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Chronic Myeloid Leukemia

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M.T. is a 26-year-old woman with chronic myeloid leukemia (CML) diagnosed during her annual physical examination. Her disease is in the chronic phase, without any high-risk features.[1,2] *She has no significant prior medical history. Her sister is a 6/6 HLA antigen match and is in excellent health. Neither sister has been pregnant. M.T. presents for consultation about whether to be treated with imatinib or to undergo allogeneic stem cell transplantation (SCT). She is well informed and has downloaded several articles from the Internet.*

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In attempting to apply evidence-based medicine in the treatment of chronic myeloid leukemia (CML), it must be acknowledged that a randomized study comparing imatinib mesylate therapy and allogeneic stem cell transplantation (SCT) has not been conducted. The question that will remain at the end of this chapter is whether such a study is feasible, or even ethical. The treatment of CML could represent a paradigm in oncology as well as a unique set of challenges.

Definitions and Molecular Pathogenesis

CML is a clonal expansion of a hematopoietic stem cell resulting from a reciprocal translocation between chromosomes 9 and 22. This translocation results in the head-to-tail fusion of the breakpoint cluster region *(BCR)* gene on chromosome 22q11 with the *ABL* (named after the abelson murine leukemia virus) gene located on chromosome 9q34. Untreated, the disease is characterized by the inevitable transition from a clinically benign chronic phase, often with an interposed accelerated phase, to blast crisis.

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The cytogenetic hallmark of CML, found in 90% to 95% of patients, is the t(9;22)(q34;q11.2). The reciprocal 9;22 translocation was originally recognized by the presence of the resultant shortened chromosome 22 (22q–), designated as the *Philadelphia chromosome*. Some patients may have complex translocations (designated as *variant translocations*) involving three, four, or five chromosomes (usually including chromosomes 9 and 22). However, the molecular consequences of these changes appear similar to those resulting from the typical t(9;22). Patients should have evidence of the translocation by either cytogenetics, fluorescence in situ hybridization (FISH), or molecular techniques to make a diagnosis of CML.

The product of the fusion gene resulting from the t(9;22) plays a central role in both the genesis and the treatment of CML. The chimeric gene is transcribed into a hybrid *BCR/ABL* messenger RNA species in which exon 1 of *ABL* is replaced by variable numbers of 5′ *BCR* exons. The Bcr/Abl fusion proteins that then result, $p210^{BCR/ABL}$, contain NH_2-terminal domains of Bcr and COOH-terminal domains of Abl. A rare breakpoint, occurring within the 3′-region of the *BCR* gene, yields a fusion protein of 230 kDa, $p230^{BCR/ABL}$. The role of the Bcr/Abl fusion proteins in leukemogenesis has been substantiated in several laboratory models.

The mechanism(s) by which $p210^{BCR/ABL}$ promotes the transition from the benign state to the fully malignant state is still unclear. Messenger RNA for *BCR/ABL* can occasionally be detected in normal individuals. However, fusion of the *BCR* sequences to *ABL* results in three critical functional changes: (1) the Abl protein becomes constitutively active as a tyrosine kinase enzyme and activates downstream kinases that prevent apoptosis, (2) the DNA protein-binding activity of Abl is attenuated, and (3) the binding of Abl to cytoskeletal actin microfilaments is enhanced.

The molecular events associated with transition to the acute phase, or blast crisis, are poorly understood. Some depend on increased activity of the oncogenic kinase [e.g., an additional t(9;22),[3] deletions adjacent to the translocation breakpoint on the derivative 9 chromosome[4]], and some most probably result from *BCR/ABL*-independent mechanisms [e.g., trisomy 8, or 17p– (p53 loss),[3] lack of production of the retinoblastoma protein, alterations in *RAS*, or presence of an altered *MYC*]. Finally, progressive de novo DNA methylation at the *BCR/ABL* locus has also been shown to herald the onset of blast crisis.[5–7]

Physical Findings

In most patients, the abnormal finding on physical examination at diagnosis is minimal to moderate splenomegaly; mild hepatomegaly is found occasionally. Persistent splenomegaly despite continued therapy is a sign of disease acceleration. Lymphadenopathy and myeloid sarcomas are unusual except late in the course of the disease; when they are present, the prognosis is poor.

Hematologic Findings

Elevated white blood cell counts, with various degrees of immaturity of the granulocytic series, are present at diagnosis. Usually less than 5% circulating blasts and less than 10%

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blasts and promyelocytes are noted. Cycling of the counts may be observed in patients followed without treatment. Platelet counts are almost always elevated at diagnosis, and a mild degree of normochromic normocytic anemia is present. Leukocyte alkaline phosphatase is characteristically low in CML cells. Serum levels of vitamin B_{12} and vitamin B_{12}-binding proteins are generally elevated. Phagocytic functions are usually normal at diagnosis and remain normal during the chronic phase. Histamine production secondary to basophilia is increased in later stages, causing pruritus, diarrhea, and flushing.

At diagnosis, bone marrow cellularity, primarily of the myeloid and megakaryocytic lineages, with a greatly altered myeloid to erythroid ratio, is increased in almost all patients with CML. The marrow blast percentage is generally normal or slightly elevated. Marrow or blood basophilia, eosinophilia, and monocytosis may be present. Although collagen fibrosis in the marrow is unusual at presentation, significant degrees of reticulin stain-measured fibrosis are noted in about half the patients.

Disease acceleration is defined by the development of increasing degrees of anemia unaccounted for by bleeding or chemotherapy, cytogenetic clonal evolution, or blood or marrow blasts between 10% and 20%, blood or marrow basophils 20% or greater, or platelet count less than 100,000/μL. *Blast crisis* is defined as acute leukemia, with blood or marrow blasts 20% or more. Hyposegmented neutrophils may appear (Pelger–Huet anomaly). Blast cells can be classified as myeloid, lymphoid, erythroid, or undifferentiated, based on morphologic, cytochemical, and immunologic features. About half the cases are myeloid, one-third lymphoid, 10% erythroid, and the rest are undifferentiated.

Prognostic Factors

Several prognostic models have been developed that identify different risk groups in CML. The most commonly used staging systems were derived from multivariate analyses of prognostic factors. The Sokal index[1] was based on chemotherapy-treated patients and the Hasford system[2] on interferon-treated patients. Table 66.1 compares the two prognostic systems. When applied to a data set of 272 patients treated with interferon-alpha (IFN-α), the Hasford system predicted survival time more accurately than the Sokal score; it identified more low-risk patients but left only a small number of cases in the high-risk group.[8] Preliminary results suggest that the Hasford system is applicable to imatinib-treated patients, but it has not yet been validated in patients undergoing transplantation.

TABLE 66.2. Response criteria in chronic myeloid leukemia (CML).

Hematologic	
Complete response[a]	White blood cell count <10,000/μLl, normal morphology, normal hemoglobin and platelet counts
Incomplete response	White blood cell count ≥10,000/μL
Cytogenetic	Percentage of bone marrow metaphases with t(9;22)
Complete response	0
Partial response	≤35
Minor response	36–85[b]
No response	85–100
Molecular	Presence of *BCR/ABL* transcript by RT-PCR
Complete response	None
Incomplete response	Any
Major response	≥3 log reduction
Minor response	<3 log reduction

[a]Complete hematologic response requires the disappearance of splenomegaly.

[b]Up to 15 normal metaphases are occasionally seen at diagnosis (when 30 metaphases are analyzed).

Treatment

This chapter evaluated the treatment options for CML in chronic phase by a computerized literature search of the MEDLINE database for English-language manuscripts. Observational, retrospective, randomized studies and meta-analyses were reviewed. Case reports were excluded. Survival was the primary objective for defining treatment efficacy, but other measures, such as hematologic, cytogenetic, and molecular responses, were included. At present, the definition of cure in CML is durable, nonneoplastic, nonclonal hematopoiesis, which entails the eradication of cells containing the *BCR/ABL* transcript (Table 66.2). Only recommendations for which there was direct evidence of improved outcome are presented.

Treatment Options

The treatment paradigm for CML is undergoing rapid evolution because of the availability of a curative treatment (allogeneic SCT) that has significant toxicity, on the one hand, and on the other hand, a new seemingly effective treatment (imatinib) without significant toxicity but also without long-term follow-up data.

Allogeneic SCT

Allogeneic SCT is currently the only curative therapy for CML and, when feasible, may be the treatment of choice.

TABLE 66.1. Comparison of the Sokal and Hasford prognostic systems.

	Sokal[1] (chemotherapy-based)	*Hasford[2] (interferon-based)*
Age (years)	0.116 (age–43.4)	0.666 when age ≥50
Percentage of blasts	0.0887 (blasts–2.1)	0.0584 × blasts
Spleen size	0.0345 (spleen–7.51)	0.042 × spleen
Platelet count	0.188 [(platelet/700)^2–0.563]	1.0956 when ≥1.5 × 10^9/L
Percentage of eosinophils		0.0413 × eosinophils
Percentage of basophils		0.20399 × basophils ≥3%

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TABLE 66.3. Comparison of peripheral blood and bone marrow in recipients of matched sibling allogeneic transplantation for CML.

Study	*Design*	*No. of patients*	*Results*
Couban[18]	Multicenter randomized trial	109[a]	Benefit in overall survival favoring PBSC[b]
Champlin[19]	Retrospective database cohort	346[c]	Similar 1-year cumulative incidence of relapse, probability of leukemia-free survival, and risk of treatment failure
Elmaagaci[20]	Retrospective analysis	41[c]	Similar 3-year survival with a trend toward increased acute GVHD in patients undergoing PBSC transplantation

GVHD, graft-versus-host disease; PBSC, peripheral blood stem cell.

[a]First chronic-phase and more-advanced stages were presented together.

[b]At 30 months.

[c]Patients in first chronic phase only.

However, it is complicated by a high mortality rate. Outcome of SCT depends on multiple factors associated with (1) the patient (age, comorbidities, and phase of disease); (2) the type of donor [syngeneic (monozygotic twins) or HLA-compatible allogeneic, related or unrelated]; (3) the preparative regimen; (4) presence and severity of graft-versus-host disease (GVHD), and (5) the ability to prevent or treat relapse after transplantation.

The Patient

As experience has been gained and safety and efficacy of transplantation have been established, it has become clear that patients should have acceptable end-organ function, be younger than 65 to 75 years, and have a healthy and histocompatible donor. Furthermore, observational studies have demonstrated that survival after SCT in the accelerated and blastic phases of the disease is significantly inferior because of a very high rate of relapse.[9,10] The pre-imatinib Seattle data demonstrated that bone marrow transplantation (BMT) has a better outcome in early chronic phase (1 to 2 years from diagnosis) compared to later in the course of the disease.[11] Another issue in young patients, and particularly young female patients, is the very high likelihood of infertility following transplantation.

The Donor

Transplantation from a related donor who is either fully matched or mismatched at only one HLA locus should be considered the optimal curative treatment for CML. With HLA-identical sibling BMT in the chronic phase, observational studies have reported 5-year disease-free survival in 40% to 70% of patients, with a 25% relapse rate.[9,10,12,13] Retrospective analysis revealed that male recipients with female donors have an increased risk of developing chronic GVHD, leading to a lower relapse rate but increased mortality.[14] Moreover, for patients in chronic phase less than 1 year from diagnosis and younger than 30 years, BMT from an HLA-matched unrelated donor resulted in similar 5-year disease-free survival as matched sibling donor transplantation in comparative analyses.[15–17] For all other groups, patients receiving transplants from unrelated individuals have higher rates of graft failure (odds ratio, 5.39) and acute (relative risk, 1.31) and chronic (relative risk, 1.48) GVHD, compared to those who receive allogeneic transplants from related individuals.[17]

Peripheral blood is now being studied as a source of hematopoietic progenitor cells; it may offer less risk for the donor as well as more rapid engraftment. One randomized study[18] and two retrospective studies[19,20] compared bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants (Table 66.3). These studies demonstrated an overall survival benefit for recipients receiving peripheral blood stem cells (PBSC) in the randomized study,[18] but similar survival in the two retrospective studies.[19,20] In unrelated donors, a retrospective study[21] demonstrated no difference in incidence and severity of GVHD and improved disease-free survival for peripheral blood compared to bone marrow stem cell transplants (Table 66.4). No randomized studies have been reported so far. At the present time, some centers collect bone marrow and some collect peripheral blood from donors for newly diagnosed CML patients. Umbilical cord blood may permit mismatched SCT with notably less GVHD; graft-versus-leukemia (GVL) effects do not appear to be impaired.[22,23] A problem with cord blood as a source is obtaining an appropriate number of progenitor cells to reconstitute hematopoiesis in an adult.

Preparative Regimens

Four randomized studies compared cyclophosphamide and total-body irradiation with busulphan and cyclophosphamide.[24–27] Long-term follow-up in these studies[28] demonstrated (Table 66.5) no significant differences in the incidence

TABLE 66.4. Comparison of peripheral blood and bone marrow in recipients of unrelated allogeneic transplantation in CML.

	BMT	*PBSC*	*P*
Number	54	37	
Acute GVHD grade III–IV	13 (24)	3 (8)	<0.05
DFS at 1,000 days (%)	64	91	<0.05
Overall survival at 1,000 days (%)	66	94	<0.02

BMT, bone marrow transplant; DFS, disease-free survival; GVHD, graft-versus-host disease; PBSC, peripheral blood stem cells.

Source: Data from Elmaagacli et al.[21]

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TABLE 66.5. Long-term follow-up of four randomized studies comparing busulphan and cylophosphamide with total body irradiation and cyclophosphamide.

	Busulphan Cyclophosphamide[a]	*Total body irradiation Cyclophosphamide*[a]
Projected 10-year survival	65*	63
(95% CI)	57–74	54–73
DFS	52	46
(95% CI)	43–61	36–56
5-year cumulative incidence of clinical extensive GVHD	37	39
7-year cumulative incidence of cataracts*	16	47
7-year cumulative incidence of pulmonary disease	15	15
7-year cumulative incidence of avascular osteonecrosis**	3	10

CI, confidence interval; GVHD, graft-versus-host disease.

[a]Numbers represent percentages.

*$P = 0.0003$; remained statistically significant even after adjustment for age and acute and chronic GVHD.

**$P = 0.03$.

Source: Data from Socie et al.[28]

of venoocclusive disease of the liver, speed of engraftment, or the 3-year probabilities of relapse, event-free survival, or overall survival. Significantly more patients in the total-body irradiation arm experienced cataracts and avascular necrosis. However, chronic GVHD was associated with increased risk of irreversible alopecia in patients treated with busulphan. There was no significant association between busulphan levels and regimen-related toxicity,[29,30] but low levels were associated with an increased risk of relapse in one study.[29] Intravenous busulphan allows better control of plasma levels.[31,32] Nonmyeloblative transplants in which the preparative regimen is aimed at eliminating host lymphocytes rather than eradicated bone marrow and maximizing GVL effect are being tested.[33,44] Reduced toxicity with preserved antitumor efficacy is the goal. Table 66.6 summarizes the published observational studies. Interestingly, for studies that included only patients in chronic phase,[38,40,44] overall survival was 75%, 85%, and 87% and disease-free survival was 63%, 85%, and 80%. However, the follow-up is relatively short and no randomized studies have been published so far.

Chances of pregnancy after conditioning with busulphan and cyclophosphamide are slim.[45,46] Reduced-intensity transplantation may prevent alopecia, but little is known about its effects on fertility, nor are there long-term data on overall and disease-free survival following this conditioning method.

Development and Type of GVHD

Development of grade I GVHD (mild maculopapular rash involving less than 25% of body surface area, or less than 1000 mL diarrhea/day, or bilirubin less than 3 mg/dL[47]), as compared to no GVHD, decreases the risk of relapse.[48] A lower relapse rate is observed also in patients with grade II GVHD, but these patients have a substantially higher transplant-related mortality rate.[48] The decreased relapse rate may be caused by a GVL effect. Depletion of T lymphocytes from donor marrow can prevent GVHD but results in an increased risk of relapse, exceeding the relapse rate after syngeneic SCT. Thus, T lymphocytes from the donor marrow mediate a significant antileukemic, or GVL, effect, and even syngeneic marrow[49,50] may exhibit limited GVL activity in CML.

Treatment and Prevention of Posttransplant Relapse

Further support for the existence of an immunologically mediated GVL effect came from the observation that donor

TABLE 66.6. Reduced-intensity conditioning for allografting in CML.

	No. of patients	*Stage of disease*	*Related/ unrelated*	*Acute GVHD (>grade II; %)*	*DFS*[a] *(%)*	*OS*[a] *(%)*
Childs[33]	2	2 CP	2/0	0	—[b]	—[b]
Raiola[34]	15	9 CP/4 AP/2 BP	15/0	N/A	60	80
Giralt[35]	27	6 CP/21 TP	N/A	N/A	34[c]	32[c]
Bornhäuser[36]	44	26 CP/11 AP/7 BP	21/23	14	41	52
Khoury[37]	30	28 CP/2 BP	30/0	17	N/A	83
Okamoto[38]	8	8 CP	8/0	13	63	75
Kreuzer[39]	14	11 CP/2 AP/1 BP	4[d]/0	14	71	N/A
Or[40]	24	24 CP	19/5	21	85	85
Das[41]	17	16 CP/1 AP	17/0	18	29	35
Wong[42]	9	1 CP/2 3rd CP/[d] 4 AP/2 BP	0/9	20	44[e]	56[e]
Sloand[43]	12	7 CP/5 2nd CP	12/0	25	33[e]	67[f]
Uzunel[44]	15	15 CP	10/5	7	80[e]	87

AP, accelerated phase; BP, blastic phase, CP, chronic phase; DFS, disease-free survival; GVHD, graft-versus-host disease; N/A, not available; OS, overall survival; TP, transformed (accelerated and blastic) phase.

[a]Available time points specified in the table.

[b]At 7 and 14 months, both patients are alive in molecular remission.

[c]At 1 year.

[d]Two were nonidentical family members.

[e]By reverse transcriptase-polymerase chain reaction (RT-PCR) at 12 months.

[f]For at least 24 months.

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TABLE 66.7. Factors predicting molecular response after donor-lymphocyte infusions.

Variable	*Probability of molecular response (%)*		
Reference number	*52*	*53*	*54*
Type of relapse			
Molecular	100[a]	100	
Cytogenetic	84	88	
Hematologic (CP)	55	N/A	63
Interval SCT to relapse			
<9 months	56	N/A	N/A
≥9 months	76		
Dose of T lymphocytes			
CD3 <1 × 108/kg	N/A	N/A	90[a]
CD3 >1 × 108/kg			47

CP, chronic phase; GVHD, graft-versus-host disease; N/A, not available; SCT, stem cell transplant.

[a]Statistically significant.

TABLE 66.9. Imatinib compared with interferon-alpha (IFN-α) + cytarabine in newly diagnosed CML.

	Imatinib (n = 553)	*IFN-α + cytarabine (n = 553)*
Age (median)	50	51
Sokal risk groups (%)		
Low	52.5	48.2
Intermediate	29.0	29.7
High	18.5	22.1
Hasford risk groups (%)		
Low	45.6	44.6
Intermediate	44.3	45.4
High	10.1	10.1
Complete hematologic response at 18 months (95% CI)	95.3* 93.2–96.9	55.5 51.3–59.7
Complete cytogenetic response at 18 months (95% CI)	73.8* 69.9–77.4	8.5 6.3–11.1
Reduction of ≥3 log in *BCR/ABL* transcripts from baseline after 12 months of treatment (%)	39*	2
Improvement in quality of life from baseline to 12 months (%)	41*	16

*$P < 0.001$.

Source: Data from References 64–66.

leukocyte infusions (without any preparative chemotherapy or GVHD prophylaxis) can induce hematologic and cytogenetic remissions in patients with CML who have relapsed after allogeneic SCT (Table 66.7).[51–54]

The effect of imatinib in the chronic phase of the disease prompted its study in patients who relapse after allogeneic SCT.[55–57] Retrospective studies (Table 66.8) with small numbers of patients have shown that imatinib can control CML that has recurred after allogeneic SCT but is associated with myelosuppression and recurrence of GVHD. Studies of imatinib treatment after allogeneic SCT to prevent relapse in patients with advanced disease at the time of transplantation (patients at high risk for relapse) or patients undergoing nonmyeloblative transplants are underway. No randomized trials have compared donor lymphocyte infusions to imatinib for patients who relapse after allogeneic SCT.

Imatinib Mesylate

Imatinib mesylate (Gleevec, STI571) functions through competitive inhibition at the adenosine triphosphate (ATP)-binding site of the Abl kinase, which leads to inhibition of tyrosine phosphorylation of proteins involved in Bcr/Abl signal transduction.[58] It shows a high degree of specificity for Bcr/Abl, the platelet-derived growth factor receptors and c-*kit* tyrosine kinases. Imatinib induces apoptosis in cells expressing Bcr/Abl. Based on its antileukemic activity in vitro, it was tested in clinical trials.

Most patients with CML in chronic phase have a rapid hematologic response to imatinib therapy. In the initial studies[59] with imatinib in patients with chronic-phase CML who have been intolerant to IFN-α, 95% of patients achieved complete hematologic remissions, 60% achieved major cytogenetic remissions, and 41% achieved complete cytogenetic remissions. Those who did not achieve at least a major cytogenetic remission following 3 months of imatinib therapy had a higher risk of progression of the disease to the accelerated/blastic phases. The accelerated[60]/blastic[61–63] phases of the disease are less responsive to imatinib and the outcome of treatment is less favorable (overall survival at 12 months: accelerated phase, 74%[60]; blastic phase, 22%[61]/32%[62]/28%[63]). These studies led to U.S. Food and Drug Administration approval of imatinib for patients who were intolerant or unresponsive to IFN-α or for patients in the accelerated/blast crisis phases of the disease.

In newly diagnosed CML, a recent randomized phase III study of imatinib (400 mg/day) versus IFN-α and cytarabine[64,65] demonstrated complete hematologic remission rates of 95.3% with imatinib, compared to 55.5% with IFN-α and cytarabine, after 18 months of treatment (Table 66.9). Similarly, the complete cytogenetic remission rate was 73.8% in patients treated with imatinib, compared to 8.5% in patients treated with IFN-α and cytarabine. Progression to accelerated/blastic phases of the disease was noted in 3% of patients treated with imatinib compared to 8.5% of patients treated

TABLE 66.8. Imatinib for relapse following allogeneic transplantation.

	No. of patients	*Stage of disease*	*CHR*	*CCGR*
Kantarjian[55]	28	5 CP/15 AP/8 BP	17	10
Au[56]	8	5 CP/3 BP	7	6
Ollavarria[57]	123	50 CP/29 AP/44 BP	87	44
Total	159	60 (38%) CP/44 (28%) AP/61 55 (35%[a]) BP	111 (70%)	60 (38%)

AP, accelerated phase; BP, blastic phase; CCGR, complete cytogenetic response; CHR, complete hematologic response; CP, chronic phase.

[a]Numbers exceed 100% due to rounding.

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with IFN-α ?and cytarabine.[64] In addition, levels of *BCR/ABL* transcripts were studied in patients who had a complete cytogenetic remission following 12 months of treatment.[65] The levels decreased by at least 3 log in 57% of those on the imatinib arm, compared to 24% of those on the IFN-α and cytarabine arm. No survival data will be available from this study as it had a cross-over option and most patients on the IFN-α and cytarabine arm have crossed over to imatinib. Finally, imatinib offered a clear quality of life advantage as compared to IFN-α and cytarabine in newly diagnosed CML.[66] These results led to rapid U.S. Food and Drug Administration approval of imatinib for newly diagnosed CML patients.

Imatinib is administered orally and has an acceptable toxicity profile. The main side effects are fluid retention, nausea, muscle cramps, diarrhea, and skin rashes. The management of these side effects is usually supportive. Myelosuppression is the most common hematologic toxicity and patients with longer time from diagnosis, those previously treated with busulphan, and those who had cytopenias induced by IFN-α are at higher risk.[67] Myelosuppression may result from eradication of the malignant clone and delayed recovery of the normal nonclonal progenitor cells. Blood and platelet support should be provided, and the imatinib dose should rarely be reduced in the absence of infection. Use of erythropoietin to treat anemia during imatinib therapy has become standard practice despite the absence of clinical studies, but there is concern that erythropoietin will promote resistance against imatinib.[68] Similarly, the use of granulocyte colony-stimulating factor (G-CSF) has gained acceptance with only small observational studies to support it.[69,70] Imatinib doses below 300 mg per day seem ineffective and may lead to development of resistance.[71]

Resistance to imatinib occurs by mechanisms that are either *BCR/ABL* dependent (gene amplification, mutations at the kinase site, enhanced expression of multidrug exporter proteins) or *BCR/ABL* independent (alternative signaling pathways functionally compensating for the imatinib-sensitive mechanisms). Imatinib resistance has been shown to have an unfavorable prognosis in the accelerated and blast crisis phases of the disease. Specifically, patients who do not achieve major cytogenetic remission within 3 months of initiation of imatinib have shorter survival than patients who achieve that level of remission.[60–63] Both *BCR/ABL*-dependent and *BCR/ABL*-independent mechanisms of imatinib resistance are being targeted in clinical trials. Although no randomized studies have been published, a phase II clinical trial of high-dose imatinib in newly diagnosed patients with chronic-phase CML was recently published.[72] In comparison to a historical control group receiving standard-dose imatinib, patients treated with high-dose imatinib had significantly higher rates of complete cytogenetic response and molecular response.[72]

Interferons

When allogeneic SCT was not feasible, IFN-α therapy was previously the treatment of choice before the availability of imatinib. Only longer follow-up of patients treated with imatinib will demonstrate whether IFN-α will still have a role in the treatment of CML. The interferons are a complex group of naturally occurring proteins produced by eukaryotic cells in response to viruses, antigens, and mitogens. Three distinct groups of IFN species have been identified: IFN-α, IFN-β, and IFN-γ. Although various interferons have become available for clinical investigation, most data have been generated with IFN-α preparations.

Interferons have potent, pleiotropic biologic effects, with a spectrum of antiviral, microbicidal, immunomodulatory, and antiproliferative properties. Although interferons downregulate the expression of several oncogenes and cytokines, they also upregulate the expression of IFN regulatory factor 1 (a transcriptional activator with antioncogenic activity), adhesion molecules, and the histocompatibility genes. Interferons also inhibit angiogenesis and induce a cellular immune response. However, their mode(s) of action in CML is still unknown.

Meta-analysis of seven randomized studies revealed that patients treated with high-dose (5×10^6 units/m^2/day) IFN-α survived longer than patients treated with hydroxyurea or busulphan,[73] with 5-year survival rates of 51% and 42%, respectively. Interestingly, pegylated recombinant IFN-α and recombinant IFN-α had similar efficacy and toxicity profiles in a randomized study.[74] In addition, the combination of high-dose IFN-α with cytarabine produced better results in one randomized study[75] but not in another (Table 66.10).[76] At least two randomized trials[77,78] did not detect any significant difference between high- and low-dose (2.5×10^6 units/m^2/day or 3×10^6 units/5 days/week) IFN-α with regard to complete cytogenetic response, survival, and transformation rates. Furthermore, low-dose IFN-α with cytarabine failed to show any benefit over low-dose IFN-α with or without the addition of hydroyurea in two randomized studies.[79,80] In summary, low-dose, as opposed to high-dose, IFN-α may be used in combination with imatinib in future clinical trials aimed at increased response to imatinib or preventing imatinib resistance.

Patients develop both acute and chronic side effects from IFN-α therapy. Acute side effects (flu-like symptoms) appear early in the course of the treatment. Most flu-like symptoms respond to acetaminophen, and tachyphylaxis develops within 1 to 2 weeks. Chronic reactions, such as fatigue and lethargy, depression, weight loss, myalgias, and arthralgias, occur in about half of patients and often require dose reduction. Patients also report cough, postnasal drip, and dry skin. Infrequently, immune-mediated thrombocytopenia and anemia develop. In addition, long-term therapy has been associated with late autoimmune side effects, such

TABLE 66.10. Comparison of two randomized trials of IFN-α versus IFN-α and low-dose cytarabine for newly diagnosed chronic-phase CML patients.

	IFN-α	*IFN-α + cytarabine*
	Major cytogenetic response (%)	
Guilhot[75a]	41	24[b]
Baccarani[76c]	28	18[b]
	Overall survival (%)	
Guilhot[75d]	85.7	79.1
Baccarani[76c]	68	65

[a]Results at 12 months.

[b]Results are statistically significant.

[c]Results at 24 months.

[d]Results at 36 months.

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as hypothyroidism and occasional generalized autoimmune phenomena.

The most important persistent side effects in patients with CML who are treated with IFN-α are neuropsychiatric. All patients treated with IFN-α are subject to some neurologic toxicity, the most common symptom being lethargy. Up to 20% of patients have neurologic side effects that are associated with compromised quality of life and reduced ability to carry out their regular activity, such as full-time work. From at least one observational study,[81] it seems that patients with a pretreatment neurologic or psychiatric diagnosis are at significantly increased risk of developing severe neuropsychiatric toxicity.

Chemotherapy

Innovative approaches are still important in CML because the exact role of imatinib in the armamentarium of CML is still not clear. Initial management of patients with chemotherapy is currently reserved for rapid lowering of white blood cell counts, reduction of symptoms, and reversal of symptomatic splenomegaly. Hydroxyurea, a ribonucleotide reductase inhibitor, induces rapid disease control. The initial dose is 1 to 4 g/day, and the dosage should be reduced by half with each 50% reduction of the leukocyte count. Unfortunately, cytogenetic remissions with hydroxyurea are uncommon. Busulphan, an alkylating agent that acts on early progenitor cells, has a more prolonged effect. However, it is rarely used because of its serious side effects, which include unexpected, and occasionally fatal, myelosuppression in 5% to 10% of patients, as well as pulmonary, endocardial, and marrow fibrosis and an Addison-like wasting syndrome.

Intensive combination chemotherapy has also been used in chronic-phase CML, with 30% to 50% of patients achieving complete cytogenetic responses. However, these cytogenetic remissions have been short lived. Consequently, intensive combination chemotherapy regimens are being used today only to mobilize normal progenitors in the blood to collect circulating stem cells for autologous transplantation.

Autologous SCT

Autologous SCT could potentially cure CML if a means to select the residual normal progenitors, which coexist with their malignant counterparts, could be developed. As a source of autologous hematopoietic stem cells for transplantation, blood offers certain advantages over marrow (e.g., faster engraftment and no necessity for general anesthesia). Normal hematopoietic stem cells appear with increased frequency in the blood of patients with CML during the recovery phase after chemotherapy, with G-CSF priming. A role for imatinib prestem cell collection to achieve minimal residual disease and to maintain this status following transplantation is being currently investigated.[82–84] However, only a few patients have been reported to successfully engraft following imatinib therapy. Therefore, such approaches should be implemented only in clinical trials.

Leukapheresis and Splenectomy

Intensive leukapheresis may control the blood counts in chronic-phase CML; but this procedure is expensive and cumbersome. It is useful in emergency situations in which leukostasis-related complications such as pulmonary failure or cerebrovascular accidents are likely. It may also have a role in the treatment of pregnant women in whom it is important to avoid potentially teratogenic drugs.

Splenectomy was used in CML in the past because of the suggestion that evolution to the acute phase might occur in the spleen. However, this does not appear to be the case, and splenectomy is now reserved for relief of pain associated with splenomegaly unresponsive to chemotherapy or with recurrent splenic infarcts, or improvement of significant anemia or thrombocytopenia associated with hypersplenism. Splenic radiation is used rarely to reduce the size of the spleen.

Minimal Residual Disease

After allogeneic SCT, residual disease may be detected by reverse transcriptase-polymerase chain reaction (RT-PCR) analysis during the first 6 months in patients who subsequently achieve a long-lasting remission, according to a multivariate analysis of 346 patients.[85] However, RT-PCR results, by 6 months, classified as negative, positive at a low level (less than 100 *BCR/ABL* transcripts/μg RNA and/or *BCR/ABL-ABL* ratio of less than 0.02%), or positive at a high level (transcripts levels exceeding the above) did predict outcome in one observational study,[86] with probabilities of relapse of 16.7%, 42.9%, and 86.4%, respectively. Late persistence of RT-PCR positivity appears to indicate a reduced probability of cure.[85,87] Therefore, after allogeneic SCT, patients are often divided according to RT-PCR results into one of three groups: (1) persistently positive, (2) intermittently negative, and (3) persistently negative. These three groups have low, intermediate, and high probability of disease-free survival, respectively. Although these data suggest that patients who are persistently RT-PCR positive more than 6 months after allogeneic SCT need additional therapeutic interventions, this conclusion has not been rigorously established. The studies have used an assortment of techniques for measuring minimal residual disease, the level of sensitivity has been variable, and the durations of patient follow-up have been short. For example, quantitative real-time RT-PCR may provide a less-sensitive tool (sensitivity in the range of $1:10^4$ to $1:10^5$) to predict relapse in CML as compared to competitive nested PCR (sensitivity in the range of $1:10^5$ to $1:10^6$).[88] In patients who do not have any evidence of GVHD and are intermittently or persistently RT-PCR positive, GVL may be induced by administering donor lymphocytes to eradicate the residual leukemia cells.[51–54] Another approach is the use of imatinib to eradicate minimal residual disease.[55–57]

In contrast to the results achieved with allogeneic SCT, only a minority (5% to 10%) of patients develop molecular remission following imatinib therapy.[65,89–92] Extrapolating from the SCT data, patients without molecular remission are likely to be at high risk of relapse. However, patients with AML with t(8;21) who are in long-term remission have persistent multipotent progenitor cells expressing *AML1/ETO* transcripts.[93] Therefore, it is unclear whether achieving durable molecular remission with imatinib should indeed be the goal of treatment in CML. This question will be answered only with long-term follow-up of imatinib-treated patients.

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Recommendations

The encouraging results with imatinib have steered many clinicians to offer it as a first-line therapy for newly diagnosed CML patients, including those who otherwise would have benefited from transplant (e.g., young patients with sibling-matched donors). This approach may be unwise because the clinical studies so far have very short follow-up, thus limiting knowledge regarding the cure rate associated with imatinib. There is a risk that, by delaying transplantation, either new clonal cytogenetic abnormalites will develop in Philadelphia chromosome-negative cells[94–106] or transplantation after the development of resistance may be associated with worse outcome.[107,108]

If transplantation is selected, evidence-based data are available to recommend BMT with a preparatory regimen that includes busulphan and cyclophosphamide. Only one randomized trial[18] with 30 months follow-up demonstrated better survival with PBSC versus bone marrow as a source of stem cells. Further, the data from reduced-intensity preparative regimens are intriguing, but no randomized studies or long-term follow-up data are available at this point. Therefore, physician experience and patient preference must be factored into the treatment selection process.

Discussion of both treatment options with a patient is indicated. The decision should focus on the outcomes, risks, and toxicities of the two approaches. Some centers would employ allogeneic SCT in patients younger than 30 years of age, as the risk of transplant-related toxicity is minimal in that population. A proposed treatment plan for the newly diagnosed patient with CML is presented in Figure 66.1.

There is no clear answer for M.T. However, if she elects to start treatment with imatinib, it is imperative that her response be followed carefully. Consensus based on clinical experience suggests monitoring cytogenetics or peripheral blood FISH every 3 to 6 months. Patients who achieve a complete cytogenetic remission should have bone marrow cytogenetics every 6 months, alternating with peripheral blood quantitative RT-PCR. SCT will be revisited at any sign of disease progression, for example, increasing BCR/ABL transcript levels.

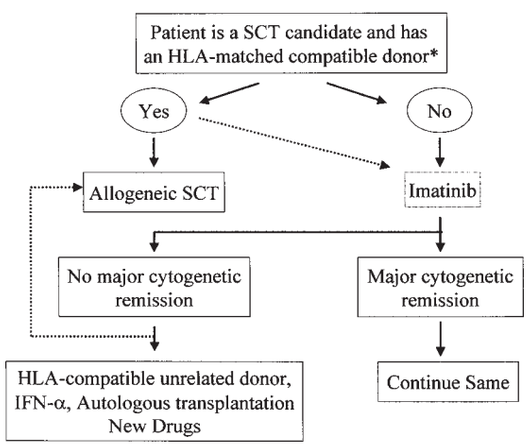

FIGURE 66.1. Flow chart for the therapy of newly diagnosed chronic myeloid leukemia (CML). Patients with an HLA-compatible donor have the possibility to undergo allogeneic stem cell transplantation (SCT) as initial therapy or treatment with inatinib. The *asterisk* denotes centers that employ allogeneic SCT only if imatinib fails to induce a response. *Dotted lines* denote lack of long-term survival data.

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