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Unmet Needs in the Management of Chronic Myelogenous Leukemia

Discussants

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Abstract: Approximately 5,000 cases of chronic myelogenous leukemia (CML) are diagnosed each year in the United States. The introduction of tyrosine kinase inhibitors (TKIs) has dramatically improved survival time for many CML patients. Current first-line treatment options include imatinib and the second-generation agents nilotinib and dasatinib. Second- and third-line agents include nilotinib, dasatinib, bosutinib, and the new agent ponatinib. Despite the effectiveness of TKIs, some patients develop resistance or intolerance to these agents. A number of mutations of the *BCR-ABL* gene have been identified and are associated with TKI resistance. Patients may benefit from switching to a second-line TKI, undergoing hematopoietic stem cell transplant, or receiving newly emerging agents. Although early response is associated with improved patient outcome, clinicians lack tests that can determine which patients will benefit from which therapies. To ensure adequate response, patients should be monitored by both polymerase chain reaction and cytogenetic analysis of the bone marrow. This roundtable monograph reviews key unmet needs in patients with CML related to disease management and treatment options.

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Table of Contents

Chronic Myelogenous Leukemia: Current Approaches to Management

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Chronic myelogenous leukemia (CML) is a type of cancer known as the chronic myeloid proliferative neoplasms, which are characterized by the proliferation and accumulation of cells in the bone marrow. Approximately 5,000 cases of chronic CML are diagnosed each year in the United States.[1] Most patients with CML have a translocation of chromosomes 9 and 22, resulting in an abnormally short chromosome 22, called the Philadelphia chromosome. This translocation forms the *BCR-ABL* fusion gene that causes the overproduction of tyrosine kinase. In turn, too many abnormal white blood cells (blasts) are generated that do not grow or die like typical white blood cells.

Patients often present with symptoms that may be caused by a number of conditions. These symptoms include fatigue, weight loss, night sweats, fever, pain or fullness below the ribs on the left side, easy bleeding, and frequent infections. CML may also cause no symptoms at all. Physical examination, patient history, complete blood count with differential, and bone marrow aspiration and biopsy are used to diagnose CML. A cytogenetic analysis is performed on the blood or bone marrow samples; fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) assays are used to analyze the samples for the presence of the Philadelphia chromosome or the *BCR-ABL* gene.

Since the discovery of the *BCR-ABL* oncogene, a treatment has been developed to target this oncoprotein, thus completely changing the outcome of CML. Prior to the clinical introduction of tyrosine kinase inhibitors (TKIs) in 2001, patient outcome was very poor, with a survival of only 3–5 years. Today, patients with CML can have a normal lifespan, with a projected median survival of 25 years or longer for those patients who take their medication and achieve a good response. Currently, the 10-year survival is 90%, with an estimated mortality of 1% or less per year.[1]

Management of CML

The first TKI, imatinib, was approved in 2001.[2] Other agents approved since then include the second-generation drugs nilotinib and dasatinib, as well as the recently approved drug bosutinib.[3-5] As of 2010, both nilotinib and dasatinib were approved for the frontline management of CML. Thus, the frontline treatment options for patients with CML are imatinib, nilotinib, and dasatinib; the second-line treatment options are nilotinib, dasatinib, and bosutinib. Additionally, ponatinib is a very promising drug that may soon receive approval for treatment of CML.[6] For those patients in advanced-stage disease who have not responded to treatment with a TKI, hematopoietic stem cell transplant (HSCT) remains an option. Given the effectiveness of these therapies, CML has become like any chronic disease, such as hypertension, for which patients can be expected to have a normal lifespan provided they are taking their medication as prescribed.

Recommendations for the expected TKI treatment milestones were published in 2006 and 2009 by the European LeukemiaNet and were adapted by the National Comprehensive Cancer Network (NCCN).[7-9] Many patients treated with a TKI experience an early response, as assessed by cytogenetics, FISH, and PCR. Patients are monitored for treatment milestones every 3–6 months until complete cytogenetic response (the absence of Philadelphia-chromosome positive metaphases in 2 consecutive bone marrow biopsies) is achieved, after which time patients are monitored by PCR and annual bone marrow biopsies.[8,9] If the treatment is effective, at 3–6 months, the *BCR-ABL* transcript levels should be 10% or less using the International Scale (IS), and there should be at least a partial response on bone marrow cytogenetics; patients are then followed every 3 months by PCR. At 1 year, patients should have *BCR-ABL* transcript levels of 1% or less on the IS for complete cytogenetic response. Patients who do not reach these milestones should be considered for a different treatment option.

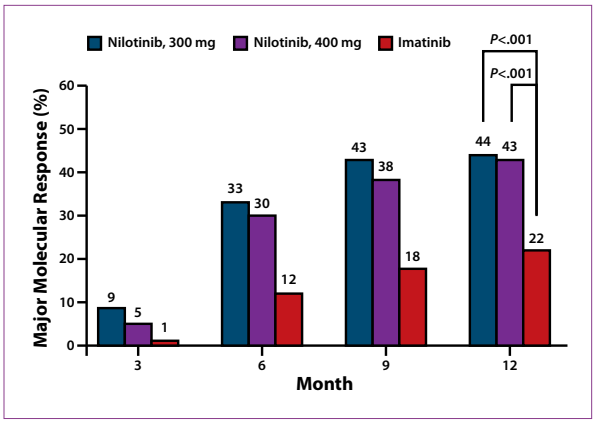

Figure 1. Rates of major molecular response in the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients) trial. Adapted from Saglio G et al. *N Engl J Med*. 2010;362:2251-2259.[12]

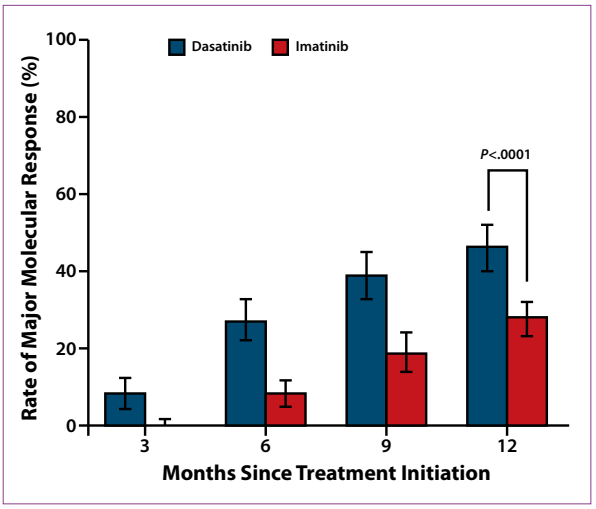

Figure 2. Rates of major molecular response in the DASISION (Dasatinib versus Imatinib Study in Treatment-Naive CML Patients) trial. Adapted from Kantarjian H et al. *N Engl J Med*. 2010;362:2260-2270.[13]

The overall goal of treatment is to induce a complete molecular response or undetectable level of disease. Hopefully, this will indicate that these patients are cured. A preliminary study in France, the STIM (Stop Imatinib) trial, indicated that patients who can achieve such a level of response might be candidates for cure.[10] The study enrolled 100 patients on imatinib who had been in complete molecular response for a minimum of 2 years before treatment discontinuation. Of the patients with a follow-up of at least 12 months, 61% relapsed; however, those patients who relapsed responded to retreatment with imatinib. Overall, the probability of persistent complete molecular response at 12 months was 39%. Although promising, this study requires confirmation and further evaluation in future trials.

Among the 3 frontline treatment options, both nilotinib and dasatinib have shown superiority compared to imatinib therapy in terms of complete cytogenetic response rate, molecular response rate, and rate of progression (Figures 1 and 2).[11,12] However, it remains unclear whether all newly diagnosed patients should be treated with one of these second-generation inhibitors. Although patients who do achieve an early response have a better outcome, and second-generation TKIs do improve the rate of early response, improvements in overall survival have yet to be determined. For those patients who failed to respond to frontline therapy, dasatinib or nilotinib remain good treatment options. For patients who fail TKI therapy and have disease progression, ponatinib is a very promising treatment option. Ponatinib is a multi-targeted kinase inhibitor that has activity against all *BCR-ABL* mutations tested, including the panresistant T315I mutation. In preliminary data from a phase II study, ponatinib has shown promising activity in patients who failed at least 2 TKIs. Approximately 41% of patients in the chronic phase and 57% of patients with the T315I mutation achieved a complete cytogenetic response.[13]

The introduction of imatinib and other TKIs has dramatically reduced the number of allogeneic HSCTs offered to CML patients.[14] For some patients with CML, allogeneic HSCT remains an effective treatment option. HSCT should be offered in a frontline setting for patients who are in advanced-stage disease, particularly blast phase, since these patients are more likely to develop TKI resistance. In the chronic phase of disease, frontline therapy with HSCT should not be offered. However, patients in the chronic phase of disease who are harboring a T315I mutation should have TKI therapy and blast chemotherapy followed by HSCT. HSCT remains a good treatment option for patients with TKI-resistant mutations and for patients who have had poor responses to frontline treatment with a TKI. Otherwise, if patients fail the frontline treatment with a TKI, they should be treated with a second TKI. Transplant is used as a third-line treatment option.

In summary, the outcome of CML has completely changed. Today, patients are expected to have a normal lifespan. There are several effective agents, but what remains of major prognostic value for the long-term outcome is early response, whether it is assessed molecularly or by cytogenetic response. Patients who have a good response early on are expected to have a great outcome, whereas those who do not should be considered for alternative options such as clinical trials, new agents, ponatinib, and HSCT.

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Unmet Needs in CML Management With Currently Available Therapies

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The clinical introduction of TKIs has revolutionized the outcomes and expectations for patients with newly diagnosed chronic phase CML (CP-CML). Results from trials with frontline imatinib appear untouchable at first glance. However, close review of the 5 largest frontline imatinib trials for patients with chronic phase disease shows that, on average, 25% of patients will fail to achieve complete cytogenetic response or will lose their previously obtained complete cytogenetic response by 18 months, an endpoint that has been associated with poor event-free survival and poor overall survival.[1] When coupled with those experiencing primary or secondary resistance, as well as those with intolerance, it has been estimated that approximately one-third of patients will no longer maintain therapy with imatinib after 5 years.[2]

As Dr. Jabbour noted, 3 additional second-generation TKIs have been subsequently approved for patients with relapsed or intolerant chronic phase disease: dasatinib, nilotinib, and bosutinib. In the phase II START (SRC/ABL Tyrosine Kinase Inhibition Activity Research) trial, dasatinib demonstrated activity in patients with imatinib resistance or intolerant disease.[3] The START C and START R trials demonstrated that among patients with imatinib-resistant disease, approximately 50% achieved a major cytogenetic response and 40% achieved a complete cytogenetic response with dasatinib treatment.[4] However, estimates indicated that approximately 20% of those patients will lose the response within the first 18 months. As a result, only 30% of patients will remain on second-line dasatinib after changing therapy. Likewise, nilotinib has been evaluated in patients with imatinib-resistant or intolerant disease.[5] Again, approximately 50% of patients achieved a major cytogenetic response, and 40% achieved a complete cytogenetic response. The progression-free survival was estimated to be 70% at 18 months and 50% at 36 months. Similar to dasatinib, approximately 30% of patients receiving second-line nilotinib will remain on therapy long-term. Bosutinib has also demonstrated activity in patients with imatinib-resistant or imatinib-intolerant disease.[6] Results are similar to those seen with

dasatinib and nilotinib; approximately 50% of patients achieved a major cytogenetic response rate, and 40% achieved a complete cytogenetic response rate with bosutinib treatment. Once again, only 20–30% of patients will remain on long-term bosutinib therapy.

All 3 second-generation TKIs have also been evaluated in pivotal phase III clinical trials in patients with newly diagnosed chronic phase disease.[7-9] Despite demonstrated enhanced cytogenetic and molecular response rates compared with imatinib, the rates of primary and secondary resistance, as well as intolerance, remain significant. A recent study by Larson and colleagues indicates that approximately 30% of patients receiving nilotinib 300 mg twice daily have discontinued therapy after a median follow-up of 3 years.[10] Similar results have been noted for those receiving frontline dasatinib, with approximately 25% discontinuing treatment within the first 2 years.[11] The follow-up for patients receiving frontline bosutinib was short (median follow-up, 13.8 months), and yet 28% of patients had already discontinued therapy.[9]

Once patients have failed a second-generation TKI, few consensus guidelines exist for subsequent therapy; there is only a limited amount of clinical data in these specific patient populations. Ibrahim and colleagues published their experience in 26 patients failing imatinib and at least 1 additional TKI.[12] Approximately 50% of patients achieved a major cytogenetic response, and 35% achieved a complete cytogenetic response. Unfortunately, the 30-month event-free survival and overall survival were only 45%. A study by Garg and associates also demonstrated limited responses, with only 25% of patients achieving a major cytogenetic response and 12% of patients achieving a complete cytogenetic response with third-line therapy.[13] At the 2-year follow-up, the event-free survival and overall survival rates were only 50%. Nilotinib has also been evaluated in 39 CP-CML patients who failed prior treatment with imatinib and bosutinib.[14] A major cytogenetic response was achieved by 43% of patients, and a complete cytogenetic response was achieved by 24% of patients. Unfortunately, by 18 months of follow-up, only 59% of patients were progression-free. Bosutinib has also been evaluated in patients with resistance to imatinib and at least 1 additional TKI.[15] Of the 118 patients with chronic phase disease who were evaluated, 32% achieved a major cytogenetic response and 24% achieved a complete cytogenetic response. The estimated 2-year progression-free survival was 73%, with higher rates of continued therapy seen in patients who were treated for intolerant disease.

Tyrosine kinase domain mutations have been identified in patients with resistant disease, including those treated with multiple TKIs. There are at least a half dozen proposed mechanisms of TKI resistance; however, mutational testing remains the only approved test for patients with resistant disease. Current NCCN and European LeukemiaNet guidelines recommend mutational testing in patients with TKI-resistant disease.[16,17] The *BCR-ABL* kinase domain mutation (*BCR-ABL* KD) has been identified in approximately 50% of patients with secondary resistance to imatinib; more than 90 mutations have been identified to date. The 7 most common mutations in imatinib-resistant patients are the E255K/V, T315I, M351T, Y253H, H396R/P, G250E, and F359V mutations.[18] Although the presence of a mutation never guarantees that it alone is the sole driving force behind the resistance, current European LeukemiaNet guidelines set recommendations for second-line therapy based upon the specific mutations present.[18] Likewise, the current 2013 NCCN guidelines also prompt recommendations based upon specifically identified mutations; however, these recommendations are not based upon randomized trials.[16] Ibrahim and coworkers previously noted that treatment of patients with multi-TKI–resistant disease did not exhibit changes in major cytogenetic response rates based upon the presence or absence of mutations. Forty-five percent of patients with no identified mutations achieved a major cytogenetic response compared to 53% of patients with an identified mutation.[12] The study by Garg and colleagues also examined response rates based on the presence or absence of mutations in CML patients who received nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors (Figure 3).[13] Among those chronic phase patients treated with dasatinib in third-line therapy, 7 of 10 achieved a major cytogenetic response when the mutation was present, whereas only 1 of 4 achieved the same milestone when a mutation was not present. When nilotinib was administered as third-line therapy, 4 of 7 patients achieved a major cytogenetic response when the mutation was present compared to 0 of 2 patients when a mutation was not present. Giles and associates evaluated nilotinib as third-line therapy following failure of imatinib and dasatinib therapies.[14] Of the 25 chronic phase patients evaluated, 12 had *BCR-ABL* mutations, and response rates were similar regardless of the presence or absence of mutations. A major cytogenetic response was achieved in 3 of 12 patients when a mutation was present, and 4 of 12 patients achieved that same milestone when no baseline mutation was present. None of the 4 patients with the T315I mutation achieved a response. There were no data regarding the presence of new mutations during third-line therapy in either the dasatinib or the nilotinib studies noted above.

Khoury and coworkers evaluated the response to bosutinib based on the presence or absence of mutations.[15] A similar response rate was observed regardless of mutation status. A major cytogenetic response was achieved by 35% of patients without a mutation and 31% of patients with at least 1 baseline mutation. Emergent mutations were seen in 9 patients throughout the clinical trial.

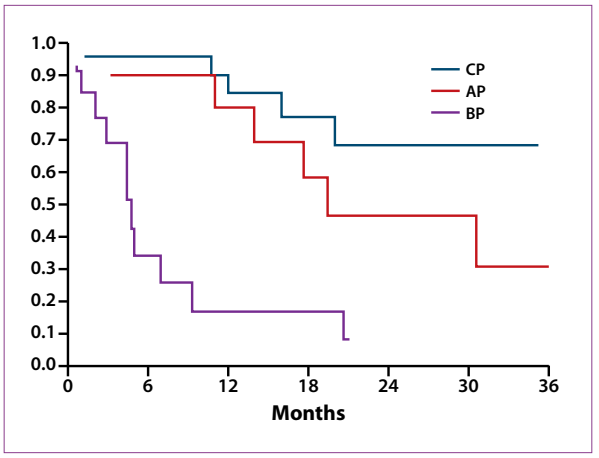

Figure 3. Overall survival in 48 chronic myeloid leukemia patients sequentially treated with 3 tyrosine kinase inhibitors. AP=accelerated phase; BP=blast phase; CP=chronic phase. Adapted from Garg RJ et al. *Blood*. 2009;114:4361-4368.[13]

Ponatinib has also been evaluated in both phase I and phase II settings for patients with multi-TKI–resistant disease. Among 43 patients with chronic phase disease treated on the phase I trial, 98% achieved a complete hematologic response, 72% achieved a major cytogenetic response, and 63% achieved a complete cytogenetic response.[19] After a follow-up of approximately 1 year, 29 of 31 patients achieving a major cytogenetic response remained on-study. Response rates appeared to be higher in those patients with resistance to imatinib who were treated with 1 additional second-generation TKI versus those patients with resistance to imatinib who were treated with 2 second-generation TKIs. Notably, all 12 patients with the T315I mutation achieved a complete hematologic response, 92% achieved a major cytogenetic response, and 75% achieved a complete cytogenetic response; all patients currently remain on-study. Responses were also noted in those patients with other mutations; 67% of patients with other mutations achieved a major cytogenetic response, and 62% of patients without mutations achieved a major cytogenetic response.

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Treatment Options for CML Patients With the T315I KD Mutation

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Prior to the development of TKIs, one of the primary indications for the performance of allogeneic or donor transplants was CML. Prior to 2001 and the clinical introduction of TKIs, patients with CP-CML had a 70–80% cure rate. In contrast, patients with accelerated phase CML had a 35–45% cure rate, and patients with blast phase CML had a significantly worse cure rate of only 10–20%. At that time, there were numerous studies looking at how to improve upon outcomes in allogeneic HSCT. It was clear that patients in the blast phase would have better outcomes if they could be treated out of blast phase into a second chronic phase, where the outcome would be similar to the accelerated disease phase. In addition, there were several studies that sought to improve outcome based upon the source of stem cells (bone marrow vs peripheral blood). It was observed that transplants from unrelated donors do well, but transplants from well-matched sibling donors do better. Therefore, when the outcomes of transplants are compared to alternative medical therapy, care must be taken in defining such factors as the disease phase (chronic, accelerated, or blast), the source of the cell product that will be used for transplant (unrelated donor vs sibling donor), and the donor status.[1]

Because of these studies, scoring systems were developed to minimize risk and facilitate the determination of whether a patient should undergo a transplant. One such scoring system that was useful in the pre-TKI era, as well as today, is the European Bone Marrow Transplant (EBMT) score. The EBMT risk assessment includes age (20–40 years vs older than 40 years), the disease stage (early, intermediate, or late), time from diagnosis to transplant (less than 12 months or more than 12 months), human leukocyte antigen identical sibling donor versus any other type of donor, and sex of the recipient versus the donor (female donor to male recipient does worse than any other donor-recipient sex match).

HSCT Prior to the TKI era

In the pre-TKI era, 70–80% of patients in chronic phase could be cured with a matched sibling donor, but these patients could also be cured by an unrelated donor, albeit at a lower rate. A 2010 study by Goldman and associates[2] analyzed data from more than 2,000 patients in CP-CML who had been in complete remission for 5 years following HSCT. The patient data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR). The 15-year overall survival rate of these patients was 88% for sibling-matched donor HSCT and 87% for unrelated donor HSCT. Interestingly, the rate of relapse was low for both sibling-matched donor HSCT (8%) and unrelated donor HSCT (2%), with the last relapse occurring 18 years after HSCT. Despite the fact that patients appeared to have been cured, there remains a small relapse rate on the order of 5% after 5 years. There is also additional non-relapse–related mortality due to transplant-related issues such as chronic graft-versus-host disease. Although the presence of graft-versus-host disease was associated with an increased mortality rate, it was also associated with a decreased rate of relapse. The overall mortality of the HSCT patients was significantly higher than matched normal populations for 14 years post-HSCT, after which time the patients with CML finally matched the life expectancy of the general population. Although the cure rate for CP-CML was very high, the HSCT treatment-related mortality was at least 10–20% due to the toxicity of the regimen and graft-versus-host disease.

HSCT in the TKI Era

Prior to the year 2001, there were approximately 5,000 HSCTs performed each year worldwide. With the introduction of the efficacious TKIs, that number fell to 500 HSCTs per year by 2009 (Figure 4).[3,4]

Since most patients on TKIs achieve a durable long-term response, during the last decade the use of allogeneic HSCT has been reserved only for those patients who fail or are likely to fail TKI therapy. Therefore, it becomes important to identify those patients who will do poorly on the TKIs. For patients with advanced disease (either accelerated phase or blast phase CML), allogeneic HSCT remains an effective treatment option. There have been several studies on this subject, most recently an analysis by Khoury and colleagues from the CIBMTR.[5] This study

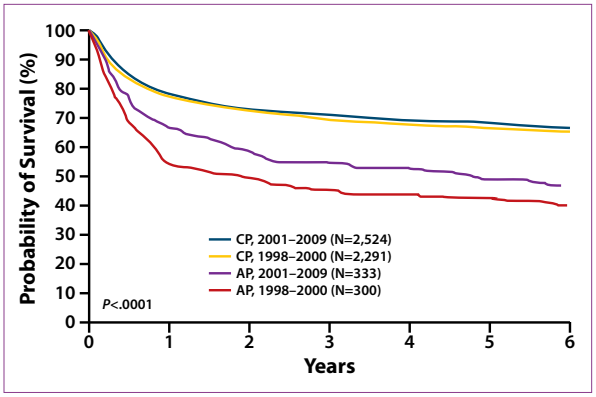

Figure 4. Probability of survival after HLA-identical sibling donor transplants for chronic myelogenous leukemia. Data are shown for 1998–2009 and stratified by disease status and transplant years. AP=accelerated phase; CP=chronic phase; HLA=human leukocyte antigen. Adapted from Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2011. Available at: http://www.cibmtr.org.[3]

suggested that patients with advanced CML who received treatment with imatinib prior to HSCT have outcomes similar to those observed in the pre-TKI era. Since the goal for patients in the blast phase is to achieve a second chronic phase before moving ahead to transplant, and TKIs have transient but significant efficiency in advanced CML, there appears to be no downside to the short-term use of TKIs on the ultimate outcome of transplant. Therefore, patients who have accelerated phase CML or blast phase CML at presentation are considered candidates for transplant. However, when evaluating patients with advanced phase CML, one difficulty is the definition of accelerated phase disease. In fact, there are some patients who present with accelerated phase disease who actually do well on TKIs and may not be candidates for transplant; it is difficult trying to assess their risk.[6,7] Unfortunately, this area has not had enough research. Clearly, there is also a group of accelerated phase patients who are presenting in a more advanced phase of disease, closer to blast phase, who are going to do poorly even with TKIs and are candidates for HSCT.

There has been a clear improvement in CML outcome with the use of imatinib and the second-generation drugs; however, there are inadequate responses in 25–35% of CP-CML patients. These patients need to respond to either a second-generation drug or are candidates for transplant. The question then becomes, which patients are candidates for transplant? One group of patients are those who fail 2 TKIs. Among patients who fail 2 TKIs, only 20–25% will respond to a third TKI, and their long-term response will be relatively poor. The issue then becomes whether we can predict which patients will do poorly on

Table 1. Indications for Bone Marrow Transplantation

Blast phase CML
Accelerated phase CML
Failure of 2 tyrosine kinase inhibitors
Failure of 1 tyrosine kinase inhibitor with the presence of a T315I mutation
Failure of 1 tyrosine kinase inhibitor and the presence of additional cytogenetic abnormalities or multiple tyrosine kinase mutations
Failure of 1 tyrosine kinase inhibitor in childhood CML

second-generation TKIs. At both the MD Anderson Cancer Center[8] and Hammersmith Hospital,[9] scoring systems are used to predict clinical outcomes on TKIs. These scoring systems include the Sokal score at diagnosis, the best cytogenetic response to initial therapy with imatinib, and the presence or absence of recurrent neutropenia on imatinib. Patients who have a high Sokal score, a poor cytogenetic response to imatinib, and neutropenia on imatinib are likely to fail treatment with a second-line TKI. In this higher risk population, one might consider HSCT in patients who fail only 1 TKI. Patients who fail 2 TKIs are almost always considered candidates for allogeneic HSCT if a well-matched donor can be found. Initial data on patients who have failed 2 TKIs suggest that the responses are going to be at least similar to those observed with CP-CML in the pre-TKI era.

Failure of 1 TKI is an indication to perform mutation testing. Those patients who have additional mutations, at least initially, appear to have a reasonable response to a second-generation drug. However, there are some patients whose mutations do not respond well to nilotinib, dasatinib, or bosutinib. If patients have these TKI-resistant mutations, the second-generation drugs may not work as well. It would be beneficial for these patients to move on to HSCT earlier rather than later. Dr. Jabbour's group recently published a study examining the outcome of HSCT in patients who failed TKI therapy after developing *BCR-ABL* KD mutations.[10] The patients with mutations were more likely to progress to accelerated phase or blast phase disease at the time of imatinib failure. These patients were further into their disease, and thus even with HSCT, the likelihood of having a good outcome was relatively poor. The 2-year event-free survival was 36% for the patients with the mutations and 58% for patients without mutations. The 2-year overall survival was 44% for the patients with the mutations compared to 76% for patients without mutations. This study implies that by the time patients are failing 1, 2, or even 3 TKIs, their disease has progressed, and they are already at higher risk of relapse. The central issue to consider is whether certain

Table 2. Outcome in the PACE Trial

	Patients With Response (%)		
Outcome	**Overall (N=267)**	**Resistant/Intolerant Cohort (n=203)**	**T315I Cohort (n=64)**
Complete hematologic response	249 (93%)	191 (94%)	58 (91%)
Major cytogenetic response	144 (54%)	99 (49%)	45 (70%)
Complete cytogenetic response	118 (44%)	76 (37%)	42 (66%)
Major molecular response	79 (30%)	47 (23%)	32 (50%)

PACE=Ponatinib Ph+ ALL and CML Evaluation.
Adapted from Cortes JE et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30(suppl): Abstract 6503.[12]

patients should be considered for transplant earlier when they fail TKI treatment. Currently, there are few concrete data available that address this issue.

Patients with one particular mutation, the T315I mutation, are clear candidates for HSCT because of poor results following second-line and third-line therapy with TKIs. These patients also have an increased likelihood of progressing to the accelerated phase and blast phase. A presentation at the 2009 meeting of the American Society of Hematology assessed clinical outcomes in patients who underwent allogeneic HSCT after the T315I mutation was detected.[11] At the time the transplant was performed, most of the patients were in accelerated phase or blast phase CML. For those patients who underwent transplant in chronic phase (n=8), the 2- or 3-year survival was approximately 70%. The patients in the blast phase did relatively poorly, with an approximately 20% 2-year survival rate and a 0% 3-year survival rate due to relapse. Thus, patients who have the T315I mutation who underwent HSCT in the chronic phase have positive outcomes and may be cured. However, recent data from the PACE (Ponatinib Ph+ ALL and CML Evaluation) trial suggest that patients in chronic phase with the T315I mutation, who failed prior TKIs, can be successfully treated with ponatinib (Table 2).[12] These patients, most of whom had a major cytogenetic response at 1 year, had a greater than 80–90% likelihood of survival. These studies highlight that even in the best of circumstances, patients who were more than a year into their illness would still anticipate a 10% mortality rate. Further studies are necessary to determine if patients with the T315I mutation should move ahead to transplant or try one of the newer drugs, such as ponatinib.

Perhaps the strongest data for the use of allogeneic HSCT in the era of TKIs come from a study published by the German CML Study Group.[13] The study included 84 patients who underwent HSCT. The patients were divided into 3 groups: low EBMT score, imatinib failure, and advanced disease. The 3-year survival of patients with chronic phase disease (including patients with low EBMT scores or imatinib failure) was more than 90%, and the treatment-related mortality was 4%. For patients with advanced disease, the 3-year survival was 59%, and the treatment-related mortality was 10%.

In summary, HSCT is an effective treatment option for those patients who fail TKI therapy. Some patients who fail 1 or 2 TKIs are going to have poor outcomes. With these patients, the goal is to find a better way to identify them early. With early identification, these patients can move on to HSCT before they develop multiple mutations or new cytogenetic abnormalities and have a high risk of relapse. However, there are some patients with the T315I mutation who are offered transplant but may have a good response with ponatinib. Therefore, I think that the rules regarding bone marrow transplant are a work in progress.

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Dr. Akard has received research support from Pfizer, Novartis, BMS, ARIAD, and Lilly. He is an advisor for Teva, and he is on the Speakers Bureau of Novartis, BMS, Millennium, Eisai, and Celgene.

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Discussion: Unmet Needs in Chronic Myelogenous Leukemia

H&O What are the unmet needs for effective therapy in CML patients who are intolerant or resistant to dasatinib and nilotinib or who have the T315I mutation?

Luke P. Akard, MD An area of uncertainty relates to the new NCCN guidelines.[1] These guidelines suggest that our patients should have a partial cytogenetic response or at least a 1-log improvement in molecular testing at the 3-month mark. Data from published studies have found that approximately 30% of patients on imatinib and approximately 10% of patients on the second-generation TKIs do not hit this 3-month target. Patients who fail imatinib have a poor prognosis, with approximately half of these patients dying during the first 5 years of follow up.[2] For the second-generation TKIs, patients who do not reach the 3-month target tend to do poorly, with approximately 20% of patients dying prior to the passage of 3–5 years. These statistics are fairly high and discordant as compared with the less than 1% mortality rate per year for patients who are responding to TKIs. In my view, for those patients who are doing poorly, we either need to come up with a better drug that results in improved initial response, switch to a different TKI, try combination therapy, or use transplant earlier.

Elias J. Jabbour, MD An unmet need in our practice today is what we call treatment a la carte, or more personalized therapy. We have 3 options for frontline treatment: imatinib, nilotinib, and dasatinib, with the possibility of more TKIs in the future. Currently, every patient is treated blindly; although their Sokal score and Hasford score are known, these scoring systems were developed during the interferon and alkylator agent era and are not very relevant for the second-generation TKIs. In the future, better prognostic features that can tell us which patients would benefit from which drug are needed.

Today, the most relevant prognostic factor is early response. Patients who have an early response by 3–6 months typically have a great outcome. Patients who do not achieve this early response should be monitored very carefully and offered new options that become available (eg, ponatinib, clinical trials) or transplant. In addition, the introduction of a second TKI has the advantage of increasing the chance of a high early response, which may translate into improvement of overall survival.

In addition, it remains unanswered whether CML can be cured. According to the STIM study, certain patients may be cured.[3] Hopefully, over time, treatments will be developed that result in a cure for more patients with CML. This may be the result of a single agent or a combination of a TKI plus peg-interferon, hypomethylating agents, or others. Recently, several studies were reported regarding the combination of a TKI and peg-interferon.[4,5] The result was improvement in complete molecular response. Unfortunately, there was no translation into survival improvement, and there was significant toxicity. However, these results need to be confirmed.

Finally, it is important to patients that side effects of treatment be addressed. For those patients with chronic disease, the side effects, even grades 1 or 2, are also chronic. As a result, patients may discontinue their medication and could develop resistance.

Dale Bixby, MD, PhD In addition to what Drs. Akard and Jabbour already discussed, there is also a need for greater consistency in testing and treatment. Pasquini and colleagues conducted a study that evaluated what we as physicians are doing for our patients with CML, and how we are approaching patients with a possible diagnosis

of CML.[6] Unfortunately, the study found that clinicians are not closely following either the NCCN or European LeukemiaNet guidelines. The study noted that less than half of patients have a bone marrow biopsy at the time of diagnosis. As a result, we are possibly missing patients with either accelerated or blast crisis disease. In addition, the outcomes in the clinical trials that we discussed previously do not necessarily reflect what is happening in the community. In 2008, Lucas and colleagues published a study of the community experience of patients with CML in Northern England.[7] They evaluated the rate of complete cytogenetic response with imatinib using data from 11 different sites that used the same reference cytogenetics laboratory. The investigators noted that only 49% of patients achieved complete cytogenetic response while being treated in the community. Obviously, clinical trials have extensive inclusion and exclusion criteria, whereas the community experience includes a wide range of patient demographics and characteristics. Overall, I believe it is important to encourage proper assessments at the time of diagnosis to accurately understand the phasing of the disease, which has a profound impact on the effectiveness of treatment.

Another challenge in CML is proper monitoring of the disease. Different genetic techniques can be used to assess for responses, including cytogenetic assays, FISH testing, and PCR analysis. However, the recommendations for monitoring change frequently. As Dr. Akard noted, there is an increasing reliance on PCR testing in the latest version of the NCCN guidelines; however, this is dependent on the availability of laboratories that have the techniques to perform the IS scale for PCR. In fact, the most recent assessment of PCR technology in the United States found that only 25–35% of labs offer the IS scale. This leaves a significant number of patients around the United States without access to that technology.

Finally, I would like to echo Dr. Jabbour's comment on adherence. As physicians, we can be tied up in the degree of molecular response that patients have in an effort to ensure they are meeting milestones. As a result, we sometimes forget to adequately emphasize the importance of adherence to our patients. A number of studies have been published indicating the importance that adherence has in not only achieving appropriate milestones for therapy, but also maintaining those responses to treatment.[8] These studies indicated that the likelihood of achieving a major molecular response or complete cytogenetic response to frontline imatinib was best when those patients had greater than 90% adherence. In a study by Dr. Marin and colleagues, patients who had taken at least 90% of their medication were significantly more likely to achieve major molecular response and complete molecular response than patients taking less than 90%.[9] In addition, no major molecular response was observed if adherence was 80% or less, and no complete molecular response was observed if adherence was 90% or less. Likewise, the risk of losing prior cytogenetic responses was strikingly high for those with an adherence rate of less than 85%.[10] I think our patients need to hear from us that it is critically important that they maintain therapy to ensure optimal outcomes with their disease.

H&O What is the importance of diagnostic testing early and throughout care?

Elias J. Jabbour, MD First, we need an appropriate diagnosis. Many patients undergo efficient PCR and blood analysis, but that is all. CML is a disease that can be accurately diagnosed based on pathology when the bone marrow is assessed. At the time of initial diagnosis, we need to check for the Philadelphia chromosome. This diagnostic karyotype assists in obtaining accurate disease staging. Therefore, although both PCR and blood tests are beneficial, the bone marrow analysis is mandatory.

Dale Bixby, MD, PhD There is a reluctance to perform bone marrow biopsies at the time of diagnosis, and there seems to be a reluctance to confirm complete cytogenetic response by bone marrow testing. In the United States, there is a strong reliance on peripheral blood testing in an effort to prevent patients from having to undergo a bone marrow biopsy. However, one of the strongest endpoints to date that has been associated with overall survival is complete cytogenetic response. That is why it remains a strong point of emphasis in nearly all guidelines for monitoring patients with CML. Bone marrow biopsy performed at appropriate intervals ensures that patients are achieving a complete cytogenetic response. This remains an important point in the management of patients.

The appropriate time to do mutational testing is one point that commonly arises. I think there is significant disagreement around the world. In Australia, the current guidelines for mutational testing recommended by Drs. Branford and Hughes from the Adelaide Group is the presence of a two-fold rise in the patient's PCR.[11] In England, David Marin and colleagues recommend mutational testing when patients have a 5-fold rise in the burden of disease.[12] Finally, the most recent NCCN guidelines, which are based upon data coming from Dr. Jabbour's group and the MD Anderson Cancer Center experience, indicate that mutational testing should be considered when patients have a 10-fold rise or 1 log rise in the PCR.[1] Currently, there are no data to support mutational testing at the time of diagnosis, especially in those patients with chronic phase disease and patients with complete cytogenetic response. For this reason, PCR should be monitored

every 3 months in an effort to identify a patient who has taken a step backwards and is potentially demonstrating secondary resistance to therapy.

H&O Do you have any recommendations for community oncologists?

Luke P. Akard, MD In a real practical sense, the first 3 years of monitoring patients is extremely important to long-term outcomes. In the IRIS (International Randomized Study of Interferon and STI571) trial, patient problems most often occurred during the first 3 years of treatment.[13] In addition to emphasizing the importance of taking the medication, following patients appropriately in the first 3 years of therapy is absolutely critical because that is the time frame when either intolerance or lack of response will occur. It is our goal to identify those patients who are at risk of accelerated phase and blast phase and avoid these advanced phases of disease at all costs. To reach this goal, appropriate blood and bone marrow monitoring should be performed in the first 3 months of treatment and every 3 months thereafter. The United States has the unique problem of the lack of standardized quantitative *BCR-ABL* testing at commercial laboratories. I hope that will change over time as new commercial reagents that have been standardized by the IS become more widely available. At any rate, the important thing in my mind is early identification of those patients who are going to do poorly in order to find alternative treatments for them.

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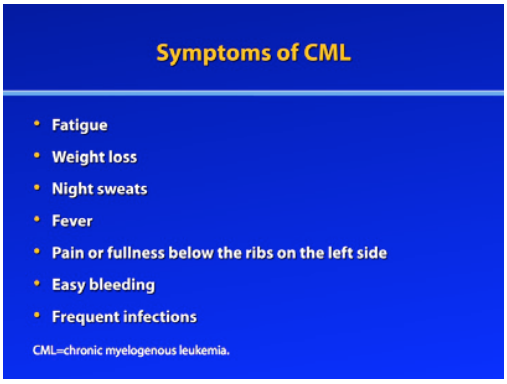

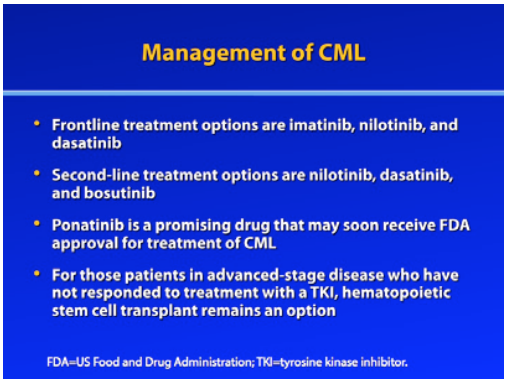

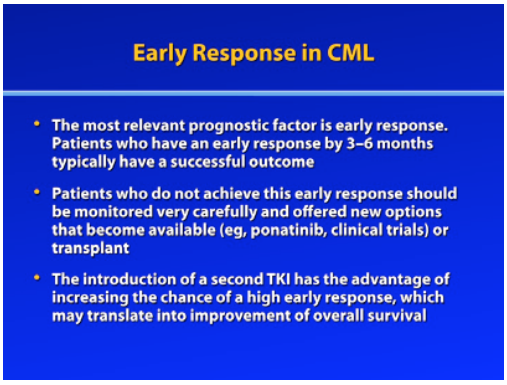

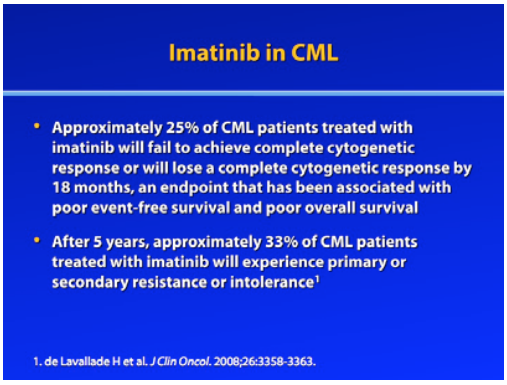

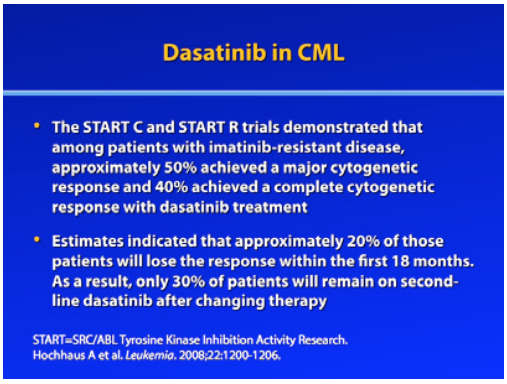

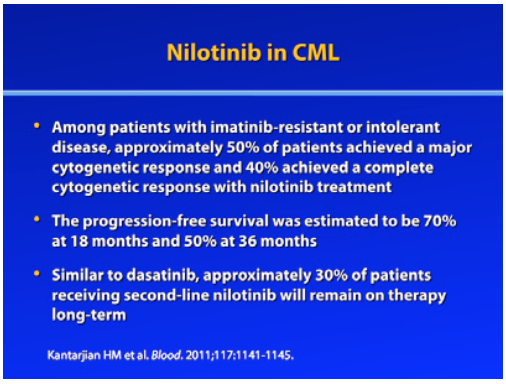

Bosutinib in CML

- Among patients with imatinib-resistant or intolerant disease, approximately 50 achieved a major cytogenetic response rate and 40% achieved a complete cytogenetic response rate with bosutinib treatment
- Only 20–30% of patients will remain on long-term bosutinib therapy

Cortes JE et al. *Blood*. 2011;118:4567-4576.

Ponatinib in CML

- Ponatinib is a multi-targeted kinase inhibitor that has activity against all BCR-ABL mutations tested, including the panresistant T315I mutation
- In preliminary data from the phase II PACE trial, ponatinib showed promising activity in patients who failed at least 2 TKIs. Approximately 41% of patients in the chronic phase and 57% of patients with the T315I mutation achieved a complete cytogenetic response

ΠΑΧΕ=Ποναπινιβ Πη+ ΑΛΛ ανδ ΧΜΛ Εϖαλυατιον.
Cortes JE et al. *J Clin Oncol*. 2012;30(suppl): Abstract 6503.

The Role of HSCT in CML

- Prior to the year 2001, there were approximately 5,000 HSCTs performed each year worldwide. With the introduction of TKIs, that number fell to 500 HSCTs per year by 2009[1,2]
- Since most patients on TKIs achieve a durable long-term response, during the last decade the use of allogeneic HSCT has been reserved only for those patients who fail or are likely to fail TKI therapy
- It is important to identify those patients who will do poorly on the TKIs. For patients with advanced disease (either accelerated phase or blast phase CML), allogeneic HSCT remains an effective treatment option

HSCT=hematopoietic stem cell transplant.
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Data from the German CML Study Group

- The study included 84 patients who underwent HSCT. The patients were divided into 3 groups: low EBMT score, imatinib failure, and advanced disease.
- The 3-year survival of patients with chronic phase disease (including patients with low EBMT scores or imatinib failure) was more than 90%, and the treatment-related mortality was 4%
- For patients with advanced disease, the 3-year survival was 59%, and the treatment-related mortality was 10%

EBMT=European Bone Marrow Transplant.
Saussele S et al. *Blood*. 2010;115:1880-1885.

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