaeda J, *et al.* Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: Review and recommendations for harmonizing current methodology for detecting BCR–ABL transcripts and kinase domain mutations and for expressing results. *Blood* 2006;**108:**28–37.

20 Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, *et al.* Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2006;**108:**1809–20.

21 Stephens DJ, Lawrence JS. The therapeutic effect of solution of potassium arsenite in chronic myelogenous leukemia. *Ann Intern Med* 1936;**9:**1488.

22 Medical Research Council's working party for therapeutic trials in leukaemia. Chronic granulocytic leukaemia: Comparison of radiotherapy and busulphan therapy. Report of the Medical Research Council's working party for therapeutic trials in leukaemia. *BM J* 1968;**1:**201–8.

23 Socie G, Clift RA, Blaise D, Devergie A, Ringden O, Martin PJ, *et al.* Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: Long-term follow-up of 4 randomized studies. *Blood* 2001;**98:**3569–74.

24 Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, *et al.* Efficacy and safety of a specific inhibitor of the *BCR–ABL* tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;**344:**1031–7.

25 Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 2003;**21:**1637–47.

26 Ozer H, George SL, Schiffer CA, Rao K, Rao PN, Wurster-Hill DH, *et al.* Prolonged subcutaneous administration of recombinant alpha 2b interferon in patients with previously untreated Philadelphia chromosome-positive chronic-phase chronic myelogenous leukemia: Effect on remission duration and survival: Cancer and Leukemia Group B study 8583. *Blood* 1993;**82:**2975–84.

27 Alimena G, Morra E, Lazzarino M, Liberati AM, Montefusco E, Inverardi D, *et al.* Interferon alpha-2b as therapy for patients with Ph'-positive chronic myelogenous leukemia. *Eur J Haematol* (*Suppl*) 1990;**52:**25–8.

28 Kloke O, Niederle N, Qiu JY, Wandl U, Moritz T, Nagel-Hiemke M, *et al.* Impact of interferon alpha-induced cytogenetic improvement on survival in chronic myelogenous leukaemia. *Br J Haematol* 1993;**83:**399–403.

29 Thaler J, Gastl G, Fluckinger T, Niederwieser D, Huber H, Seewann H, *et al.* Treatment of chronic myelogenous leukemia with interferon alfa-2c: Response rate and toxicity in a phase II multicenter study. The Austrian Biological Response Modifier (BRM) Study Group. *Semin Hematol* 1993;**30:**17–19.

30 Mahon FX, Montastruc M, Faberes C, Reiffers J. Predicting complete cytogenetic response in chronic myelogenous leukemia patients treated with recombinant interferon alpha. *Blood* 1994;**84:**3592–4.

31 Schofield JR, Robinson WA, Murphy JR, Rovira DK. Low doses of interferon-alpha are as effective as higher doses in inducing remissions and prolonging survival in chronic myeloid leukemia. *Ann Intern Med* 1994;**121:**736–44.

32 Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M. Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-alpha therapy. The Leukemia Service. *Ann Intern Med* 1995;**122:**254–61.

33 Kumar L, Gangadharan VP, Rao DR, Saikia T, Shah S, Malhotra H, *et al.* Safety and efficacy of an indigenous recombinant interferon-alpha-2b in patients with chronic myelogenous leukaemia: Results of a multicentre trial from India. *Natl Med J India* 2005;**18:**66–70.

34 The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. *N Engl J Med* 1994;**330:**820–5.

35 Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha for chronic myeloid leukaemia: Improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. *Lancet* 1995;**345:**1392–7.

36 Ohnishi K, Ohno R, Tomonaga M, Kamada N, Onozawa K, Kuramoto A, *et al.* A randomized trial comparing interferon-alpha with busulfan for newly diagnosed chronic myelogenous leukemia in chronic phase. *Blood* 1995;**86:**906–16.

37 The Benelux CML Study Group.Randomized study on hydroxyurea alone versus hydroxyurea combined with low-dose interferon-alpha 2b for chronic myeloid leukemia. *Blood.* 1998;**91:**2713–21.

38 Hasford J, Baccarani M, Hehlmann R, Anseri H, Tura S, Zuffa E. Interferon-alpha and hydroxyurea in early chronic myeloid leukemia: A comparative analysis of the Italian and German chronic myeloid leukemia trials with interferon-alpha. *Blood* 1996;**87:**5384–91.

39 Chronic Myeloid Leukemia Trialists' Collaborative Group. Interferon alfa versus chemotherapy for chronic myeloid leukemia: A meta-analysis of seven randomized trials. *J Natl Cancer Inst* 1997;**89:**1616–20.

40 Kumar L, Gulati SC. Alpha-interferon in chronic myelogenous leukaemia. *Lancet* 1995;**346:**984–6.

41 Kluin-Nelemans HC, Buck G, le Cessie S, Richards S, Beverloo HB, Falkenburg JH, *et al.* Randomized comparison of low-dose versus high-dose interferon-alfa in chronic myeloid leukemia: Prospective collaboration of 3 joint trials by the MRC and HOVON groups. *Blood* 2004;**103:**4408–15.

42 Deininger MWN. Chronic myeloid leukemia: Management of early stage disease. In: Berliner N, Lee SJ, Linenberger M, Bogelsang GB (eds). *American Society of Hematology Education Program Book.* Atlanta, Georgia:American Society of Hematology; 2005:174–82.

43 Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F, *et al.* Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. *N Engl J Med* 1997;**337:**223–9.

44 Baccarani M, Rosti G, de Vivo A, Bonifazi F, Russo D, Martinelli G, *et al.* A randomized study of interferon-alpha versus interferon-alpha and low-dose arabinosyl cytosine in chronic myeloid leukemia. *Blood* 2002;**99:**1527–35.

45 Michallet M, Maloisel F, Delain M, Hellmann A, Rosas A, Silver RT, *et al.* Pegylated recombinant interferon alpha-2b vs recombinant interferon alpha-2b for the initial treatment of chronic-phase chronic myelogenous leukemia: A phase III study. *Leukemia* 2004;**18:**309–15.

46 Savage DG, Antman KH. Imatinib mesylate—A new oral targeted therapy. *N Engl J Med* 2002;**346:**683–93.

47 Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, *et al.* Activity of a specific inhibitor of the *BCR-ABL* tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001;**344:**1038–42.

48 O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, *et al.* Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;**348:**994–1004.

49 Hahn EA, Glendenning GA, Sorensen MV, Hudgens SA, Druker BJ, Guilhot F, *et al.* Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: Results from the IRIS Study. *J Clin Oncol* 2003;**21:**2138–46.

50 Arora B, Kumar L, Kumaru M, Sharma A, Wadhwa J, Kochupillai V. Therapy with imatinib mesylate for chronic myeloid leukemia. *Indian J Med Paediatr Oncol* 2005;**26:**5–18.

51 Deshmukh C, Saikia T, Bakshi A, Amare-Kadam P, Baisane C, Parikh P. Imatinib mesylate in chronic myeloid leukemia: A prospective, single arm, non-randomized study. *J Assoc Physicians India* 2005;**53:**291–5.

52 Kantarjian HM, O'Brien S, Cortes J, Giles FJ, Rios MB, Shan J, *et al.* Imatinib mesylate therapy improves survival in patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in the chronic phase: Comparison with historic data. *Cancer* 2003;**98:**2636–42.

53 Kantarjian H, Talpaz M, O'Brien S, Giles F, Faderl S, Verstovsek S, *et al.* Survival benefit with imatinib mesylate therapy in patients with accelerated-phase chronic myelogenous leukemia—Comparison with historic experience. *Cancer* 2005;**103:**2099–108.

54 Lahaye T, Riehm B, Berger U, Paschka P, Muller MC, Kreil S, *et al.* Response and resistance in 300 patients with BCR–ABL-positive leukemias treated with imatinib in a single center: A 4.5-year follow-up. *Cancer* 2005;**103:**1659–69.

55 Velpandian T, Mathur R, Agarwal NK, Arora B, Kumar L, Gupta SK. Development and validation of a simple liquid chromatographic method with ultraviolet detection for the determination of imatinib in biological samples. *J Chromatogr B Analyt Technol Biomed Life Sci* 2004;**804:**431–4.

56 Kantarjian H, Talpaz M, O'Brien S, Garcia-Manero G, Verstovsek S, Giles F, *et al.* High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome-positive chronic phase chronic myeloid leukemia. *Blood* 2004;**103:**2873–8.

57 Aoki E, Kantarijian HM, O'Brien S, Talpaz M, Giles F, Garcia-Manero G, *et al.* High dose imatinib mesylate treatment in patients (Pts) with untreated early chronic phase (CP) chronic myeloid leukemia (CML): 2.5 year follow up. *Proc Am Soc Clin Oncol* 2006;**24:**345a (Abstract 6535).

58 Gardembas M, Rousselot P, Tulliez M, Vigier M, Buzyn A, Rigal-Huguet F, *et al.* Results of a prospective phase 2 study combining imatinib mesylate and cytarabine for the treatment of Philadelphia-positive patients with chronic myelogenous leukemia in chronic phase. *Blood* 2003;**102:**4298–305.

59 Baccarani M, Martinelli G, Rosti G, Trabacchi E, Testoni N, Bassi S, *et al.* Imatinib and pegylated human recombinant interferon-alpha 2b in early chronic-phase chronic myeloid leukemia. *Blood* 2004;**104:**4245–51.

60 Talpaz M, Shah NP, Kantarjian H, Donato N, Nicoll J, Paquette R, *et al.* Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006;**354:**2531–41.

61 Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassmann B, *et al.* Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006;**354:**2542–51.

62 Druker BJ. Circumventing resistance to kinase-inhibitor therapy. *N Engl J Med* 2006;**354:**2594–6.

63 Arora B, Kumar L, Sharma A, Wadhwa J , Kochupillai V. Pigmentary changes in chronic myeloid leukemia patients treated with imatinib mesylate. *Ann Oncol* 2004;**15:**358–9.

64 Vora A, Bhutani M, Sharma A, Raina V. Severe tumor lysis syndrome during treatment with STI 571 in a patient with chronic myelogenous leukemia accelerated phase. *Ann Oncol* 2002;**13:**1833–4.
65 Lokeshwar N, Kumar L, Kumari M. Severe bone marrow aplasia following imatinib mesylate in a patient with chronic myelogenous leukemia. *Leuk Lymphoma* 2005;**46:**781–4.
66 Goldman J, Gordon M. Why do chronic myelogenous leukemia stem cells survive allogeneic stem cell transplantation or imatinib: Does it really matter? *Leuk Lymphoma* 2006;**47:**1–7.
67 Shah NP. Loss of response to imatinib: Mechanisms and management. In: Berliner N, Lee SJ, Linenberger M, Bogelsang GB (eds). *American Society of Hematology Education Program Book*. Atlanta, Georgia:American Society of Hematology; 2005:183–7.
68 Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, *et al.* Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2003;**349:**1423–32.
69 Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, *et al.* Clinical resistance to STI-571 cancer therapy caused by BCR–ABL gene mutation or amplification. *Science* 2001;**293:**876–80.
70 Goldman JM, Melo JV. Chronic myeloid leukemia—Advances in biology and new approaches to treatment. *N Engl J Med* 2003;**349:**1451–64.
71 Talpaz M, Apperley JF, Kim DW, Silver RT, Bullorsky EO, Iyer M, *et al*. Dasatinib (D) in patients with accelerated phase chronic myeloid leukemia (AP-CML) who are resistant or intolerant to imatinib: Results of the CA180005 'START-A' study. *Proc Am Soc Clin Oncol* 2006;**24:**343a (Abstract 6526).
72 Coutre S, Martinelli G, Dombret H, Hochhaus A, Larson R, Saglio G, *et al.* Dasatanib (D) in patients (pts) with chronic myelogenous leukemia (CML) in lymphoid blast crisis (LB-CML) or Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ALL) who are imatinib (IM)-resistant (IM-R) or intolerant (IM-I): The CA180015 'START-L' study. *Proc Am Soc Clin Oncol* 2006;**24:**6528.
73 Estrov Z, O'Brien S, Giles F, Garcia-Manero G, Borthakur G, Ravandi F, *et al.* Dasatinib (BMS 354825), a dual Src–abl inhibitor, is active in Philadelphia chromosome positive chronic myelogeneous leukemia (Ph+ve CML) following treatment with imatinib mesylate and AMN 107. *Proc Am Soc Clin Oncol* 2006;**24:** 344a (Abstract 6530).
74 Cortes JE, Kim DW, Rosti G, Rousselot P, Bleickrdt E, Zinc R, *et al.* Dasatinib (D) in patients (pts) with chronic myelogenous leukemia (CML) in myeloid blast crisis (MBC) who are imatinib-resistant (IM-R) or IM-intolerant (IM-I): Results of the CA180006 'START-B' study. *Proc Am Soc Clin Oncol* 2006;**24:**6529.
75 Le Coutre PD, Ottmann O, Gatterman N, Larson R, Rafferty T, Alland L, *et al.* A phase II study of AMN107, a novel inhibitor of BCR–ABL, administered to imatinib-resistant or intolerant patients (pts) with chronic myelogenous leukemia (CML) in accelerated phase (AP). *Proc Am Soc Clin Oncol* 2006;**24:**6531.
76 Gratwohl A, Hermans J, Goldman JM, Arcese W, Carreras E, Devergie A, *et al.* Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Lancet* 1998;**352:**1087–92.
77 Passweg JR, Walker I, Sobocinski KA, Klein JP, Horowitz MM, Giralt SA. Validation and extension of the EBMT Risk Score for patients with chronic myeloid leukaemia (CML) receiving allogeneic haematopoietic stem cell transplants. *Br J Haematol* 2004;**125:**613–20.
78 Goldman JM, Rizzo JD, Jabocinski KA, *et al*. Long term outcome after allogeneic stem cell transplantation for CML (Abstract). *Hematol J* 2004;**5:**98 (Abstract 288).
79 Gratwohl A, Brand R, Apperley J, Crawley C, Ruutu T, Corradini P, *et al.* Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: Transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Haematologica* 2006;**91:**513–21.
80 Clift RA, Anasetti C. Allografting for chronic myeloid leukaemia. *Baillieres Clin Haematol* 1997;**10:**319–36.
81 Hansen JA, Gooley TA, Martin PJ, Appelbaum F, Chauncey TR, Clift RA, *et al.* Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. *N Engl J Med* 1998;**338:**962–8.
82 Schattenberg AV, Dolstra H. Cellular adoptive immunotherapy after allogeneic stem cell transplantation. *Curr Opin Oncol* 2005;**17:**617–21.
83 Dazzi F, Szydlo RM, Cross NC, Craddock C, Kaeda J, Kanfer E, *et al.* Durability of responses following donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. *Blood* 2000;**96:**2712–16.
84 Kumar L. Leukemia: Management of relapse after allogeneic bone marrow transplantation. *Leukemia* 2004;**7:**202–10.
85 Crawley C, Szydlo R, Lalancette M, Bacigalupo A, Lange A, Brune M, *et al.* Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: An analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. *Blood* 2005;**106:**2969–76.
86 Bocchia M, Gentili S, Abruzzese E, Fanelli A, Iuliano F, Tabilio A, *et al.* Effect of a p210 multipeptide vaccine associated with imatinib or interferon in patients with chronic myeloid leukaemia and persistent residual disease: A multicentre observational trial. *Lancet* 2005;**365:**657–62.
87 Sharma P, Mohanty S, Kumar L. A vaccine for chronic myeloid leukaemia. *Natl Med J India* 2005;**18:**146–7.

Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attraction of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

The National Medical Journal of India wishes to recognize the efforts of these doctors. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his or her education and training and highlight the achievements as well as disappointments. A photograph should accompany the obituary.

—Editor