Role of Allogeneic Stem Cell Transplantation for Adult Chronic Myeloid Leukemia in the Imatinib Era

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Received January 6 2006; accepted March 29, 2006

**ABSTRACT**

Due to superior survival in the short to medium term, the first-generation ABL kinase inhibitor imatinib mesylate has generally supplanted all other therapies as the initial treatment of choice in chronic phase chronic myeloid leukemia. The role of allogeneic stem cell transplantation (alloSCT) has shifted from a preferred first-line therapy to a possible second- or third-line therapy. However, despite generally excellent responses to imatinib, some patients respond poorly or lose response, and the risk-benefit equation in these cases may rapidly shift in favor of the alloSCT option. These patients need to be identified as soon as possible so that the alloSCT option can be applied while they are still in controlled chronic phase. Monitoring of imatinib response in patients who have suitable donors and are potentially eligible for alloSCT needs to be frequent, sensitive, and accurate. Clear criteria for switching from imatinib therapy to the alloSCT option should be established for each patient according to the specific risk profile of the transplant. The potential efficacy and safety of clinical trials combining reduced intensity alloSCT with ABL kinase inhibitor therapy warrants further consideration.

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**KEY WORDS**

Chronic myeloid leukemia ● Allograft ● Imatinib ● Kinase inhibitors

**INTRODUCTION**

The ABL tyrosine kinase inhibitor imatinib has become the standard first-line therapy for nearly all patients with newly diagnosed chronic phase chronic myeloid leukemia (CML), even though allogeneic stem cell transplantation (alloSCT) remains the only proven curative therapy. Although imatinib dramatically decreases the risk of disease progression in CML, it rarely, if ever, eradicates the leukemic clone and emerging resistance is an ongoing concern. As a consequence, patients and clinicians need to regularly review the response to imatinib and be prepared to switch therapeutic strategies if a good molecular response to imatinib is not achieved or not maintained. Based on the most recent data on the safety and efficacy of these 2 approaches, it is timely to address 2 questions: (1) Is imatinib always the best first-line option? (2) If alloSCT is reserved for second-line therapy, when should it be applied? This review discusses the current safety and efficacy of both approaches and makes some recommendations based on the evidence available, which we recognize are open to challenge and are likely to change as new evidence becomes available.

**SAFETY AND EFFICACY OF ALLOSCT IN 2005**

**Myeloablative Allografts with Sibling Donors**

The most recent large series is from the Seattle group in 2003 [1]. Between 1995 and 2000, 131 consecutive patients with CML in first chronic phase (CP1) received conditioning with targeted busulphan doses and cyclophosphamide followed by infusion of stem cells, most of which were collected from marrow (n = 100) rather than peripheral blood (n = 31). Most patients (n = 114) underwent transplantation within a year of diagnosis. The estimated probabilities at 1 year and 3 years, respectively, of nonrelapse transplant-related mortality (TRM) were 10% and 14%, of relapse 3% and 8%, and of survival 91% and 86%.
Although less relevant for early TRM than recent series, registry studies provide relevant data on long-term complications, including late relapse. An International Bone Marrow Transplant Registry (IBMTR) review documented a cytogenetic and/or hematologic relapse rate of 17% between 5 and 15 years after sibling allografting for CML-CP1 and a 5% to 7% cumulative incidence of TRM over this period [2]. Relapses may not affect substantially survival; however, because reversion to a durable second remission in most late relapses can be achieved by 1 of, or a combination of, imatinib, donor leucocyte infusion, or interferon [3-7].

Recent advances in molecular monitoring have allowed early detection of relapse after transplantation, often before cytogenetic or overt hematologic relapse [8]. Imatinib is particularly effective in inducing cytogenetic and molecular remission in this context and may be preferable to donor leukocyte infusions, which have a higher risk of graft-versus-host disease (GVHD) [4]. However, the durability of imatinib-induced remissions, the effectiveness in patients in whom imatinib before transplantation fails, and the requirement for long-term imatinib therapy in this context are issues that are not yet resolved [7].

**Myeloablative Transplants with Unrelated Donors**

An analysis by the National Marrow Donor Program of transplantations between 1988 and 1999 for CML-CP1 within a year of diagnosis found that 5-year disease-free survivals of matched unrelated recipients <30 and 30-40 years old were 61% and 57%, respectively [9]. Outcome was only significantly worse than sibling allografts if the transplantation was performed >1 year after diagnosis and/or the recipient was >30 years old.

The current situation may be a little different. Recent improvements in molecular matching of unrelated donors have led to lower TRM [10]. In a report from the Seattle group, patients <50 years old who underwent transplantation within a year of diagnosis from an HLA-A, -B, and -DRB1-matched donor and receiving modern antimicrobial prophylaxis had an estimated 3-year overall survival of 87% (95% confidence interval, 74-99) [11]. This suggests that an unrelated donor allograft may be a reasonable consideration in some younger patients without a sibling donor who have a suboptimal response or lose response to imatinib.

**Pretransplantation Factors Influencing Outcome**

The European Group for Blood and Marrow Transplantation (EBMT) registry, using transplant data from 1989 to 1996, found that favorable factors were donor source (HLA-identical sibling vs unrelated), disease stage (CP1 vs later phase), recipient age (<20, 20-40, >40 years), sex combination (other vs male recipient/female donor), and time from diagnosis to transplantation (<12 vs >12 months) [12]. A prognostic EBMT scoring system derived from these factors was recently validated by a separate IBMTR study [13]. In contrast, the recent single institution Seattle study, which enrolled patients between 1995 and 2000, did not demonstrate a trend to any effect of age (<40, 40-50, >50 years) or patient/donor gender combinations (P = .55 and .42, respectively), but there was a trend for increased mortality with a longer time from diagnosis to transplantation (P = .10) [1].

**Optimal Myeloablative Conditioning Regimen**

Cyclophosphamide plus total body irradiation has been compared with busulphan plus cyclophosphamide in CP1, with no conclusive evidence that either regimen is superior with respect to overall survival and relapse or nonrelapse mortality [14].

**Stem Cell Source**

Published reports from single institutions, prospective randomized studies, and a recent meta-analysis have evaluated the outcome of peripheral blood stem cells (PBSCs) versus marrow sibling allografts for CML-CP1 (Table 1) [15-17] (Schmitz N, personal communication). The results suggest that PBSCs pro-

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<th>Table 1. PBSC Versus BM-Related Donor Allografts for CML-CP1*†‡</th>
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*BM indicates bone marrow; NA, not available.
†All HLA-matched sibling donors apart from a small number of mismatched related donors (17 of 556).
‡Cytogenetic or hematologic, not molecular.
duce a lower cytogenetic and hematologic relapse rate and a higher incidence of extensive chronic GVHD, with no effect on TRM or survival, with the latter presumably due to effective salvage. Although there are insufficient data from these papers to evaluate the effect of chronic GVHD on quality of life (QOL), other reports have demonstrated poorer QOL with extensive chronic GVHD [18]. In the Seattle series of predominantly narrow allografts, only 10% of survivors had a Karnofsky score <80% [1].

Effect of GVHD on Outcome

A retrospective EBMT analysis of >4000 allografts for CML-CP1 found that survival was best in patients with limited chronic GVHD because the risk of relapse was (1) equivalent to that of extensive chronic GVHD with lower TRM or (2) lower than that of no chronic GVHD with equivalent TRM [19]. Overall, these studies suggest that given (1) the increased risk of extensive chronic GVHD with PBSCs and its adverse effect on QOL and (2) the absence of a survival advantage with PBSCs, marrow is the preferred source of stem cells for sibling allografts in CML-CP1, at least in patients without prior exposure to imatinib. However, it is conceivable that prior imatinib resistance increases the risk of relapse after allografting, in which case PBSCs may be preferable due to the lower risk of relapse. There are insufficient data to recommend a preferred stem cell source for unrelated donor allografts.

Reduced Intensity Conditioning

Reduced intensity conditioning regimens such as fludarabine (flu)-busulphan have been associated in a small series of patients with CML and relatively short follow-up with a low risk of TRM and relapse [20]. Nevertheless, a concern is that the incidence and severity of chronic GVHD may not be substantially different after reduced intensity compared with myeloablative PBSC allografts [21]. There are conflicting data as to whether the graft-versus-CML effect obviates aggressive conditioning and allows very low dose regimens such as flu/low-dose total body irradiation [22] or flu-cyclophosphamide [23] to be effective. A retrospective EBMT analysis suggested a lower risk of relapse with flu-busulphan compared with flu-cyclophosphamide or low-dose total body irradiation, but the numbers of patients in CP1 included in this study were too small to draw definitive conclusions [24]. A promising experimental approach that warrants further assessment is initial disease reduction with imatinib followed by a reduced intensity allograft (see Future Prospects section).

Autografts

In the pre-imatinib era there was considerable interest in autografting for CML in patients without an allograft option by using unpurged Philadelphia chromosome-positive (Ph+) stem cells collected at diagnosis or in vivo purged predominantly Philadelphia chromosome-negative (Ph-) stem cells collected after interferon or chemotherapy [25,26]. Current recommendations in Australasian Leukemia Group studies have included the collection of granulocyte colony-stimulating factor mobilized PBSCs in imatinib-treated patients who achieve a complete cytogenetic response (CCR) [27]. The rationale is to consider a later autograft by using these cells if there is subsequent progression. In practice there is little current experience with this approach because the vast majority of patients have maintained their response to imatinib in the short to medium term.

SAFETY AND EFFICACY OF IMATINIB IN 2005

The pivotal International Randomized Study of Interferon Versus STI571 (IRIS) study in newly diagnosed CML compared imatinib 400 mg daily with interferon-α and cytosine arabinoside. After an average of 38 months of follow-up, 96% of patients receiving imatinib achieved a complete hematologic response (CHR), 88% a major cytogenetic response (MCR; Ph+ >65%), and 81% a CCR [28]. The estimated progression-free survival at 42 months was 84%; progression in this context was defined as the development of accelerated phase (AP) or blast crisis (BC), loss of CHR or MCR, or death from any cause. The incidence of AP or BC was approximately 2% per year for the first 3 years of follow-up, with a lower incidence (9%) in the fourth year. Most responding patients had progressive improvement in their molecular response, as defined by quantification of BCR-ABL, even in the third or fourth year of therapy [29]. Longer follow-up is clearly required, however, because, even in responding patients, there are concerns about the long-term risk of resistance. The ongoing risk of mutations in a study of mainly late chronic phase patients was approximately 5% in each of the first 2 years after achieving CCR [30].

Early results from nonrandomized dose escalation studies have demonstrated a higher rate of MCR and CCR and superior molecular responses by 12 months compared with historical controls receiving 400 mg [31,32]. Whether this superior early response ultimately translates into lower rates of progression and improved long-term survival is unknown. These issues will be addressed by the recently activated randomized studies, which compare daily doses of 400 with 800 mg of imatinib as initial therapy.
COMPARISONS BETWEEN IMATINIB AND ALLOGENEIC TRANSPLANTATION

Survival

Figure 1 compares the short-term survival curves of patients with CML-CP1 and treated with imatinib with those undergoing HLA-identical sibling allografting as reported by the Center for International Blood and Marrow Transplant Research (CIBMTR). Although these groups may not be equivalent with respect to age and underlying prognostic factors (median age, 50 years; 62% male in IRIS study; median age, 37 years; 58% male in CIBMTR cohort), it is clear that early survival is higher in the imatinib group. It is not known when or if these survival curves will cross with longer follow-up. If the survival curve for imatinib recipients eventually falls below that of allograft recipients, it seems likely, based on current trends, that the crossover point will be well beyond 10 years.

Using the cytogenetic response data from the IRIS study and long-term survival data according to cytogenetic response from a prior study with interferon and low-dose cytosine arabinoside, the estimated life expectancy after treatment with imatinib alone was 15.3 years [33]. This estimate does not take into account strategies to improve the cytogenetic response such as higher initial doses of imatinib, dose escalation in suboptimal responders, newer more potent tyrosine kinase inhibitors, or the effect of an allograft in patients who do not respond to imatinib or respond but whose disease subsequently progresses.

Molecular Remission

A German group recently compared the durability of molecular remissions in imatinib versus allograft recipients [34]. The projected risk of molecular relapse at 12 months after the first negative molecular test was 83% versus 20%, respectively, suggesting that the “quality” of molecular remission was superior in the allograft group. This may reflect a more gradual decrease in the rate of leukemia on imatinib therapy. For this reason, imatinib recipients tend to fluctuate between polymerase chain reaction positive and negative for a longer period before becoming consistently polymerase chain reaction negative. However, <20% of patients treated with imatinib for 3 to 4 years have BCR-ABL transcript levels consistently below the level of detection [29], in contrast to most allograft survivors.

Complete eradication of CML is unlikely with imatinib alone because primitive, quiescent Ph+ stem cells are insensitive to imatinib in vitro and bcr-abl–positive CD34 progenitors may persist in long-term recipients of imatinib [35,36]. Although the “emergence” of abnormal clones in Ph− cells has been reported, its long-term significance is unclear because cytogenetic abnormalities are often transient, seen in only a few metaphases and not generally associated with morphologic evidence of myelodysplasia [37,38]. Advanced myelodysplasia or acute myeloid leukemia was observed in only 2 of 1186 patients with CML (.1%), both with monosomy 7, who were treated with imatinib at MD Anderson [39].
Quality of Life

The QOL of 51 long-term survivors after allografting (mainly marrow) for CML was recently reported [40]. Compared with an age-adjusted reference population, transplantation survivors had impaired role function and cognition and sexual functioning, but relatively normal scores for physical function. The published QOL data for imatinib is not directly comparable, but generally the drug does not significantly adversely affect physical function and well-being [41]. Serious side effects of imatinib include pneumonitis [42], severe skin reaction [43], renal failure [44], hepatic necrosis [45], and various fluid retention syndromes such as pleuroperticardial effusions [46], cardiac tamponade [47], cerebral edema [48], and severe periorbital edema that causes visual obstruction [49]. However, these are uncommon and, unlike severe GVHD, usually rapidly reversible with cessation of therapy without long-term sequelae.

Myeloablative allografts cause infertility in most patients, although spermatogenesis may recur in some men [50]. The effect of imatinib on male and female fertility is largely unknown. Azoospermia has been reported in a single case [51], but the frequency, severity, and reversibility of sperm count reduction has not been characterized in an interpretable cohort of patients. When relevant, sperm cryopreservation before commencing imatinib should be discussed. Although pregnancies in partners of male patients have usually resulted in the birth of health infants [52], data are limited and sexually active males should be advised to use contraception. Similarly, the effect of imatinib on fertility and pregnancy outcome in women has not been comprehensively studied. Although pregnancies in partners of male patients have usually resulted in the birth of health infants [52], data are limited and sexually active males should be advised to use contraception. Similarly, the effect of imatinib on fertility and pregnancy outcome in women has not been comprehensively studied. Although a recent series suggested there was no evidence that brief exposure to imatinib during conception and pregnancy adversely affected development [53], fatal and severe nonfatal congenital abnormalities have been reported [54]. These observations, together with teratogenicity in rats, means that administration of imatinib to pregnant women currently poses an unacceptable risk and effective contraception should be used during therapy to prevent pregnancy.

Donor Searches for Patients on Imatinib

For younger patients who are potential candidates for an allograft if their response to imatinib is suboptimal or they develop resistance, is it necessary to proceed with a donor search immediately after diagnosis? Because >80% of patients will not have an indication for allografting in the first 5 years, the cost effectiveness of this approach needs to be considered. However, based on the IRIS study, 3% to 5% of de novo patients will develop resistance in the first year, 5% to 10% will have a suboptimal response, and the occasional patient may suddenly develop rapidly progressive disease [55]. Because a search for an unrelated donor can often take many months, donor searches immediately after diagnosis are probably justified for patients who would be considered potential allograft candidates if they develop resistance to medical therapy.

IS IMATINIB THE BEST FIRST-LINE OPTION FOR ALL DE NOVO CHRONIC PHASE CML PATIENTS?

Although it is generally accepted that most patients with de novo CML should receive imatinib as first-line therapy, it is possible that a subset of patients could be identified who would be expected to respond poorly to imatinib and might be appropriate candidates for a first-line allograft. With currently available prognostic indicators, can such a group be identified?

Factors Predictive of a Suboptimal Response to Imatinib

There are a number of in vitro and clinical features that may be useful in identifying patients with a poor or suboptimal response to imatinib who may benefit from an allograft.

The Sokal and Hasford prognostic scores are somewhat discriminatory. The rates of CCR by 12 months in Sokal high, intermediate, and low groups are 49%, 67%, and 76%; the respective rates of major molecular response (MMR; >3 log reduction in BCR-ABL) are 18%, 30%, and 50% [56]; and those of estimated survival at 42 months are 84%, 91%, and 94% [28]. Of note, Sokal risk group is not discriminatory for survival in patients achieving a CCR [28]. Investigators have demonstrated that in vitro sensitivity to imatinib-induced inhibition of ABL kinase activity is predictive of molecular response in de novo CML, particularly in patients with a low Sokal score [57]. There is somewhat conflicting literature on whether imatinib overcomes the adverse prognostic significance of deletions of the derivative chromosome 9 [58,59]. Of note, allografting reverses the poor prognosis of this abnormality [60].

Overall, however, none of these variables is sufficiently predictive in their current form to argue against a trial of imatinib in a specific patient subset. In current practice it is the early response to imatinib that is more clinically relevant.

Clinically Relevant Definition of Suboptimal Response to 400 mg/d

Hematologic. To our knowledge, there are no published data on the outcome in the small percentage of patients, in the order of 6% to 7%, who do not achieve a CHR within the first 6 months. However, it is likely that the outcome of these patients is not favorable. Failure to achieve a CHR should be confirmed with
cytogenetic and molecular analyses because persistent leucocytosis or thrombocytosis may be due to causes other than resistant disease.

Cytogenetics. Analysis of the IRIS study showed that most patients (55% to 68%) who achieved no, minimal (60% to 95% Ph+), or minor (36% to 65% Ph+) at 3 months achieved a CCR at 32 months [61]. At 6 months, the response was more discriminatory; although approximately 50% of patients with a minimal or minor response still achieved a CCR at 42 months, this occurred in only 25% of those with no response. This has led to the proposal that achieving at least a minimal cytogenetic response at 6 months is an important parameter for continuing imatinib [61]. Practically, however, the most relevant clinical endpoints are rates of progression and survival. IRIS data demonstrate that for patients who achieved MCR within 6 months, the estimated transformation-free survival (transformation defined as accelerated or blastic phase) at 30 months is 97% versus 89% for those who did not (P < .001). The estimated survival at 30 months for the same patients was 97% versus 92%, respectively (P = .02). Achievement or not of a MCR at 12 months appears to be even more discriminatory, with the rate without progression to AP/BC at 42 months being 97% and 73% (P < .001) and estimated survival at this time being 95% and 83% (P < .001), respectively [28]. Failure to achieve CCR (equivalent to a >2 log reduction in BCR-ABL) at 12 months resulted in an approximate 19% risk of progression over the next 2 years [62].

How best to use these data in making therapeutic decisions is difficult. A key issue is whether intervention (see next section) is warranted in patients with a “suboptimal” early response who are still likely statistically to ultimately respond and have a favorable outcome. Ideally, the effect of any therapeutic intervention should be assessed prospectively in a clinical trial. In the absence of this, we argue for an aggressive approach on the basis that higher initial doses and early dose intensity have been associated with higher molecular and cytogenetic responses [31,32]. Accordingly, we contend that early dose escalation is a reasonable consideration in patients who do not achieve MCR by 6 months or CCR by 12 months, based on the significantly higher risk of transformation and death. Mutation analysis, as will be discussed, may be very useful in this context by allowing therapy tailored to drug sensitivity of the predominant leukemic clone.

Molecular. Failure to achieve a MMR by 12 months is associated with a significantly lower probability of progression-free survival over the next 3 years (93% vs 100%) [62]. However, the Australian substudy showed that a significant number of IRIS patients who had not achieved MMR at 12 months went on to achieve it by 18 months [28], but very few not in MMR at 18 months achieved MMR with longer follow-up. Therefore, failure to achieve MMR should be regarded as a suboptimal response only if not achieved by 18 months.

OPTIONS IF SUBOPTIMAL RESPONSE OR RESISTANCE TO IMATINIB

Dose Escalation

There have been no systematic studies to determine under what circumstances an increase in imatinib dose is likely to lead to an improved cytogenetic and/or molecular response. Early experience suggests that dose escalation in suboptimal responders can be associated with substantial improvements in response, particularly in those with cytogenetic rather than hematologic resistance [63]. Subsequent investigators reported that dose escalation led to durable response in only 25% of patients who did not achieve a CCR on 400 mg [64,65]. Responses were limited essentially to patients with some degree of initial Ph negativity; only 1 of 18 patients with 100% Ph+ had sustained cytogenetic improvement [64].

For patients with a suboptimal response (as defined earlier) to imatinib 400 to 600 mg/d, it is reasonable to increase the dose to 800 mg/d (or maximal tolerated dose if this is <800 mg/d). After another 3 to 6 months on the higher dose, if there has been no improvement in cytogenetic response, a change of therapy should be considered.

Mutation analysis may be very useful in determining the appropriateness of dose escalation. Patients who respond suboptimally and those with a persistent ≥2-fold increase in BCR-ABL transcript levels should ideally have analysis performed [66]. With ABL kinase mutations, there is usually a steady increase in the level of BCR-ABL transcripts, thus supporting the notion that the mutant leukemic clone is able to expand because of the relatively low level of imatinib-induced kinase inhibition in the mutant clone. Overall, the effect of dose escalation in patients with mutations is likely to be modest, with cytogenetic or molecular improvement in only 2 of 42 such cases reported recently by a German group [67]. Nevertheless, others have demonstrated that higher doses of imatinib can lead to a decrease in BCR-ABL transcript levels and cytogenetic improvement in selected cases in which mutation-related resistance is minor or moderate. Therefore, in the absence of alternative therapies, it seems reasonable to increase the dose of imatinib to 800 mg/d when low-level resistant mutations have emerged at lower doses. The mutant T315I, is completely resistant to imatinib in vitro and in vivo [68,69] and other mutations, particularly in the P loop, are also unlikely to respond to dose increases but this is not certain [70-72].
used only in the context of a clinical trial. Term safety and efficacy data, these drugs should be option, at present, in the absence of at least medium-imatinib-resistant disease and no allogeneic transplant represent useful additional therapies in patients with inhibitor of BCR-ABL[77]. Although these agents may another novel adenosine triphosphate competitive in- promising activity has been described with AMN107, quiescent CML stem cells to this agent[76]. A phase native therapy as soon as suboptimal response is iden- donors, an allograft is a reasonable first-choice alter- nate therapy as soon as suboptimal response is ident- ified. The “salvageability” of imatinib-resistant CML by allografting is a crucial issue, but there are limited published data thus far. A retrospective review from the Seattle and City of Hope groups demonstrated a 1-year survival of 93% in 28 CP patients previously treated with imatinib, but only a minority had imatinib-resistant disease or clonal evolution [78]. The prolonged use of imatinib before transplantation did not appear to adversely affect TRM.

Unavailability of New Inhibitors or Allografting

The options in this circumstance include ongoing imatinib, hydroxyurea, interferon, homoharringtonine, or experimental therapy within a trial setting. There is conflicting and indirect evidence on the usefulness of ongoing imatinib in the context of cytoge- netic resistance. Two studies have compared the sur- vival of patients who did not respond to interferon-α and subsequently obtained no cytogenic response to imatinib, with historical controls not responding to interferon-α and subsequently managed with conven- tional, non-imatinib therapy. The MD Anderson group reported a survival benefit for imatinib; a Brit- ish group found the opposite [79,80].

We are not aware of published clinical studies evaluating the role of interferon-α or autografting for imatinib-resistant disease. Interferon-α appears to act against CML stem cells, which may harbor mutations and be resistant to imatinib whose action is directed primarily against committed CML progenitors [81]. An Australian study is currently evaluating the addi- tion of pegylated interferon to imatinib in patients with persistent BCR-ABL positivity. Preliminary re- sults of the addition of homoharringtonine to imatinib in patients with persistent BCR-ABL positivity after imatinib alone are promising, with a decrease in tran- script level in all 10 patients enrolled [82].

**New Tyrosine Kinase Inhibitors**

Dasatinib (BMS-354825, Bristol-Myer Squibb, Wallingford, CT) is a dual SRC/ABL kinase inhibitor with >300-fold greater potency in vitro than imatinib and preclinical activity against most imatinib-resistant BCR-ABL mutants [73]. Preliminary results of a phase 1 dose escalation study have demonstrated promising activity of this agent in patients with imatinib intolerance or resistance [74]. In 40 patients in CP, the rates of CHR, MCR, and CCR were 88%, 40%, and 33%, respectively, with responses maintained at a median follow-up of 13 months. MMR occurred in 4 of 19 evaluated patients [75]. Of concern is the emergence of the resistant T3151 mutation in 6 of 33 patients who received BMS-354825 for CP or AP/BC, which was associated in each case with significant increases in BCR-ABL transcript levels [75] and the resistance of quiescent CML stem cells to this agent [76]. A phase II study using 70 mg twice daily is ongoing. Similar promising activity has been described with AMN107, another novel adenosine triphosphate competitive in- hibitor of BCR-ABL [77]. Although these agents may represent useful additional therapies in patients with imatinib-resistant disease and no allogeneic transplant option, at present, in the absence of at least medium-term safety and efficacy data, these drugs should be used only in the context of a clinical trial.

**Allograft**

At this time we recommend an allograft, if available, and the anticipated TRM is “acceptable” as the intervention of choice in patients with a suboptimal response to imatinib who do not respond to dose escalation or who have a resistant mutation. In some circumstances, such as younger patients with sibling donors, an allograft is a reasonable first-choice alter- native therapy as soon as suboptimal response is iden- figure. 2. Suggested monitoring and treatment algorithm for patients with newly diagnosed CML-CP1 receiving imatinib. QPCR indicates quantitative polymerase chain reaction.

**Figure 2.** Suggested monitoring and treatment algorithm for pa-

patients with newly diagnosed CML-CP1 receiving imatinib. QPCR indicates quantitative polymerase chain reaction.

**Figure 3.** Suggested approach to suboptimal response to imatinib 400 mg/d in the absence of mutational analysis. CHR indicates complete hematologic response; MCR, major cytogenetic response (Ph~ >65%); CCR, complete cytogenetic response; MMR, major molecular response (>3 log reduction in BCR-ABL).
RECOMMENDATIONS

Figures 2 and 3 summarize a proposed monitoring and therapeutic algorithm for patients with newly diagnosed CML-CP1, based on the preceding discussion. We recommend an initial trial of imatinib in all patients and initiating a donor search in those whom transplantation is an option if imatinib is ineffective. In the absence of mutational analysis, an initial trial of increased dose of imatinib is recommended in suboptimal responders, with an allograft or a second-generation inhibitor (if available) recommended if there is no improvement over the subsequent 3 to 6 months. Note, however, that in patients who do not achieve a MMR at 18 to 24 months, the risk of AP/BC over the next 3 to 4 years is only 5% to 10%, so the specific risk profile for each patient of intervention with an allograft needs to be very carefully considered in this context. For example, in the context of imatinib resistance, transplantation would be the therapy of choice in a younger patient with a compatible sibling, but a trial of a second-generation inhibitor may be preferred in a patient with a high-risk EBMT score.

In reality, each patient with CML will have a unique mixture of clinical factors such as age, disease response, mutation status, comorbidities, and donor characteristics. Accordingly, recommendations as outlined in Figures 2 and 3 can be used only as broad guidelines and therapeutic decisions have to be individualized. To illustrate this, Table 2 presents the outcome with various treatment alternatives (imatinib dose escalation, new tyrosine kinase inhibitors, allografting) in 3 hypothetical clinical scenarios, noting that the new inhibitors are only currently available in clinical trials.

ACCELERATED PHASE CML

The MD Anderson group recently reported their experience with imatinib for CML-AP, describing a CCR of 43% and an estimated 4-year survival of 53%, the latter results comparable with allografting [87]. In comparison with 400 mg, imatinib doses of 600 mg improved cytogenetic responses, duration of response, and overall survival [88]. AP defined by clonal evolution alone responded particularly well to imatinib, with a CCR of 60% and no treatment failures at 1 year in a cohort of 15 patients [89]. In contrast, results with imatinib are worse in patients with other hematologic evidence of AP and particularly poor in those with hematologic criteria and clonal evolution.

Accordingly, imatinib is a reasonable initial option at presentation in patients with CML-AP defined only by clonal evolution or in patients with other hematologic criteria for AP at high risk for early allograft TRM according to the EBMT score, with an allograft reserved for patients with failure to achieve an early cytogenetic response or in whom progression occurs after an initial favorable response.

BLAST PHASE CML

Imatinib is not generally effective as a single agent in CML-BP, with a low incidence of MCR and a median survival of 6 to 7 months, although a small number of patients has ongoing hematologic responses up to 2 years after therapy [90,91]. Toxicity is less and response rates higher with imatinib compared with standard cytarabine combinations [91]. Results for allografting in CML-BP have generally been poor, although the outcome appears better for patients with chemosensitive disease transplanted in second CP [92].

For patients who present in CML-BP, have not previously received imatinib, and are eligible for a transplant, it is reasonable to promptly allograft those who achieve a hematologic response, sustained at least in the short term, to imatinib. An allograft is probably inappropriate in patients resistant to imatinib or conventional chemotherapy and a trial of the newer tyrosine kinase inhibitors, if available, should be considered.

SYNGENEIC TRANSPLANTS

Rarely, patients with CML will have an identical twin. The largest series of syngeneic transplants for CML described a low TRM (3% at 3 years) but a high relapse rate, approaching 60% at 52 months after transplantation [93]. These transplants have been associated with GVHD, particularly from parous donors [94], but it is not known whether this translates into a clinically relevant graft-versus-CML effect. A syngeneic transplant, using myeloablative conditioning and with imatinib before and after transplantation, is a reasonable consideration in eligible patients.

FUTURE PROSPECTS

Several groups are evaluating treatment with imatinib to reduce the CML burden followed by a reduced intensity allograft [95] or the reverse, ie, a reduced intensity allograft followed by imatinib [96]. Preliminary results suggest a low TRM with these approaches but longer-term follow-up is needed to ascertain whether durable remissions can be achieved. Potential studies include (1) myeloablative versus reduced intensity conditioning allografts versus newer tyrosine kinase inhibitors for imatinib-resistant disease and (2) reduced intensity allografts versus ongoing imatinib for imatinib-responsive disease.
Table 2. *Three Hypothetical Scenarios*

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<td>30-y-old male. After 6 mo of imatinib (400 mg), loss of molecular and CG response. T315I mutation. AP on marrow. One antigen mismatched (at DRB1), female donor (age 25 y).</td>
<td>Unlikely to be effective as mutant highly resistant to imatinib [71]</td>
<td>Inactive in vitro and probably in vivo against T315I mutant [73, 75]</td>
<td>EBMT score does not distinguish between matched and mismatched unrelated donors or analyze donor age. DRB1 mismatch associated with worse 5-y survival for unrelated donor allografts for CML-CP1 (30 ± 10% vs 45 ± 5% if matched) [83]. Allograft</td>
</tr>
<tr>
<td>45-y-old female. After 15 mo of imatinib (400 mg), loss of molecular and CG response with G250E (P loop) mutation, CP on marrow. Sibling donor (age 55 y).</td>
<td>Unlikely to respond as most P-loop mutations, relatively resistant in vitro to imatinib [71], but clinical data limited</td>
<td>Preliminary data suggest activity against all P-loop mutants [73, 77], but durability of response not established</td>
<td>Increasing donor age reduces 5-y survival for matched and mismatched unrelated allografts [84]. Second-generation tyrosine kinase inhibitor or allograft</td>
</tr>
<tr>
<td>55-y-old male. 40% Ph* after 12 mo of imatinib (400 mg). No mutation. Sibling donor.</td>
<td>≥20% chance achieving CCR at 24 mo and approximately 18% risk of progression by 30 mo with no change in dose [61, 85]. Increase to 800 mg likely to improve CG response [63].</td>
<td>Limited data. In phase I study, BMS-354825 produced cytogenetic improvement in 40% patients in late CP intolerant/resistant to imatinib [74]. Data awaited on phase II studies with BMS-354825 and AMN107.</td>
<td>Minimal data on allograft outcome in imatinib-resistant CML, including optimal intensity of conditioning regimen in this context. Fludarabine/low-dose busulphan conditioning associated with improved overall survival and lower TRM compared with cyclo-TBI* in patients &gt;50 y [86]. Increased imatinib dose; if no response second-generation tyrosine kinase inhibitor in the context of a clinical trial or reduced intensity conditioning allograft</td>
</tr>
</tbody>
</table>

*Cyclo-TBI indicates cyclophosphamide plus total body irradiation.*
CONCLUSIONS

Based on the most recent data available for alloSCT and imatinib, it seems reasonable for clinicians to recommend to all patients with newly diagnosed CML-CP1 an initial trial of imatinib therapy, reserving alloSCT for second-line therapy. Selected younger patients with an estimated low risk of TRM who express a clear preference for a potentially curative approach, despite the clinician’s recommendation, could still be offered an upfront alloSCT.

Although imatinib has been a major advance in terms of a greatly decreased risk of early death, the vast majority of patients will be left with a need for life-long therapy and the possibility of resistance and disease progression some time in the next 5 to 20 years. Future progress with effective combination therapy may further improve the outlook for these patients on long-term imatinib therapy. In the short term, the most important issue for patients treated with imatinib is regular and accurate disease monitoring so that the minority with suboptimal response or early resistance can be identified at a stage when other modalities, including allografting, can be effectively applied.

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