

Perspectives on the treatment of chronic phase and advanced phase CML and Philadelphia chromosome positive ALL¹

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Chronic myeloid leukaemia (CML) is a malignant disease of the bone marrow characterised by the presence of the Philadelphia (Ph) chromosome. About 20% of acute lymphoblastic leukaemia (ALL) patients also show this genetic abnormality. A new drug, imatinib (Glivec[®], Novartis Pharma AG, Basel, Switzerland, and formerly ST1571) is having a profound effect on the treatment and management of all stages of CML and Philadelphia chromosome positive (Ph+) ALL. New treatment algorithms are being developed. Should imatinib replace or be combined with existing therapies? To address this question, we review the pros and cons of therapy with interferon- α (IFN- α), allogeneic transplantation, autologous transplantation, imatinib, and in the case of Ph+ ALL, chemotherapy and experimental approaches. Conservative and aggressive treatments will be discussed and new molecular methods of monitoring cytogenetic response and their significance will also be reviewed.

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Introduction

Chronic myeloid leukaemia (CML) is a clonal disorder thought to originate in a single abnormal haematopoietic stem cell. The diagnosis of CML is usually based on the detection of the Philadelphia (Ph) chromosome, which is the underlying abnormality of the disease.¹ The Ph chromosome results from the translocation of genetic material between chromosomes 9 and 22, t(9;22).² The molecular consequence is the creation of the fusion protein Bcr–Abl, a cytoplasmic tyrosine kinase with increased phosphorylation activity that is critical to the transformation of cells.

In most cases, CML runs a triphasic course, which includes an initial chronic phase that transforms eventually into a blastic phase resembling acute leukaemia. In 60–80% of patients, an intermediate or accelerated phase precedes the blastic phase. The chronic phase is characterised by a hypercellular marrow with high peripheral white blood cells (WBC) counts; this phase may last for a median of 5–6 years. Clinical criteria for the definition of the accelerated phase are vague and include basophilia, clonal evolution and increased peripheral-blood blast and promyelocyte counts.³ Generally, after 6–9 months, the accelerated phase is followed by a blastic phase, which may

cause death within 3–6 months. The blastic phase is usually defined by the presence of extramedullary infiltrates of blasts or blast counts in excess of 30% in peripheral blood or marrow.

The management of CML has become more complex due to the availability of improved diagnostic procedures and new life-prolonging treatment strategies. The only proven curative therapy for CML is allogeneic stem cell transplantation (SCT), but this is available to only a fraction of patients because of either advanced patient age or limited donor availability.⁴ Chemotherapy such as hydroxyurea, is used to control the signs and symptoms of CML, prolong life and induce cytoreduction before initiating other treatments.⁵ Interferon- α (IFN- α) although noncurative, has been shown to prolong life when compared to hydroxyurea.⁶ Imatinib, a tyrosine kinase inhibitor,⁷ induces very high response rates,^{8–10} and has been approved for patients with CML who have failed or are intolerant of IFN- α , and more recently for newly diagnosed patients.

Prognostic factors

Several pretreatment clinical characteristics have been found to have prognostic significance in CML. The prognostic scoring system proposed by Sokal (the Sokal index) is widely accepted and has been shown to reproducibly segregate chemotherapy-treated patients into high- and low-risk groups of prognostic significance.^{11,12} Sokal's model identified four independent prognostic factors at diagnosis: (1) patient age, (2) degree of splenomegaly, (3) platelet count, and (4) higher peripheral blast percentage. The Sokal score can be calculated for individual patients by accessing the Web site: <http://www.nrhg.ncl.ac.uk/cgi-bin/cml/sokal.pl>. Sokal's index is less efficient in discriminating outcome in IFN- α -treated patients. A new CML Score incorporating spleen size, patient age, and peripheral-blood eosinophils, basophils, blasts, and platelet count has been suggested to predict outcome in IFN- α -treated CML patients with high accuracy.¹³ The new CML Score can be calculated using an on-line calculator at: <http://www.pharmacoepi.de>. The scoring systems identify patients belonging to three risk groups. Low-risk patients have a score of less than 0.8 with the Sokal Score and at most 780 with the CML Score. Intermediate-risk patients have a score between 0.8 and 1.2 with the Sokal Score and between 781 and 1479 with the CML Score. High-risk patients have a score greater than 1.2 with the Sokal Score and at least 1480 with the CML Score. Patients in the low-risk group have a median survival of 100 months, patients in the intermediate-risk group have median survival of 69 months, and patients in the high-risk group have a median survival of 45 months.¹³ Other nonclinical factors have also recently been shown to have prognostic impact. For example, patients with deletions of part of the derivative chromosome 9 detectable by

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¹These topics were discussed at the annual meeting of the American Society of Hematology, Orlando, FL, 7–11 December, 2001 in a CME session titled 'Controversies in the management of CML' (Moderator: SD Nimer).

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fluorescence *in situ* hybridisation (FISH), have a shorter chronic phase and decreased survival. This finding was more predictive of poor outcome than the clinically calculated prognostic indices in this same population of patients.¹⁴ The mechanism of this effect is unknown but it is likely that in the future, other molecular testing, including gene array analyses, will identify changes suggestive of differences in clinical course.

What are the treatment goals in CML?

The goal of therapy should not only be symptomatic disease control but also should be aimed at suppressing the effects of the *bcr-abl* abnormality by eliminating the malignant clone represented by the Ph chromosome. Responses in CML are based on haematological and cytogenetic criteria. Haematological responses are defined by the degree of normalisation of peripheral-cell counts and spleen size and by the presence or absence of immature myeloid cells. Haematological improvement must be maintained for 1 month to qualify as a response. Disappearance of signs (eg, splenomegaly or hepatomegaly) and symptoms of disease is also required (Table 1). The cytogenetic response is classified into four response groups, according to the percentage of residual Ph+ cells (Table 1).

In CML, conventional chemotherapy with hydroxyurea is used to control the WBC count and the symptoms associated with the myeloid hyperplasia and splenomegaly (haematological response). Hydroxyurea is commonly used to lower tumour burden before IFN- α therapy. However, when a haematological response is the only response achieved, the disease will eventually progress and ultimately cause the patient's death.

Experience with allogeneic SCT has shown that the most important factor in achieving long-term disease control is the achievement of complete and durable cytogenetic responses.¹⁵ Patients treated with IFN- α who achieve a major cytogenetic response also experience prolonged survival compared with patients with no or minor cytogenetic response.^{16,17} Patients treated with IFN- α who achieve a complete cytogenetic response tend to have the highest survival.¹⁸ In comparison to other therapies, imatinib produces high rates of complete cytogenetic responses in all phases of CML,^{8-10,19,20} but the durability of these responses is still unknown.

Methods used to monitor the response to therapy in patients with CML

Cytogenetic responses are traditionally based on bone marrow analysis of dividing myeloid cells in metaphase to quantify the number of detectable Ph+ cells. This is a time-consuming method and, depending on the type of therapy used (eg, IFN- α),

Table 1 Response Assessment in CML

Haematological response	Cytogenetic response
Complete	Complete response 0% Ph+ cells
Normal peripheral blood count	Major (partial) response 1-34% Ph+
WBC < 10 × 10 ⁹ /l	Minor response 35-95% Ph+
Platelets < 450 × 10 ⁹ /l	No response ≥96% Ph+
Normal differential	
No palpable splenomegaly	

the number of assessable metaphases might be extremely low. Therefore, techniques enabling response evaluation on interphase blood cells would be highly desirable.

FISH is a molecular method that enables rapid detection of chromosomal rearrangements, even in interphase, and thus avoids the requirements that cells be dividing. The limit of detection of CML cells is typically 1-5%.²¹ However, because FISH can be performed on peripheral blood, it is less invasive and less costly than repeated marrow cytogenetics, and studies have shown that there is an excellent correlation between FISH on peripheral-blood specimens and cytogenetics on bone marrow specimens (Figure 1).²² FISH is currently being used to monitor remission status in Ph+ CML.²³ It is also used for the evaluation of mixed chimerism following SCT,²⁴ but its sensitivity is not sufficient for early detection of relapse.²⁵ Since cytogenetic analyses represent the historical standard with the largest body of follow-up information, repeat marrow cytogenetic studies, in part to detect clonal evolution, are advisable when there are changes in the patient's clinical condition, worsening of blood counts or progressive increases in the % positivity by FISH analysis. Theoretically, because cytogenetic analysis depends on the study of cells which divide *in vitro*, it may also be a reflection of the presence of more proliferative clones.

Reverse transcriptase-polymerase chain reaction (RT-PCR) for the detection of *bcr-abl* mRNA is up to four orders of magnitude more sensitive than cytogenetics or FISH. *bcr-abl* messages can be detected from a single leukaemia cell in a background of 10⁵-10⁶ normal cells. Like FISH, RT-PCR can be performed on peripheral blood instead of the marrow. Qualitative RT-PCR in CML expresses results as 'positive' or 'negative' and it is critical that the laboratory provide the sensitivity of the assay being used. Currently, it is the method most commonly used to monitor the presence or absence of *bcr-abl* mRNA after SCT. Patients treated with IFN- α rarely, if ever, become RT-PCR negative and there is very limited information following imatinib therapy.

Quantitative *bcr-abl* RT-PCR assays were developed to monitor patients after SCT²⁶ or treatment with IFN- α .²⁷ These assays allow the kinetics of *bcr-abl* transcripts to be monitored more precisely over time. In order to standardise results for both quality and quantity of the blood samples used in the assay,

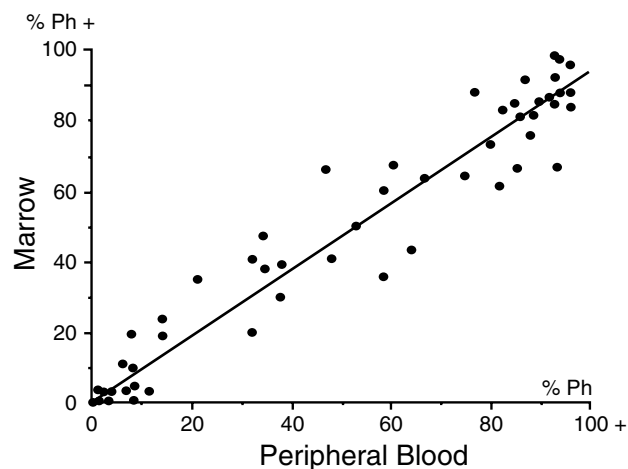


Figure 1 Correlation between interphase FISH on bone marrow (x-axis) and peripheral blood (y-axis) specimens. Adapted from Le Gouill et al.²²

parallel quantification of transcripts of housekeeping genes, such as *abl* or glucose-6 phosphate dehydrogenase (G6PD), has been used. The standardised results are expressed as the ratio of *bcr-abl* to *abl* or *bcr-abl* to G6PD. Some groups have initially used competitive RT-PCR strategies to quantify *bcr-abl* transcripts but this method is cumbersome. Novel real-time RT-PCR procedures have been developed that simplify the existing protocols. Procedures for quantification of *bcr-abl* mRNA using the TaqMan[®] system (Applied Biosystems, Foster City, CA, USA),^{28,29} or the LightCycler technology[™] (Roche Group, Basel, Switzerland)³⁰ have been described and are becoming commercially available. Currently, the molecular techniques, the requirements for cell handling before testing and the fashion in which data are expressed vary considerably amongst different laboratories and it is expected that there will be more standardisation in the future. As data become available comparing clinical outcome with the levels of *bcr-abl* transcripts and their pattern of change over time, these tests may be used more routinely in clinical decision making.

The median *bcr-abl/abl* ratio is significantly different between patients who have either a complete cytogenetic response, a partial response, or no response to IFN- α , (Figure 2).³¹ Interestingly, even in patients achieving a complete cytogenetic response with IFN- α , molecular evidence of disease is rarely eliminated and the ratio of *bcr-abl/abl* in complete responders spans a range over four orders of magnitude.³¹ In general, *bcr-abl* transcripts are inversely related to the duration of the cytogenetic response and patients with low ratios of *bcr-abl/abl* transcripts ($\leq 0.045\%$) infrequently relapse (Figure 3).³² Any consistent change in a patient's RT-PCR results should warrant a reassessment of their therapy.

Treatment of chronic phase CML

In 1999, an American Society of Hematology consensus panel⁶ documented the evidence-based benefits and risks of treating CML with busulphan, hydroxyurea, IFN- α , and SCT. The conclusions of the panel were that SCT should be the first option for patients with CML, but candidacy is dependent on

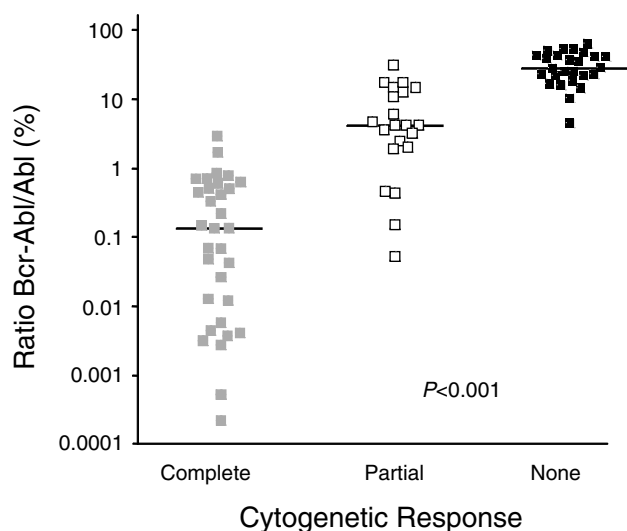


Figure 2 *bcr-abl* levels correlate with cytogenetic response. Adapted from Hochhaus et al.³¹ *bcr-abl/abl* ratios of Ph+ CML patients on IFN- α therapy. Results are significantly different between the cytogenetic response groups ($P < 0.0001$).

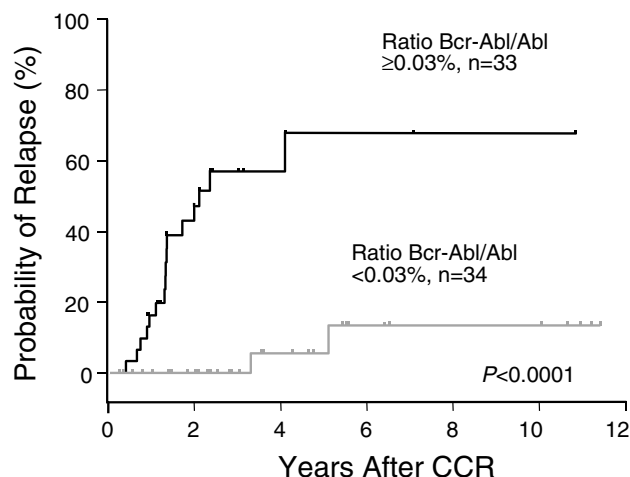


Figure 3 *bcr-abl* levels predict relapse in complete cytogenetic responders on IFN- α therapy. Updated from Hochhaus et al.³² Relapse-free survival is significantly different between patients with residual *bcr-abl/abl* ratios $\geq 0.003\%$ (complete cytogenetic responders) as compared to patients with ratios 0.003 ($P = 0.0001$, two-sided log-rank test).

patient age and health, and availability of a matched donor. If SCT is not possible, IFN- α should be offered. Optimal dosing, duration, and combination with other drugs must be considered by the physician. As a general rule, a systematic plan should be established for evaluating the degree and duration of cytogenetic and molecular response, as this definition of treatment efficacy has been associated with prolonged survival.

With the introduction of imatinib, new algorithms are being proposed,³³ and the National Comprehensive Cancer Network (NCCN) has established new CML treatment guidelines that include the use of imatinib as first-line therapy or when other treatments have failed, (www.nccn.org/physician_gls/index.html). In addition, more recent data have demonstrated a higher initial response rate as well as a longer time to disease progression using imatinib therapy for newly diagnosed patient with CML in the chronic phase as compared to patients treated with IFN- α + ara-C.³⁴

Should a patient in chronic phase CML on IFN- α be switched to another therapy?

Until now, most patients who were not eligible for SCT were offered treatment with IFN- α , as several randomised trials have shown that IFN- α was superior to chemotherapy.³⁵ Patients defined as low risk by the prognostic scores have been shown to have the best outcome when treated with IFN- α . Low-risk patients have a 10-year survival rate of about 40% (Figure 4).^{13,36}

Other studies showed that achieving a cytogenetic response within 12–24 months was associated with a statistically significant survival benefit.³⁷ In particular, major cytogenetic responders fare better than patients with no or only a minor cytogenetic response (Figure 5).³⁶ Complete cytogenetic responders may fare even better, with 72% of patients alive at 10 years (Figure 6).¹⁸ Although these patients have the best outcome, they represent a minority of patients; most studies report a complete cytogenetic response rate ranging from 5 to 13% with two studies reporting rates as high as 26 and 33%.¹⁸ Within the patient cohort with a complete cytogenetic response

SPOTLIGHT

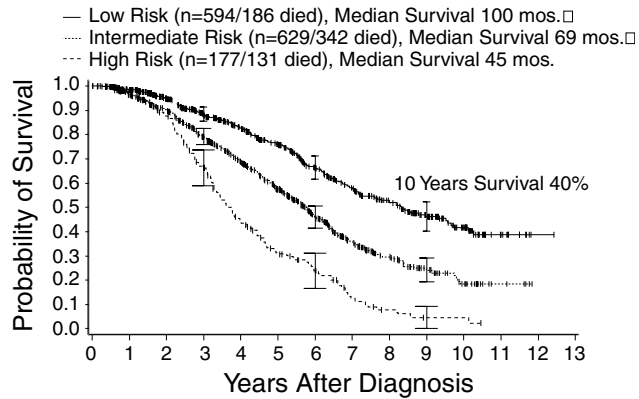


Figure 4 Survival stratified for risk groups according to the New Score. Updated from Hasford *et al.*¹³ The New CML score applied to 1400 patients with early phase CML treated with IFN- α . Lengths of horizontal crossbars indicate the upper and lower 95% confidence limits. Crossbars increase from the lowest-risk group to the highest-risk group.

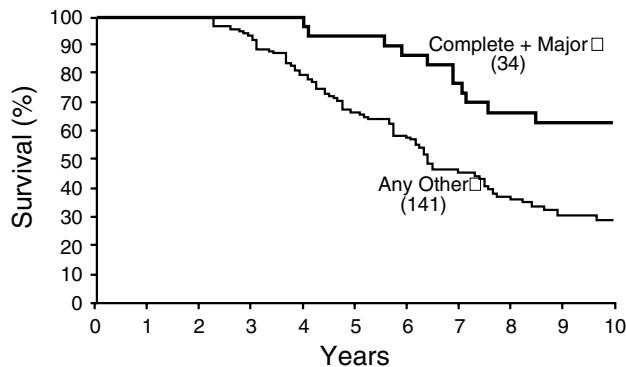


Figure 5 Overall survival of cytogenetic responders on IFN- α treatment. Adapted from The Italian Cooperative Study Group on Myeloid Leukemia.³⁶ Overall survival of patients who were assigned to receive IFN- α and were alive and in chronic phase after 24 months when the cytogenetic response was assessed (landmark analysis). Patients who achieved a complete or major cytogenetic response during the first 24 months survived longer ($P=0.001$).

to IFN- α therapy, patients with low-risk scores survived the longest (10-year survival probability of 89% for Sokal low-risk patients).¹⁸

Thus, IFN- α therapy offers prolonged survival to a limited number of patients. In addition, tolerability to IFN- α is poor and requires dose reduction in more than 50% of patients. Furthermore, severe side effects may result in discontinuation of treatment in up to 25% of patients.³⁷ Therefore, there is a need for an alternative to IFN- α in order to offer the potential of a cure, to further prolong survival, and to manage patients who are suffering from IFN- α -induced adverse events or whose disease is progressing.

Stem cell transplantation

Allogeneic SCT from human leukocyte antigen (HLA)-matched donors is still currently considered the only potential cure for CML. However, most patients are not eligible for SCT. Access to the procedure is limited by availability of a suitable donor and

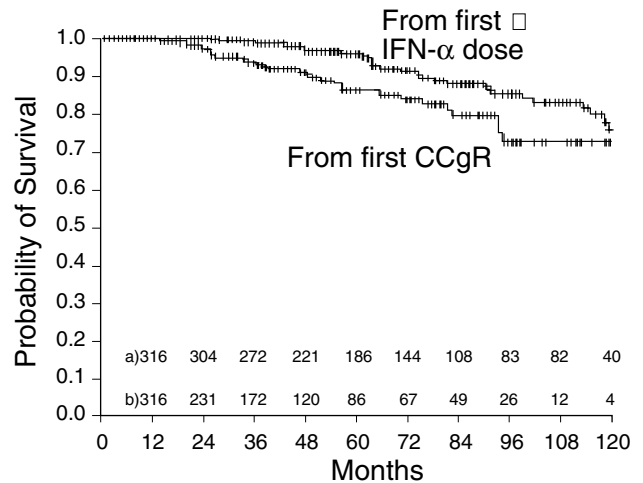


Figure 6 Complete cytogenetic responders: overall survival. Adapted from Benifazi *et al.*¹⁸ Overall survival is shown from the first IFN- α dose (10-year survival 75%) or from the date of first complete cytogenetic response (10-year survival 72%). (a) Number of cases at risk from first IFN- α dose. (b) Number of cases at risk from the first complete cytogenetic response.

patient age (many centres do not accept candidates > 55 years of age).

Transplantation within 1 year of diagnosis is preferred in patients previously treated with hydroxyurea or interferon.^{33,38} Only 15–20% of patients with CML meet these criteria for SCT.³⁹ The 5-year survival for patients who undergo transplantation during the chronic phase of the disease ranges from 45 to 80%, depending on patient age and other risk factors, and survival rates decrease with advanced stages of disease.⁴⁰ If switching to allogeneic SCT, IFN- α treatment should be withheld at least 3 months before transplantation if possible.⁴¹

The relapse rate following SCT in patients in chronic phase CML is 10–20%. The infusion of T cells obtained by leukapheresis from the original bone marrow donor has improved the outcome of relapse after allogeneic SCT. Donor lymphocyte infusions (DLI) can induce a graft-versus-leukaemia effect with complete cytogenetic and haematological remission in two-thirds of the patients. However, approximately one-third of DLI recipients will develop graft-versus-host-disease (GVHD).⁴² Several reports have indicated that imatinib may be useful in combination with DLI in the treatment of leukaemia relapse after SCT.^{43–45} The systematic use of imatinib in the post-SCT setting is being evaluated in clinical trials.

Patients who are not candidates for 'full' myeloablative conditioning regimens may benefit from nonmyeloablative SCT. Nonmyeloablative SCT consists of low-dose, less toxic preparative regimens designed to provide sufficient immunosuppression for donor cells to engraft, allowing the graft-versus-leukaemia effect to eradicate the tumour. Long-term efficacy of nonmyeloablative SCT in patients with CML remains to be determined.⁴⁶

SCT with matched unrelated donors (MUD) identified by bone marrow-donor registries can increase the percent of patients with CML who are candidates for transplantation to 30+%.⁴⁷ Progress in molecular typing has improved the ability to match HLA-A, -B, and DRB1 antigens.⁴⁸ Recent studies report long-term disease-free survival rates of 60–70% in younger patients and very little difference in outcome compared to the use of HLA identical sibling donors. As with matched sibling

Table 2 Phase II results of imatinib in chronic phase CML patients following interferon failure

	Total (%)	Haematological failures (%)		Cytogenetic failures (%)		IFN- α intolerant (%)
		Resistant	Relapsed	Resistant	Relapsed	
Major cytogenetic response	60	41	57	55	83	66
Complete	41	25	41	31	76	47
Partial	19	16	16	24	7	19
Minor	5	8	1	8	2	2
Minimal	11	16	16	9	2	11
Haematological response						
Complete	95	89	99	97	98	93

Adapted from Kantarjian *et al.*⁸

donor transplantation, outcome is highly dependent on patient characteristics such as age, stage of disease, and time to transplantation, although pretreatment with IFN- α may have less of an apparent adverse effect on unrelated donor transplantation.⁴⁹

Autologous SCT after intense chemoradiotherapy may prolong survival and reduce complications and mortality during peritransplantation. The procedure is not regarded as curative,⁴² but with the development of new purging techniques, collecting stem cells when the patient is in complete cytogenetic response for use in case of relapse is an interesting investigative option.⁵⁰ Trials of autologous SCT following the induction of cytogenetic response by imatinib are in progress.

Imatinib

Imatinib has been shown to produce very high response rates in patients in chronic phase CML who have failed or are resistant to IFN- α therapy.^{8,20} A complete haematological response (CHR) was achieved in 95% of patients overall (Table 2) and the response time was rapid (median time to response was 0.7 months). Responses occurred in 86% of patients within 3 months.⁸ Major cytogenetic responses (MCR) were achieved in 60% of patients, with complete responses in 41% (Table 2).⁸ The time to onset of MCR ranged from 2.4 to 19 months. Among patients who achieved an MCR, 84% have maintained their responses to date and the estimated survival rate at 18 months was 95%.⁸ The median duration of prior chronic phase in the patients on this study was almost 3 years suggesting, but not proving, that the treatment may produce a significant improvement over the expected survival. Imatinib was generally well tolerated with mild-to-moderate side effects, the most common being nausea, fluid retention, vomiting, and diarrhoea.

However, experience with imatinib is relatively short (3 years), and it is not known yet if it is curative or significantly improves survival. Even in complete cytogenetic responders to imatinib, low levels of *bcr-abl* transcripts persist, as was also seen with IFN- α therapy,^{51,52} although RT-PCR negativity can be observed in a subset of patients. Whether more sensitive nested RT-PCR techniques will also be negative, and the clinical relevance of such findings, awaits further follow-up. Although resistance is thus far uncommon in chronic phase, if the patient relapses, the impact of prior treatment with imatinib on the long-term outcome of SCT is unknown.

The major dilemma faced by patients in chronic phase with available matched donors is whether to immediately opt for allogeneic transplant or to pursue initial therapy with imatinib. Although disagreements abound, most clinicians feel comfor-

table in recommending early transplantation for younger, otherwise healthy patients with expected low rates of transplant-related mortality.³³ The median age of patients with CML is probably 50 years, so initial treatment with imatinib represents the recommendation for the majority of newly diagnosed patients. With the experience from interferon therapy, and the early results of the imatinib trials that long-term benefit is likely to be associated with cytogenetic complete response, it is appropriate to reconsider transplant in medically suitable patients with less than major cytogenetic responses. Since cytogenetic responses occur very rapidly, the determination of cytogenetic response can usually be made within 9 months of initiation of treatment. Nonresponders who are not suitable for transplantation can be offered dose increase or new experimental protocols, although obviously the results of such manoeuvres are not known. It is also not known how long the duration of cytogenetic CR will persist, and the *in vitro* observation that Ph+ stem cells may be insensitive to imatinib, may be sobering in this regard.⁵³

Therapies for advanced phase CML

Accelerated phase

Accelerated phase CML is heterogenous. More than 10–15% (but less than 30%) blasts in either peripheral blood or bone marrow may be present. Symptoms may include unexplained fever, bone pain, splenomegaly, and hepatomegaly. Basophilia, increased or decreased platelet counts, and cytogenetic progression may also be observed. Cytogenetic abnormalities such as duplication of the Ph chromosome, iso17q, or trisomy 8 are the most common additional chromosomal abnormalities described during cytogenetic progression. These patients have few options other than SCT, and the heterogeneity of responses to therapy reflects the heterogeneity of the patient population.

Although IFN- α has little effect on patients in the accelerated phase,³⁷ imatinib has shown some success in these patients.⁹ In a large phase II trial in patients in the accelerated phase of CML, imatinib induced a haematological response in 69% of patients, which was complete in 34% of patients (Table 3).⁹ Importantly, a MCR was observed in 24% of patients, which was complete in 17% of patients. In this trial, patients received either 400 or 600 mg of imatinib daily and there was a trend toward a higher rate of cytogenetic response in the 600 mg group (28%) as compared with the 400 mg group (16%) as well as superior progression free and overall survival (Table 3). Median time to cytogenetic response was rapid (2.8 months, range 0.8–12

Table 3 Phase II results of imatinib in accelerated phase CML

	400 mg (%)	600 mg (%)	Overall (%)
Haematological response	65	71	69
Complete	27	37	34
No evidence of leukaemia	10	13	12
Return to chronic phase	27	21	23
Major cytogenetic response	16	28	24
Complete	11	19	17
Partial	5	8	7

Adapted from Talpaz *et al.*⁹

months).⁹ Nonhaematological toxicity was usually mild or moderate, and haematological toxicity was manageable.⁹

Although imatinib showed remarkable clinical activity in this group of patients, a substantial fraction of patients ultimately relapsed with resistant disease. Importantly, disease progression in accelerated phase patients was much more rapid in cytogenetic nonresponders compared to cytogenetic responders, further emphasising the importance of a cytogenetic response. Patients with advanced phase CML (or Ph+ acute lymphoblastic leukaemia [ALL]) who relapse during treatment with imatinib have been reported to have *bcr-abl* gene amplification or point mutations resulting in conformational changes in the ATP binding domain of the Bcr-abl kinase.⁵⁴ At least six possible point mutations in the tyrosine kinase domain have been reported.⁵⁵⁻⁵⁹ These mutations result in the reactivation of Bcr-abl kinase activity, although the overall contribution of these mutations to potential resistance mechanisms remains to be defined. Other mechanisms of clinical resistance to imatinib are also postulated to exist including overexpression of Bcr-abl, p-glycoprotein-mediated drug efflux and variations in protein binding and imatinib pharmacokinetics.⁵⁹

Patients in the accelerated phase responding to imatinib who achieve a complete cytogenetic response should be considered for SCT if a suitable donor is available, because most such patients will eventually relapse. Patients who decline transplantation, or in whom the risk of SCT is considered very high, should be monitored closely at the molecular level if possible for a pattern of rising levels of *bcr-abl* transcripts and should again be considered for SCT if progression occurs. The precise level of transcripts predictive of clinical relapse remains to be determined.

Myeloid blast crisis

Myeloid blast crisis is characterised by more than 30% blasts in peripheral blood or bone marrow and increased symptomatology, especially relating to anaemia and infection, lymphadenopathy, and bleeding. Approximately 50% of patients are in myeloid blast crisis, 25% are in lymphoid blast crisis, and 25% are mixed.⁶⁰ Patients with CML in blast crisis have a poor prognosis due to the lack of effective therapy. This phase is rapidly fatal because of marked resistance to chemotherapy, with a median survival of 3-6 months.⁶⁰ These patients are candidates for transplantation and most therapies are administered until a suitable matched or unmatched donor is found.

Since myeloid blast crisis CML resembles acute myeloid leukaemia (AML), AML-type induction chemotherapy such as continuous infusions of cytarabine (ara-C) and anthracycline has

been used to treat these patients.⁶¹ This therapy generally produces a haematological response in the range of 40%, but much lower complete response rates and prolonged myelosuppression often leads to significant organ toxicity, which compromises the ability to proceed to SCT. Investigational therapies include high-dose cladribine [a chlorinated purine analogue];⁶² decitabine [a pyrimidine analogue that inhibits DNA methylation];⁶³ and troxacitabine [a novel dioxolane nucleoside analogue].⁶⁴ The anti-CD33 immunoconjugate gemtuzumab (Mylotarg[®], gemtuzumab ozogmicin for Injection, Wyeth Pharmaceuticals, Philadelphia, PA, USA), in combination with other therapies, may have some application in myeloid blastic phase but remains to be evaluated more thoroughly.⁶⁵

Imatinib is able to induce haematological responses lasting at least 4 weeks in 31% of patients in myeloid blast crisis, including complete haematological responses in 8% of cases.¹⁰ Unexpectedly, a major cytogenetic response was achieved in 16% of patients with a complete cytogenetic response in 7%.¹⁰ Not surprisingly, achievement of a sustained haematological response appears to be associated with more prolonged survival (Figure 7).¹⁰ The median survival time of patients with a sustained haematological response was 19 months, compared to 6 months for patients with an unsustained response and only 3 months for patients with no response.¹⁰ However, most patients relapse and the current estimate of the 12-month rate of survival is 32%.¹⁰ The outcome of SCT is better in blast crisis patients who return to chronic phase prior to transplantation than in patients who undergo transplantation during blast crisis. Thus, the achievement of a haematological response with imatinib in these patients suggests that imatinib may be useful as a bridge to transplantation.

Although imatinib produces haematological and even cytogenetic responses in patients in myeloid blast crisis, the rate of relapse and the data on resistance at that stage of disease⁵⁴ strongly suggest the need to combine imatinib with other therapies.⁵⁵

In addition to combinations with chemotherapy, farnesyl-transferase inhibitors (FTI) represent a new class of agents that target signal transduction pathways responsible for proliferation and survival of diverse malignant cell types. FTIs have shown activity in advanced leukaemia⁶⁶ and the combination with imatinib may be another rational strategy to increase the

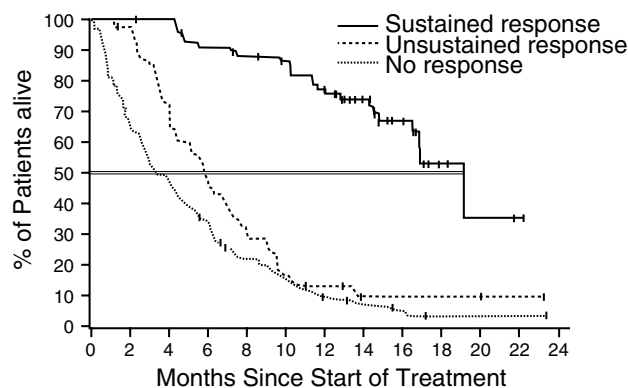


Figure 7 Median survival time according to response in patients in blast crisis treated with imatinib. Adapted from Sawyers *et al.*¹⁰ Median survival time was 19 months for the 70 patients with a sustained response, 6 months for the 49 patients with an unsustained response, and only 3 months in the 110 patients with no documented response during treatment with imatinib.

Table 4 Frequency of t(9;22) Among CD19⁺ ALL Patients

	CD10 ⁺ /CD34 ⁺	CD10 ⁺ /CD34 ⁻	CD10 ⁻ /CD34 ⁺	CD10 ⁻ /CD34 ⁻
Ph ⁻	35	11	24	7
Ph ⁺	34 (46%)	2 (15%)	7 (23%)	0

Adapted from Czuczman *et al*⁶⁸ Ph⁺ positive refers to patients that were bcr-abl positive by molecular assay and/or had a t(9;22) karyotype.

cytogenetic response rate and improve survival in advanced stage CML.⁶⁷

Therapies for Ph⁺ ALL

ALL is a heterogeneous group of diseases characterised by malignant proliferation and accumulation of immature lymphoid cells within the bone marrow, blood and lymphoid organs. Features of a B-lineage phenotype occur in ~80% of patients.⁶⁸ Depending on their immunophenotypic characteristics, as well as their karyotype and molecular genetics, leukaemic cells in ALL will be variably sensitive to systemic therapies.⁶⁸

A subset of ALL patients harbour the Ph chromosome, which is known to be associated with poor prognosis.⁶⁹ It is important to identify these patients rapidly in order to offer the most appropriate therapy. Within the B-cell-lineage group (characterised by the CD19⁺ marker), the subgroup with the CD10⁺/CD34⁺ markers has a statistically higher than expected number of Ph⁺ cases (Table 4).⁶⁸ The frequency of Ph⁺ ALL increases with age and can represent up to 44% of all patients older than 50 years.⁷⁰ Molecular testing with FISH or RT-PCR can confirm the diagnosis of Ph⁺ ALL within a day of initial presentation.

The HyperCVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and ara-C) can achieve a complete response in up to 90% of newly diagnosed Ph⁺ ALL patients, but the disease-free survival rate is only 7%.⁷¹ Other chemotherapy programmes have produced similar results. Allogeneic SCT can produce disease-free survival rates of up to 65% of patients,⁷² clearly indicating that patients with Ph⁺ ALL, like patients in myeloid blast crisis, are candidates for transplantation.

Imatinib produces initial extremely rapid cyto-reduction in patients with Ph⁺ ALL or lymphoid blast crisis, but patients invariably relapse, sometimes explosively.⁷³ Combinations of imatinib and the HyperCVAD regimen and other regimens are being evaluated and may be useful to prolong the clinical response sufficiently to identify a donor for these patients. Other combination studies using imatinib either simultaneously or in sequence with chemotherapy are being developed.

Conclusion

The optimal fashion in which to incorporate imatinib in the treatment of CML will require further study. Although the rates of responses to imatinib have been dramatic, the durability and the possible long-term side effects are unknown. Several prospective clinical trials are being planned to investigate imatinib in combination with other antileukaemic therapies to improve the depth and durability of responses.

The only curative therapy, SCT, in spite of recent advances, is linked to high early mortality in older patients and the effects of imatinib on the outcome of SCT are still under investigation.

IFN- α therapy is associated with serious side effects, although for the category of patients with a low-risk prognostic score it offers a 10-year survival rate of 40%. For patients who show no response to IFN- α , imatinib is clearly the drug of choice.

Recent data indicate that for newly diagnosed patient with CML in the chronic phase, imatinib induces higher haematologic and cytogenetic response rates compared to IFN- α + ara-C.³⁴ with preliminary evidence suggesting a delay in time to disease progression and to progression to accelerated phase or blast crisis. These results have already changed the treatment algorithm of CML, such that most newly diagnosed patients are offered treatment with imatinib.

In advanced phases of CML or Ph⁺ ALL, treatment with imatinib and/or other investigational drugs may prolong survival enough to find a related or unrelated donor and can be useful as a 'bridge' therapy to allogeneic transplantation.

References

- Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. *Science* 1960; **132**: 1497–1497.
- Rowley JD. Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 1973; **243**: 290–293.
- Kantarjian HM, Dixon D, Keating MJ, Talpaz M, Walters RS, McCredie KB *et al*. Characteristics of accelerated disease in chronic myelogenous leukemia. *Cancer* 1988; **61**: 1441–1446.
- Gale RP, Hehlmann R, Zhang MJ, Hasford J, Goldman JM, Heimpel H *et al*. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. The German CML Study Group. *Blood* 1998; **91**: 1810–1819.
- Anonymous. Hydroxyurea versus busulphan for chronic myeloid leukaemia: an individual patient data meta-analysis of three randomized trials. Chronic myeloid Leukemia Trialists' Collaborative Group. *Br J Haematol* 2000; **110**: 573–576.
- Silver RT, Woolf SH, Hehlmann R, Appelbaum FR, Anderson J, Bennett C *et al*. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. *Blood* 1999; **94**: 1517–1536.
- Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S *et al*. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-abl positive cells. *Nat Med* 1996; **2**: 561–566.
- 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**: 645–652.
- Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti-Passerini C, Guilhot F *et al*. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 2002; **99**: 1928–1937.
- Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG *et al*. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* 2002; **99**: 3530–3539.
- Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE *et al*. Prognostic discrimination in 'good-risk' chronic granulocytic leukemia. *Blood* 1984; **63**: 789–799.
- Sokal JE, Baccarani M, Russo D, Tura S. Staging and prognosis in chronic myelogenous leukemia. *Semin Hematol* 1988; **25**: 49–61.
- Hasford J, Pffirmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC *et al*. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. *J Natl Cancer Inst* 1998; **90**: 850–858.

- 14 Huntly BJ, Reid AG, Bench AJ, Campbell LJ, Telford N, Shepherd P et al. Deletions of the derivative chromosome 9 occur at the time of the Philadelphia translocation and provide a powerful and independent prognostic indicator in chronic myeloid leukemia. *Blood* 2001; **98**: 1732–1738.
- 15 van Rhee F, Szydlo RM, Hermans J, Devergie A, Frassoni F, Arcese W et al. Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: a report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 1997; **20**: 553–560.
- 16 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**: 254–261.
- 17 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**: 223–229.
- 18 Bonifazi F, de Vivo A, Rosti G, Guilhot F, Guilhot J, Trabacchi E et al. Chronic myeloid leukemia and interferon- α : a study of complete cytogenetic responders. *Blood* 2001; **98**: 3074–3081.
- 19 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**: 1038–1042.
- 20 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**: 1031–1037.
- 21 Hochhaus A, Weisser A, La Rosee P, Emig M, Muller MC, Saussele S et al. Detection and quantification of residual disease in chronic myelogenous leukemia. *Leukemia* 2000; **14**: 998–1005.
- 22 Le Gouill S, Talmant P, Milpied N, Daviet A, Ancelot M, Moreau P et al. Fluorescence *in situ* hybridization on peripheral-blood specimens is a reliable method to evaluate cytogenetic response in chronic myeloid leukemia. *J Clin Oncol* 2000; **18**: 1533–1538.
- 23 Duba HC, Hilbe W, Mehringer A, Erdel M, Thaler J, Utermann G. Hypermetaphase and interphase fluorescence *in situ* hybridisation for monitoring of remission status in Philadelphia chromosome positive chronic myeloid leukaemia. *Int J Oncol* 2000; **17**: 1245–1249.
- 24 Tamura S, Saheki K, Takatsuka H, Wada H, Fujimori Y, Okamoto T et al. Early detection of relapse and evaluation of treatment for mixed chimerism using fluorescence *in situ* hybridization following allogeneic hematopoietic cell transplant for hematological malignancies. *Ann Hematol* 2000; **79**: 622–626.
- 25 Schoch C, Schnitter S, Bursch S, Gerstner D, Hochhaus A, Berger U et al. Comparison of chromosome banding analysis, interphase- and hypermetaphase-FISH, qualitative and quantitative PCR for diagnosis and for follow-up in chronic myeloid leukemia: a study on 350 cases. *Leukemia* 2002; **16**: 53–59.
- 26 Cross NC, Feng L, Chase A, Bungey J, Hughes TP, Goldman JM. Competitive polymerase chain reaction to estimate the number of BCR-ABL transcripts in chronic myeloid leukemia patients after bone marrow transplantation. *Blood* 1993; **82**: 1929–1936.
- 27 Hochhaus A, Lin F, Reiter A, Skladny H, Hehlmann R, Goldman JM et al. Quantitative molecular methods to monitor the response of CML patients to interferon-alpha. *Bone Marrow Transplant* 1996; **17** (Suppl 3): S41–S44.
- 28 Mensink E, van de Locht A, Schattenberg A, Linders E, Schaap N, Geurts vK et al. Quantitation of minimal residual disease in Philadelphia chromosome positive chronic myeloid leukaemia patients using real-time quantitative RT-PCR. *Br J Haematol* 1998; **102**: 768–774.
- 29 Preudhomme C, Revillion F, Merlat A, Hornez L, Roumier C, Duflos-Grardel N et al. Detection of BCR-ABL transcripts in chronic myeloid leukemia (CML) using a 'real time' quantitative RT-PCR assay. *Leukemia* 1999; **13**: 957.
- 30 Emig M, Saussele S, Wittor H, Weisser A, Reiter A, Willer A et al. Accurate and rapid analysis of residual disease in patients with CML using specific fluorescent hybridization probes for real time quantitative RT-PCR. *Leukemia* 1999; **13**: 1825–1832.
- 31 Hochhaus A, Reiter A, Skladny H, Reichert A, Saussele S, Hehlmann R. Molecular monitoring of residual disease in chronic myelogenous leukemia patients after therapy. *Recent Results Cancer Res* 1998; **144**: 36–45.
- 32 Hochhaus A, Reiter A, Saussele S, Reichert A, Emig M, Kaeda J et al. Molecular heterogeneity in complete cytogenetic responders after interferon-alpha therapy for chronic myelogenous leukemia: low levels of minimal residual disease are associated with continuing remission. German CML Study Group and the UK MRC CML Study Group. *Blood* 2000; **95**: 62–66.
- 33 Goldman JM, Druker BJ. Chronic myeloid leukemia: current treatment options. *Blood* 2001; **98**: 2039–2042.
- 34 Druker B for the IRIS (International Randomized IFN vs STI571) Study Group. STI571 (Gleevec/Glivec, imatinib) versus interferon (IFN)+cytarabine as initial therapy for patients with CML: results of a randomized study. *Proc Am Soc Clin Oncol* 2002; **21**: 1a (Abstract).
- 35 Chronic Myeloid Leukemia Trialists' Collaborative Group. Interferon alpha versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials: Chronic Myeloid Leukemia Trialists' Collaborative Group. *J Natl Cancer Inst* 1997; **89**: 1616.
- 36 The Italian Cooperative Study Group on Myeloid Leukemia. Long-term follow-up of the Italian trial of interferon-alpha versus conventional chemotherapy in chronic myeloid leukemia The Italian The Italian Cooperative Study Group on Chronic Myeloid Leukemia. *Blood* 1998; **92**: 1541–1548.
- 37 Kantarjian HM, Giles FJ, O'Brien SM, Talpaz M. Clinical course and therapy of chronic myelogenous leukemia with interferon-alpha and chemotherapy. *Hematol Oncol Clin North Am* 1998; **12**: 31–80.
- 38 Mughal TI, Goldman JM. Chronic myeloid leukaemia: a therapeutic challenge. *Ann Oncol* 1995; **6**: 637.
- 39 Sawyers CL. Chronic myeloid leukemia. *N Engl J Med* 1999; **340**: 1330–1340.
- 40 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.
- 41 Hehlmann R, Hochhaus A, Kolb HJ, Hasford J, Gratwohl A, Heimpel H et al. Interferon-alpha before allogeneic bone marrow transplantation in chronic myelogenous leukemia does not affect outcome adversely, provided it is discontinued at least 90 days before the Procedure. *Blood* 1999; **94**: 3668–3677.
- 42 Brunstein CG, McGlave PB. The biology and treatment of chronic myelogenous leukemia. *Oncology (Huntingt)* 2001; **15**: 23–31.
- 43 Baron F, Frere P, Fillet G, Beguin Y. Treatment of leukemia relapse after allogeneic hematopoietic stem cell transplantation by donor lymphocyte infusion and STI-571. *Haematologica* 2001; **86**: 993–994.
- 44 Wassmann B, Klein SA, Scheuring U, Pfeifer H, Martin H, Gschaidmeier H et al. Hematologic and cytogenetic remission by STI571 (Glivec) in a patient relapsing with accelerated phase CML after second allogeneic stem cell transplantation. *Bone Marrow Transplant* 2001; **28**: 721–724.
- 45 Kantarjian H, O'Brien S, Cortes J, Giral S, Rios M, Shan J et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. *Blood* 2002; **299**: 100.
- 46 Barrett J, Childs R. Non-myeloablative stem cell transplants. *Br J Haematol* 2000; **111**: 6–17.
- 47 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**: 962–968.
- 48 McGlave PB, Shu XO, Wen W, Anasetti C, Nademanee A, Champlin R et al. Unrelated donor marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the national marrow donor program. *Blood* 2000; **95**: 2219–2225.
- 49 Lee SJ, Klein JP, Anasetti C, Antin JH, Loberiza FR, Bolwell BJ et al. The effect of pretransplant interferon therapy on the outcome of unrelated donor hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia in first chronic phase. *Blood* 2001; **98**: 3205–3211.

- 50 Margolis J, Borrello I, Flinn IW. New approaches to treating malignancies with stem cell transplantation. *Semin Oncol* 2000; **27**: 524–530.
- 51 Merx K, Muller MC, Kreil S, Lahaye T, Paschka P, Schoch C *et al*. Early reduction of BCR–ABL mRNA transcript levels predicts cytogenetic response in chronic phase CML patients treated with imatinib after failure of interferon alpha. *Leukemia* 2002; **16**: 1579.
- 52 Stentoft J, Pallisgaard N, Kjeldsen E, Holm MS, Nielsen JL *et al*. Kinetics of BCR–ABL fusion transcript levels in chronic myeloid leukemia patients treated with STI571 measured by quantitative real-time polymerase chain reaction. *Eur J Haematol* 2001; **67**: 302.
- 53 Graham SM, Jorgensen HG, Allan E, Pearson C, Alcorn MJ, Richmond L *et al*. Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 *in vitro*. *Blood* 2002; **99**: 319.
- 54 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**: 876–880.
- 55 Hochhaus A, Kreil S, Corbin AS, La Rosee P, Muller MC, Lahaye T *et al*. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. *Leukemia* 2002; **16**: 2190.
- 56 Branford S, Rudzki Z, Walsh S, Grigg A, Arthur C, Taylor K *et al*. High frequency of point mutations clustered within the adenosinetriphosphate-binding region of BCR/ABL in patients with chronic myeloid leukemia or Ph-positive acute lymphoblastic leukemia who develop imatinib (STI571) resistance. *Blood* 2002; **99**: 3472.
- 57 Roumiantsev S, Shah NP, Gorre ME, Nicoll J, Brasher BB, Sawyers CL *et al*. Clinical resistance to the kinase inhibitor STI-571 in chronic myeloid leukemia by mutation of Tyr-253 in the Abl kinase domain P-loop. *Proc Natl Acad Sci USA* 2002; **99**: 10700.
- 58 von Bubnoff N, Schneller F, Peschel C, Duyster J. BCR–ABL gene mutations in relation to clinical resistance of Philadelphia-chromosome-positive leukaemia to STI571: a prospective study. *Lancet* 2002; **359**: 487–91.
- 59 Sawyers CL. Research on resistance to cancer drug Gleevec. *Science* 2001; **294**: 1834.
- 60 Cortes JE, Talpaz M, Kantarjian H. Chronic myelogenous leukemia: a review. *Am J Med* 1996; **100**: 555–570.
- 61 Schiffer CA. Acute myeloid leukemia in adults: where do we go from here. *Cancer Chemother Pharmacol* 2001; **48** (Suppl 1): S45–S52.
- 62 Dann EJ, Anastasi J, Larson RA. High-dose cladribine therapy for chronic myelogenous leukemia in the accelerated or blast phase. *J Clin Oncol* 1998; **16**: 1498–1504.
- 63 Sacchi S, Kantarjian HM, O'Brien S, Cortes J, Rios MB, Giles FJ *et al*. Chronic myelogenous leukemia in nonlymphoid blastic phase: analysis of the results of first salvage therapy with three different treatment approaches for 162 patients. *Cancer* 1999; **86**: 2632.
- 64 Giles FJ, Cortes JE, Baker SD, Thomas DA, O'Brien S, Smith TL *et al*. Troxacitabine, a novel dioxolane nucleoside analog, has activity in patients with advanced leukemia. *J Clin Oncol* 2001; **19**: 762–771.
- 65 Giles FJ, Kantarjian HM, Kornblau SM, Thomas DA, Garcia-Manero G, Waddelow TA *et al*. Mylotarg (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. *Cancer* 2001; **92**: 406–413.
- 66 Karp JE, Kaufmann SH, Adjei AA, Lancet JE, Wright JJ, End DW. Current status of clinical trials of farnesyl transferase inhibitors. *Curr Opin Oncol* 2001; **13**: 470–476.
- 67 Hoover RR, Mahon FX, Melo JV, Daley GQ. Overcoming STI571 resistance with the farnesyl transferase inhibitor SCH66336. *Blood* 2002; **100**: 1068.
- 68 Czuczman MS, Dodge RK, Stewart CC, Frankel SR, Davey FR, Powell BL *et al*. Value of immunophenotype in intensively treated adult acute lymphoblastic leukemia: cancer and leukemia Group B study 8364. *Blood* 1999; **93**: 3931–3939.
- 69 Westbrook CA, Hooberman AL, Spino C, Dodge RK, Larson RA, Davey F *et al*. Clinical significance of the BCR–ABL fusion gene in adult acute lymphoblastic leukemia: a Cancer and Leukemia Group B Study (8762). *Blood* 1992; **80**: 2983–2990.
- 70 Secker-Walker LM, Craig JM, Hawkins JM, Hoffbrand AV. Philadelphia positive acute lymphoblastic leukemia in adults: age distribution, BCR breakpoint and prognostic significance. *Leukemia* 1991; **5**: 196–199.
- 71 Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M *et al*. Results of treatment with hyper-CVAD, a dose-intensive regimen in, adult acute lymphocytic leukemia. *J Clin Oncol* 2000; **18**: 547.
- 72 Snyder DS. Allogeneic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Biol Blood Marrow Transplant* 2000; **6**: 597.
- 73 Ottmann OG, Druker BJ, Sawyers CL, Goldman JM, Reiffers J, Silver RT, Tura S, Fischer T, Deininger M, Schiffer CA, Baccarini M, Gratwohl A, Hochhaus A, Hoelzer D, Fernandes-Reese S, Gathmann I, Capdeville R, O'Brien S. A phase II trial of imatinib in patients with relapsed or refractory Philadelphia chromosome positive acute lymphoid leukemias. *Blood* 2002; **100**: 1965.