Chronic myeloid leukemia in 2006: a perspective

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Chronic myeloid leukemia (CML) is caused by Bcr-Abl, a constitutively active tyrosine kinase that is the result of a reciprocal translocation between chromosomes 9 and 22, cytogenetically evident as the Philadelphia chromosome (Ph). Imatinib (Glivec®, Gleevec™), a specific small molecule inhibitor of Bcr-Abl, has become the standard drug therapy for CML, and has dramatically diminished the use of allogeneic stem cell transplantation. Despite unprecedented rates of complete cytogenetic response, residual disease remains detectable in the majority of patients, suggesting that imatinib fails to eradicate leukemic stem cells. In this perspective we will review what newly diagnosed patients can expect to achieve on imatinib monotherapy in 2006 and how they should be monitored. We will discuss what constitutes a suboptimal response to or a failure on imatinib therapy and which options exist for such patients. We will cover the merits of early intensification of therapy and the use of complementary strategies that aim at eradicating minimal residual disease. Lastly, we will discuss the current role of stem cell transplantation in the management of CML.

What is the standard approach to treating newly diagnosed patients and what results can be expected?

Standard dose imatinib. As the overwhelming majority of patients (at least in developed countries) are diagnosed in the chronic phase, such patients arguably constitute the most relevant group. The IRIS study compared imatinib at a dose of 400 mg daily with interferon-α plus cytarabine in 1106 newly diagnosed patients in first chronic phase.[1] At a median follow-up of 54 months, the estimated rate of complete hematologic response (CHR) was 98%, major cytogenetic response (MCR) 92% and complete cytogenetic response (CCR) 86%.[2] As shown in Table 1, these responses are still improving over those recorded at 42 months. Progression-free survival at 54 months is estimated to 84%, with 93% of patients free of progression at accelerated phase or blast crisis. Three observations from the IRIS trial deserve particular attention. First, the annual rate of overall progression may be declining (1.5% in the fourth year compared to 4.8% and 7.5% in the third and second years, respectively). Although longer follow-up is clearly required, this suggests that a plateau may be reached at some point in the future. Second, the response to imatinib appears to override pretherapeutic adverse prognostic features. This is demonstrated by the fact that 97% patients with a major molecular response (MMR, i.e. a reduction of *BCR-ABL* transcripts by 3-log or more) at 12 months were free from progression at 54 months, and none of these individuals had progressed to accelerated phase or blast crisis, regardless of pretherapeutic Sokal risk group. Progression-free survival at 54 months in patients who at 12 months had achieved a CCR but were without a MMR was still very good at 89%, with only 5% having progressed to accelerated phase or blast crisis. In contrast, among patients lacking a CCR at 12 months, 28% had progressed by 54 months, and 11% to accelerated phase or blast crisis. These data are consistent with an inverse relation between the depth of response and the risk of relapse. A paper by Colombat and colleagues[3] in this issue of Haematologica confirms this notion in a more heterogeneous cohort of 59 patients in CCR. Patients who remained positive at a molecular level throughout the follow-up period had a 33.3% risk of relapse, while no relapse was observed in patients whose disease became undetectable. Thus, the *in vivo* response appears to trump adverse pretherapeutic (Sokal) features. This is in contrast with what is seen in patients achieving CCR on interferon[4] and has implications for the choice of initial therapy; aggressive approaches such as stem cell transplantation are difficult to justify up front, without knowledge of the patient's response to imatinib. Third, data from the IRIS trial show that median *BCR-ABL* levels continue to decrease with longer follow-up, albeit at a slow pace;[5] the mean log reduction of *BCR-ABL* transcripts at 4 years was 3,[4] compared to 3.0 at 12 months. A pattern of ongoing reduction is also demonstrated by the fact that of the patients who were in CCR but not MMR at 12 months, at 54 months 69% have achieved MMR, while only 17% who were in MMR at 12 months have lost this response.

High-dose imatinib. Is there a role for high dose imatinib (>400 mg daily) or combinations of imatinib with interferon α and cytarabine up-front? Several large trials are underway that will answer this question definitively. While it is clear from phase I/II studies of such strategies that CCR and MMR are expedited, it is not yet clear whether more patients will eventually achieve these responses than would if they received standard dose imatinib. A recent update of the MD Anderson experience using high dose imatinib suggests that with time, the rate of MMR in patients treated with the standard dose has caught up with that in the high dose group.[6] However, the data also suggest that high dose imatinib may prevent early progression in some patients. Unfortunately, there is currently no predictive test available to identify these individuals up front, which implies that outside of clinical trials, 400 mg imatinib daily continues to be the standard treatment for all newly diagnosed patients in chronic phase. This notwithstanding, there may be circumstances that warrant a more aggressive approach. For example, it would be easy to justify an initial dose of 600 or 800 mg imatinib daily in a young

patient with high Sokal risk and a low risk allograft option as defined by the EBMT score.

Patients in "late" first chronic phase. It should be noted that the requirements for a *progression protective response* are much more stringent in patients with chronic phase disease in whom interferon-based therapy has failed. At 60 months follow-up in phase II trials, 69% of such patients overall were free from progression to accelerated phase or blast crisis. However, while 93.7% and 87.4% of the patients who had achieved a CCR or a partial cytogenetic response, respectively, at 3 months had not progressed to accelerated phase or blast crisis; this figure was only 55.3% for the remaining patients. Achieving MCR later than 3 months afforded significantly less protection from progression to accelerated phase or blast crisis.[7] Thus, only profound responses that occur very early are protective.

Diagnostic evaluation and disease monitoring

Evaluation at diagnosis. CML is defined as a *BCR-ABL*-positive myeloproliferative disease; this diagnosis can be established by cytogenetics, reverse transcription-polymerase chain reaction (RT-PCR), and fluorescence *in situ* hybridization (FISH). Staging to determine the disease phase and the Sokal or Hasford risk scores includes physical examination (noting spleen size and any sites of extramedullary disease), complete blood count, white blood cell differential, and a bone marrow biopsy. In addition, peripheral blood *BCR-ABL* levels should be included in the work-up. There appears to be increasing reluctance to perform bone marrow biopsies at diagnosis, and some patients are placed on imatinib with little more information than a high white cell count and detection of *BCR-ABL* by FISH. However, failure to perform a bone marrow biopsy at diagnosis may lead to critical information being missed, such as the presence of advanced disease-defining features like increased marrow blasts or basophils, which would firmly mandate a change in therapeutic strategy.

Monitoring on therapy. Current recommendations for monitoring are outlined in Table 2. Bone marrow biopsies are recommended at 6-month intervals until CCR to determine the cytogenetic response and to monitor for clonal cytogenetic evolution on therapy, which identifies patients at high risk of relapse.[8] Once CCR has been achieved, monitoring should continue with quantitative RT-PCR (qPCR) from peripheral blood at 3-month intervals. One debatable point is the question of whether routine bone marrow biopsies and marrow cytogenetic analyses should continue after CCR? As the diagnostic yield is low in the absence of a rise in *BCR-ABL* transcripts, this seems hard to justify. Some 5% of patients with cytogenetic responses have developed clonal cytogenetic abnormalities in Ph-negative cells, the spectrum of which resembles myelodysplastic syndromes. The significance of this finding is not yet clear but the limited data available suggest that progression to myelodysplastic syndrome or acute myeloid leukemia is rare.[9,10] Thus, outside of a research setting and in the absence of significant hematologic abnormalities such as cytopenias, dysplastic morphology or Ph-negative clonal cytogenetic abnormalities on preceding biopsies, regular bone marrow biopsies may not be required.

The fact that 86% of patients achieve CCR implies that qPCR will be the mainstay of monitoring for the majority of patients. The lack of consistency in reporting BCR-ABL transcript levels has been a source of considerable confusion. Fortunately, there is now a major drive underway to standardize reporting of results and to achieve consensus on some important technical issues. The most important advance from this effort may be that results of individual laboratories will be expressed on an international scale, using a laboratory-specific conversion factor. Thus, results will be comparable between laboratories, and value of 0.1% will uniformly correspond to MMR [*Hughes et al., manuscript in preparation*].

Table 1. First-line imatinib – results of the IRIS study at 24, 42 and 54 months of follow-up-

	CHR			*MCR*			*CCR*			*Survival without AP/BC*		
Months of follow-up	24	42	54	24	42	54	24	42	54	24	42	54
Estimated rate(%)	NA	98	98	88	91	92	79	84	86	96	94	93

AP: accelerated phase; BC: blast crisis; CCR: complete cytogenetic response; CHR: complete hematologic response; MCR: major cytogenetic response; NA: not available.

Table 2. Recommendations for monitoring response to imatinib.

	CBC	*Cytogenetics*	*qPCR*
Diagnosis	Weekly until stable	Prior to therapy	Prior to therapy
CHR	Every 2-4 weeks	Every 3-6 months	Every 3 months
CCR	Every 4-6 weeks	Every 12-18 months?	Every 3 months
MMR	Every 6 weeks	Every 12-18 months?	Every 3 weeks

CBC: complete blood count; CCR: complete cytogenetic response; CHR: complete hematologic response; MMR: major molecular response; qPCR: quantitative PCR for BCR-ABL.

Table 3. Therapeutic milestones on standard dose imatinib.

	3 months	*6 months*	*12 months*	*18 months*
Conservative approach	CHR	<95% Ph+	<36% Ph+	0% Ph+
Aggressive approach	<95% Ph+	<35% Ph+	MMR	MMR

CHR: complete hematologic response; MMR: major molecular response.

What constitutes failure of standard dose imatinib?

Primary resistance. As imatinib response appears to determine the risk of disease progression, monitoring for unsatisfactory response is crucial to identify patients at risk of progression. An emerging concept is to grade responses at critical evaluation points as *failure*, *suboptimal*, or *optimal*. Conservative milestones of response include achievement of CHR by 3 months, evidence of cytogenetic response by 6 months, and MCR by 12 months (Table 3). Non-achievement of these threshold responses defines imatinib treatment failure and warrants a change in therapy. At 6 months, a suboptimal response could be defined as a failure to attain MCR and at 12 months as failure to achieve CCR. Establishing criteria for an *optimal* response prior to the 12-month time point is more difficult. While it is obvious that CCR or even MMR should be achieved as early as possible, only patients with failure or suboptimal responses are clearly identified as being at high risk, while the differences between all other patients may be rather small. That said, achieving MMR at 12 months is optimal as it is associated with a zero risk of progression to accelerated phase or blast crisis at 54 months. The milestones proposed here are recommendations, not dogmas, and therapeutic goals need to be defined within a clinical context. For example, in a young individual with a low risk transplant option, CCR at 6 months may be defined as the minimum acceptable response, while even a minor cytogenetic response at 12 months may be a reasonable goal in an elderly patient with significant imatinib-related toxicity.

Secondary resistance. There is consensus that loss of CHR, confirmed loss of partial or complete cytogenetic response or a confirmed 30% increase of Ph-positive metaphases define relapse. Given that most patients achieve CCR, defining molecular relapse is of greater clinical relevance. In one study a single 2-fold rise of *BCR-ABL* transcripts was highly predictive of mutations in the kinase domain of *BCR-ABL* and subsequent relapse.[11] In the same study, patients with stable or declining *BCR-ABL* transcript levels had a negligible risk of kinase domain mutations or relapse. A study by Wang *et al*.[12] in this issue of Haematologica failed to confirm this stringent association. However, confirmation of a 2-fold rise on a subsequent test was highly predictive of kinase domain mutations. It is not clear what underlies this discrepancy; one possibility is fluctuations in assay performance, varying from laboratory to laboratory. Wang's study concurs with our own experience in Oregon and may represent a more realistic litmus test for molecular relapse. Overly rigid definitions of molecular relapse may lead to an unacceptable rate of false-positive *calls*, if applied irrespective of the individual laboratory's performance. A reasonable compromise may be to consider a 5 to 10-fold rise of *BCR-ABL* transcripts significant and necessitating a repeat test within a short time frame.

How should imatinib failure be managed?

A crucial observation from studies of patients with acquired resistance to imatinib was that Bcr-Abl signaling is reactivated at the time of resistance. This implies that Bcr-Abl remains the optimal target even at the time of relapse and has driven the search for alternative approaches to restore target inhibition. There is evidence in the majority of patients with acquired resistance of either increased expression of Bcr-Abl or, more frequently, mutations in the kinase domain of Bcr-Abl that interfere with drug binding.[13] Crystal structure analysis of the Abl kinase domain in complex with imatinib proved to be instrumental for understanding mutation-mediated imatinib resistance.[14] Unexpectedly, imatinib was found to capture a unique inactive conformation of the kinase, which explained its high level of specificity. Mutations that involve direct contact points between imatinib and Abl impair binding by eliminating crucial bonds or by steric hindrance. Other mutations prevent structural adjustments required to accommodate imatinib or stabilize the active conformation of Bcr-Abl, to which imatinib cannot bind. Both types of resistance can be overcome by alternative Abl inhibitors that exhibit increased potency or capture additional conformations of the Abl kinase. Two of these compounds are in phase I/II trials and have demonstrated very encouraging clinical activity. AMN107 was developed from the imatinib scaffold, with replacement of the piperazinyl group by imidazole, eliminating two energetically unfavorable hydrogen bonds.[15] As a result AMN107 is approximately 20-fold more potent than imatinib in kinase and cell proliferation assays.[16] In contrast, dasatinib (formerly BMS354-825) was initially developed as a Src kinase inhibitor but turned out to be an extremely potent inhibitor of Abl, with approximately 300-fold greater activity than imatinib.[17] Both agents are active against most imatinib-resistant kinase Abl mutants, with the notable exception of the T315I mutant, which is completely resistant to imatinib, AMN107 and dasatinib. In phase I and II studies both AMN107 and dasatinib demonstrated impressive activity[18–23] (Table 4). More than 80% of patients with imatinib resistant CML in chronic phase achieved CHR and more than 30% of patients achieved CCR. As follow-up is still short, these rates are likely to increase with time. Responses in patients in accelerated phase were also impressive and appear to be mostly stable. Even in patients with myeloid blast crisis, there are significant rates of MCR and CCR, appearing to exceed those seen in the phase II study of imatinib. Overall the results at least match the results of the early trials with imatinib in patients with advanced CML. Given these excellent results, treatment with an alternative Abl kinase inhibitor is probably the best drug therapy option available for patients with primary or acquired resistance to imatinib.

Will T315I emerge as the default mutation? The dasatinib trials suggest this may be the case, as none of the patients with T315I achieved a significant response and T315I was regularly found in patients with acquired dasatinib resistance. However, some other mutations could also be relevant. F317L and T315A were detected in two patients with relapse and there appeared to be a low cytogenetic response rate in chronic phase patients with the E255K mutation. These data correlate well with

Table 4. Responses to AMN107 and dasatinib, with IRIS trial (imatinib) data for comparison.

Drug	Studied population	Phase	Hematologic Response	CHR(%)	Cytogenetic Response	Minor CyR	MCR(%)	CCR(%)	Median follow-up (months)	Reference
Imatinib	New diagnosis CML	III	NR	98	NR	NR	92	86	54	2
AMN107 AP	Imatinib-refractory CP CML	I	NR	92	53	18	NR	35		
	Imatinib-refractory AP CML	I	76	50	55	NR	12	14		
	Imatinib-refractory MBC CML	I	42	33	29	NR	17	4	5	18
	Imatinib-refractory LBC CML, Ph+ ALL	I	33	NR	22	11	NR	11		
Dasatinib/ BMS354825	Imatinib-refractory or intolerant CP CML	I	NR	93	NR	NR	45	35	15*	19
		II	NR	90	NR	NR	45	33	6	21
	Imatinib-refractory AP CML	I	81	45	NR	NR	27	18	6*	19
		II	59	33	37	6	31	21	6	20
	Imatinib-refractory MBC CML	I	61	35	NR	NR	35	26	5*	19
		II	51	24	42	12	30	27	6	23
	Imatinib-refractory LBC CML, Ph+ ALL	I	80	70	NR	NR	80	30	2.5*	19
		II	38	26	NR	NR	54	NR	6	22

ALL: acute lymphoblastic leukemia; AP: accelerated phase; CCR: complete cytogenetic response; CP: chronic phase; LBC: lymphoid blast crisis; MBC: myeloid blast crisis; MCR: major cytogenetic response; NR: not reported.

in vitro data and suggest that mutations in addition to T315I may have clinical significance, although much more remains to be learned. Data for AMN107 are not yet available but one might expect analogous findings. Given that apart from T315I, there does not seem to be cross-resistance between AMN107 and dasatinib, there is a strong rationale for combination therapy approaches. Consistent with this, a very low incidence of resistant clones was observed with an AMN107/dasatinib combination in a saturation mutagenesis screen.[24] If tolerable, this combination may be able to prevent or delay resistance in a clinical setting. However, ultimately a T315I inhibitor may be required to close the current gap. Although T315 has a gatekeeper function for Abl and other kinases, data presented at the 2005 American Society of Hematology congress indicate that it is possible to develop ATP-competitive inhibitors with activity against T315I.[25]

Will alternative Abl kinase inhibitors replace imatinib as frontline therapy for patients with chronic phase?

The short answer to this question is that this will depend on demonstration of superiority in a head-to-head comparison. Even without these data a few theoretical considerations can be offered. Most patients on standard dose imatinib do very well, with excellent quality of life, and a subset has a zero risk, to date, of progression to advanced phase. For these individuals the gain from a more potent Abl kinase inhibitor would have to be replacing disease control with disease eradication. Whether this will be possible with the new Abl inhibitors or even with any Abl kinase inhibitor remains to be proven. Competing against the excellent safety and tolerability record of imatinib will be difficult for any new drug, unless the ultimate goal is stopping therapy altogether. The situation may be different in high-risk patients. Although imatinib response overrides adverse prognostic features, we are currently unable to identify up-front those high-risk patients who will not respond well. This in turn may justify an aggressive approach for the entire cohort - such as the use of a more potent Abl inhibitor. However, it remains to be seen whether dasatinib or AMN107 will increase the rate of profound responses rather than only expediting them. Emerging data from studies using high dose imatinib (800 mg daily) and imatinib in combination with interferon or cytarabine suggest that CCR and MMR are accelerated but not achieved in more patients, and whether dasatinib or AMN107 will penetrate this apparent ceiling is not yet known. One possible approach may be to treat aggressively until MMR, and then switch to the drug with the fewest side effects, with intense monitoring for loss of response. Clearly, this will work only if the drug or drug dose required to maintain optimal response can be separated from the drug or drug dose required to achieve this response; this is yet another issue for future studies.

The challenge of minimal residual disease

Although most patients attain CCR on imatinib, the *BCR-ABL* message remains detectable in the majority of these individuals. In addition, anecdotal observations indicate that disease recurrence is the rule after discontinuation of imatinib, even in patients with undetectable *BCR-ABL* transcripts.[6] Fortunately, almost all patients have responded when re-challenged with drug, which indicates that disease recurrence upon stopping imatinib should not be confused with relapse. Why does imatinib fail to eradicate residual leukemia? At this point, our understanding is only rudimentary. There is evidence that the most primitive leukemic progenitor cells, defined by a $CD34^+/CD38^-$ immunophenotype and functionally characterized by a quiescent state, are drug resistant.[26] Emerging data suggest that Bcr-Abl kinase remains active in these cells in the presence of imatinib and also dasatinib.[27,28] If confirmed, this would suggest that persistence is a Bcr-Abl-dependent phenomenon, implying that Bcr-Abl remains the optimal target. Since hematopoietic stem cells are known to express a wide range of drug transport proteins, including Pgp and Abcg2, drug efflux or lack of drug influx is likely to play a role. Alternatively, *atypical* kinase domain mutations have been described in some patients with CCR, which confer a modest degree of drug resistance that may be sufficient to maintain the mutant clone's viability but insufficient to support its expansion.[29] It is currently unknown whether this is a wide-spread finding or limited to patients with high-risk disease. Lastly, the expression of Bcr-Abl in primitive progenitor cells is much higher than in differentiated cells, which may confer innate drug resistance.[30] However, it is also possible that residual leukemic cells rely on physiologic signals to maintain viability in the face of Bcr-Abl inhibition. If this were the case, then stem cell-targeted rather than Bcr-Abl-targeted therapy would be required. This need may open the field for expansion of immunotherapeutic approaches.

Immunotherapy for minimal residual disease

The crucial and powerful role of an immunologic mechanism as a basis for disease control is well documented in the allograft setting. In addition, there is considerable evidence that responses to interferon are also immune-mediated. The observation that some patients have remained in stable CCR for prolonged periods of time after stopping interferon speaks of the potency of these responses in selected individuals. Consistent with this, cytotoxic T cells directed against myeloid antigens such as PR1, a peptide derived from proteinase 3, have been detected in patients with CCR on interferon but not on imatinib.[31] Interestingly, the few reported patients without disease recurrence after stopping imatinib had invariably received interferon prior to imatinib, suggesting that an interferon-induced immune effect may be operational.[32,33] Altogether, these data suggest that interferon may have a role in controlling residual leukemia. However, in order for this to work, timing may be crucial. The expression of proteinase 3 (myeloblastin), the protein from which PR1 is derived, is directly correlated with Bcr-Abl kinase activity.[31] Thus, studies that use imatinib and interferon simultaneously from the beginning or that start with an initial debulking phase of imatinib monotherapy may deprive the immune system of its crucial target antigen. Another immunotherapeutic approach is vaccines. Approaches currently under study include peptides derived from the Bcr-Abl junction, semi-specific antigens such as PR1 or WT1 and preparations based on heat shock proteins. As a concept, the most appealing might be junction-specific peptides as they represent leukemia-specific neoantigens. Peptides derived from the more frequent b14a2 (formerly b3a2) junction have been demonstrated to bind HLA class I molecules on CML mononuclear cells.[34] Proliferative T-cell responses as well as B-cell responses were demonstrated in phase I clinical trials using junction peptide vaccines.[35] Although some clinical responses were observed, the results are difficult to interpret as many patients received concomitant therapy. A more recent Italian study in patients with residual disease on imatinib or interferon showed a significant reduction of residual leukemia in the majority of patients with low disease burden, but not in patients without cytogenetic response.[36] Importantly, therapeutic responses were correlated with demonstrable immune responses. Although these data are promising, the lack of a control group precludes definitive conclusions. In contrast to the Bcr-Abl peptides, PR1-based vaccines may have a role in different types of myeloid leukemias, including CML, AML and MDS.[37] Results of a study conducted at the MD Anderson Cancer Center are expected soon. Lastly, an autologous polyvalent heat shock protein-peptide complex vaccine (AG-858) is currently under investigation. Preliminary results suggest only modest activity.[38] Although much more data are needed, there seems to be reason for cautious optimism regarding the future role of immunotherapy. An easy prediction is that the domain of immunotherapy will be minimal residual disease. Whether disease eradication will eventually be possible remains to be seen. The Italian study suggests that booster vaccinations may be required to maintain responses. What is not yet clear is whether responses could be maintained in the absence of continued treatment with imatinib. If so, a scenario of vaccine boosts at 3-month intervals to maintain response may be a very acceptable option for patients with low level residual disease.

What is the role of allogeneic transplantion in 2006?

Stem cell transplantation is usually referred to as the only treatment modality with the potential of curing CML, i.e. eradicating the disease. Whether this is true or not is impossible to prove but late relapses many years after an allograft clearly shed some doubt on this notion (*Goldman, JM, personal communication 2005*). The more relevant question may be whether disease eradication is the right therapeutic goal or whether imatinib, or alternate Abl kinase inhibitors, or a *cocktail* of non-transplant therapy can afford complete protection from disease progression in the absence of disease eradication. As outlined above this is apparently the case currently in those patients who attain MMR at 12 months of imatinib therapy. As of now the only way of identifying these patients is a therapeutic trial of imatinib. Such a trial carries a low risk, as the likelihood of disease progression to accelerat-

ed phase or blast crisis during the first year of therapy is only 1.5%. On the other hand, recent registry data show that the rate of transplant-related mortality during the first 12 months is 10-20%, even in good risk patients (first chronic phase, HLA-matched sibling donor, less than 1 year from diagnosis, aged 20-40 years old) (*Horowitz M, personal communication, 2005*). As there is no indication that the imatinib survival curve will exhibit a sudden steep drop any time soon, the cross over point with the transplant curve is currently not foreseeable. Thus it is unclear whether the early loss of life years due to transplant-related mortality will be compensated for at any time in the future. This clearly argues against early transplantation without a trial of imatinib. There is, however, one caveat. While the limited data available suggest that imatinib treatment itself does not increase transplant-related mortality[39,40] delaying the transplant will likely affect outcomes adversely. This underscores the importance of disease monitoring to make timely adjustments to the overall strategy in case of failure or suboptimal response. It is also important to integrate the patient's individual preferences into the decision process, as the prospect of lifelong drug therapy may be unacceptable for some patients. In contrast to its use in the chronic phase, there is a well-defined role for stem cell transplantation in the management of advanced CML, when imatinib responses tend to be transient. Although it remains to be seen with longer follow-up whether this will be different with the novel more potent Abl kinase inhibitors, previous experience suggests that these patients will eventually relapse. Since stem cell transplantation in advanced phase is associated with high transplant-related mortality and relapse mortality, eligible patients should proceed to transplantation while still in remission. As with imatinib, it will be important to exclude a potential detrimental effect of AMN107 or dasatinib on a subsequent allograft, and thus these patients should be carefully monitored and reported.

How does reduced intensity conditioning allografting fit in this panorama? Early studies using a fludarabine/antithymocyte globulin/busulfan-based regimen showed promising results, with a 5-year overall survival of 85% in patients transplanted in first chronic phase.[41] However, a recent retrospective study by the European Group for Blood and Marrow Transplantation (EBMT) revealed a more complex picture.[42] In patients with a low EBMT score results did not appear to be superior to those achieved with conventional conditioning. Thus, given the limited follow-up and the associated uncertainty regarding the stability of the responses, reduced intensity conditioning should clearly not replace conventional conditioning in such patients. On the other hand, outcomes were comparable if not slightly better for patients with a high EBMT score, in whom reduced intensity conditioning may, therefore, be the preferred option. Patients transplanted in accelerated phase/blast crisis had a 3.4-fold higher risk of death and a 2.7 higher risk of relapse than had patients transplanted in first or second chronic phase, confirming the dominant impact of pre-transplant disease phase on outcomes. Thus, in patients who progressed to accelerated phase/blast crisis on imatinib, the role of the novel Abl kinase inhibitors will likely be to induce a second chronic phase or remission before proceeding to stem cell transplantation while still responding.

Summary

Despite the availability of imatinib as an accepted standard approach to the treatment of newly diagnosed patients, the overall management of CML has become more complex than ever. While the majority of patients in chronic phase achieve excellent results with standard dose imatinib, state-of-the-art monitoring, including qPCR, is crucial to identify patients in whom imatinib fails or who have suboptimal responses, so that timely adjustments can be made to the overall therapeutic strategy. Since the response to imatinib in patients in first chronic phase overrides pretherapeutic risk factors it is difficult to justify aggressive therapy including allografting without a prior trial of imatinib. In contrast, eligible patients with accelerated phase or blast crisis should undergo allogeneic transplant, with imatinib used for debulking. Highly potent alternative Abl kinase inhibitors, such as AMN107 and dasatinib, with activity against mutant Bcr-Abl are the most promising drug therapy for imatinib failure, and produce excellent responses even in patients with advanced disease. Whether these responses will be durable remains to be seen with longer follow-up. The success of any drug treatment of CML may ultimately depend on whether minimal residual disease can be or needs to be eliminated or not. Immunotherapy using various vaccines may have a role in controlling or even eliminating low level residual leukemia but this must be tested in a prospective randomized fashion. There was a lot of good news for CML patients in 2005 and one can bet that more is to come in 2006.

Funding: MWD is a recipient of an American Society of Hematology Clinical/Translational Research Scholar Award.

References

1. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
2. Simonsson B. Beneficial effects of cytogenetic and molecular response on longterm outcome in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib (IM): update from the IRIS study. The IRIS study group. Blood 2005;106:52a[abstract].
3. Colombat M, Fort M-P, Chollet C, Marit G, Roche C, Preudhomme C, et al. Molecular remission in chronic myeloid leukemia patients with sustained complete cytogenetic remission after imatinib mesylate treatment. Haematologica 2006; 91:162-8.
4. 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. European Study Group on Interferon in Chronic Myeloid Leukemia; Italian Cooperative Study Group on CML; France Intergroup of CML; German CML Study Group; UK Medical Research Council Working Party on CML; Spanish CML Study Group; Australian CML Study Group; Swedish CML Study Group. Blood 2001; 98: 3074-81.
5. Goldman JM, Hughes T, Radich J. Continuing reduction in level of residual disease after 4 years in patients with CML in chronic phase responding to first-line imatinib in the IRIS study [abstract]. Blood 2005;106:51a[abstract].
6. Deininger MW. Management of early stage disease. Hematology (Am Soc Hematol Educ Program) 2005;174-82.

7. Gambacorti C, Talpaz M, Sawyers C, et al. Five year follow-up results of a phase II trial in patients with late chronic phase (L-CP) chronic myeloid leukemia (CML) treated with imatinib who are refractory/intolerant of interferon-α[abstract]. Blood 2005;106:317a[abstract].
8. Cortes JE, Talpaz M, Giles F, O'Brien S, Rios MB, Shan J, et al. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. Blood 2003;101:3794-800.
9. Deininger MW, Kantarjian H, Park B. Good prognosis of CML patients with clonal cytogenetic abnormalities in Ph-negative cells. Blood 2005;106:315a[abstract].
10. Terre C, Eclache V, Rousselot P, Imbert M, Charrin C, Gervais C, et al. Report of 34 patients with clonal chromosomal abnormalities in Philadelphia-negative cells during imatinib treatment of Philadelphia-positive chronic myeloid leukemia. Leukemia 2004;18:1340-6.
11. Branford S, Rudzki Z, Parkinson I, Grigg A, Taylor K, Seymour JF, et al. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. Blood 2004;104:2926-32.
12. Wang L, Knight K, Lucas L, Clark RE. The role of serial BCR-ABL transcript monitoring in predicting the emergence of BCR-ABL kinase mutations in imatinib-treated patients with chronic myeloid leukemia. Haematologica 2006;91:235-9.
13. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 2001; 293:876-80.
14. Schindler T, Bornmann W, Pellicena P, Miller WT, Clarkson B, Kuriyan J. Structural mechanism for STI-571 inhibition of abelson tyrosine kinase. Science 2000;289:1938-42.
15. Weisberg E, Manley PW, Breitenstein W, Bruggen J, Cowan-Jacob SW, Ray A, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell 2005;7: 129-41.
16. O'Hare T, Walters DK, Stoffregen EP, Jia T, Manley PW, Mestan J, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res 2005;65:4500-5.
17. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004;305:399-401.
18. Kantarjian H, Ottmann OG, Cortes J. AMN107, a novel aminopyrimidine inhibitor of Bcr-Abl, has significant activity in imatinib-resistant chronic myeloid leukemia (CML) or Philadelphia-chromosome positive acute lymphoid leukemia (Ph+ ALL). [abstract]. Blood. 2005;106:15a[abstract].
19. Sawyers CL, Kantarjian H, Shah N et al. Dasatinib (BMS-354825) in patients with chronic myeloid leukemia (CML) and Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to imatinib: update of a phase I study. Blood 2005; 106:16a[abstract].
20. Guilhot F, Apperley JF, Shah N. A phase II study of dasatinib in patients with accelerated phase chronic myeloid leukemia (CML) who are resistant or intolerant to imatinib: first results of the CA180005 'START-A' study. Blood 2005; 106:16a [abstract].
21. Hochhaus A, Baccarani M, Sawyers C. Efficacy of dasatinib in patients with chronic phase Philadelphia chromosome-positive CML resistant or intolerant to imatinib: first results of the CA180013 'START-C' phase II study. Blood 2005; 106:17a [abstract].
22. Ottmann OG, Martinelli G, Dombret H. A Phase II study of dasatinib in patients with chronic myeloid leukemia (CML) in lymphoid blast crisis or Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to imatinib: the 'START-L' CA180015 study. Blood 2005;106:17a[abstract].
23. Talpaz M, Rousselot P, Kim DW. A phase II study of dasatinib in patients with chronic myeloid leukemia (CML) in myeloid blast crisis who are resistant or intolerant to imatinib: first results of the CA180006 'START-B' study. [abstract]. Blood 2006;106:16a[abstract].
24. Deininger M, Bradeen H, Jia T. Comparison of imatinib, AMN107 and dasatinib in an accelerated cell-based mutagenesis screen. Blood 2005;106:204a[abstract].
25. Burley S. Application of FASTTM fragment-based lead discovery and structure-guided design to discovery of small molecule inhibitors of BCR-ABL tyrosine kinase active against the T315I imatinib-resistant mutant. Blood 2005;106:206a[abstract].
26. Holyoake TL, Jiang X, Jorgensen HG, Graham S, Alcorn MJ, Laird C, et al. Primitive quiescent leukemic cells from patients with chronic myeloid leukemia spontaneously initiate factor-independent growth in vitro in association with up-regulation of expression of interleukin-3. Blood 2001;97:720-8.
27. Elrick LJ, Hamilton A, Deininger MW, Holyoake TL. Imatinib mesylate does not inhibit BCR-ABL kinase activity in CML stem cells. Blood 2004;104:546a[abstract].
28. Copland M, Hamilton A, Baird JW. Dasatinib (BMS-354825) has increased activity against Bcr-Abl compared to imatinib in primary CML cells in vitro, but does not eradicate quiescent CML stem cells. Blood 2005;106:205a[abstract].
29. Chu S, Xu H, Shah NP, Forman SJ, Sawyers CL, Bhatia R. Detection of BCR-ABL kinase mutations in $CD34^+$ cells from chronic myelogenous leukemia patients in complete cytogenetic remission on imatinib mesylate treatment. Blood 2005; 105: 2093-8.
30. Jiang X, Zhao Y, Chan P, Eaves A, Eaves C. Quantitative real-time RT-PCR analysis shows BCR-ABL expression progressively decreases as primitive leukemic cells from patients with chronic myeloid leukemia (CML) differentiate in vivo. Exp Hematol 2003;31:228-9.
31. Burchert A, Wolfl S, Schmidt M, Brendel C, Denecke B, Cai D, et al. Interferon-α, but not the ABL-kinase inhibitor imatinib (STI571), induces expression of myeloblastin and a specific T-cell response in chronic myeloid leukemia. Blood 2003; 101: 259-64.
32. Merante S, Orlandi E, Bernasconi P, Calatroni S, Boni M, Lazzarino M. Outcome of four patients with chronic myeloid leukemia after imatinib mesylate discontinuation. Haematologica 2005;90:979-81.
33. Rousselot P, Huguet F, Cayuela JM. Imatinib mesylate discontinuation in patients with chronic myelogenous leukaemia in complete colecular remission for more than two tears. Blood 2005;106:321a[abstract].
34. Clark RE, Dodi IA, Hill SC, Lill JR, Aubert G, Macintyre AR, et al. Direct evidence that leukemic cells present HLA-associated immunogenic peptides derived from the BCR-ABL b3a2 fusion protein. Blood 2001;98:2887-93.
35. Pinilla-Ibarz J, Cathcart K, Korontsvit T, Soignet S, Bocchia M, Caggiano J, et al. Vaccination of patients with chronic myelogenous leukemia with bcr-abl oncogene breakpoint fusion peptides generates specific immune responses. Blood 2000;95: 1781-7.
36. Bocchia M, Gentili S, Abruzzese E, Fanelli A, Iuliano F, Tabilio A, et al. Effect of a p210 multipeptide vaccine associated with imatinib or interferon in patients with chronic myeloid leukaemia and persistent residual disease: a multicentre observational trial. Lancet 2005; 365:657-62.
37. Molldrem JJ, Lee PP, Wang C, Felio K, Kantarjian HM, Champlin RE, et al. Evidence that specific T lymphocytes may participate in the elimination of chronic myelogenous leukemia. Nat Med 2000;6:1018-23.
38. Marin D, Mauro MJ, Goldman J. Preliminary results from a phase 2 trial of AG-858, an autologous heat shock protein-peptide vaccine, in combination with imatinib in patients with chronic phase chronic myeloid leukemia (CML) resistant to prior imatinib monotherapy. Blood. 2005;106:318a[abstract].
39. Shimoni A, Kroger N, Zander AR, Rowe JM, Hardan I, Avigdor A, et al. Imatinib mesylate (STI571) in preparation for allogeneic hematopoietic stem cell transplantation and donor lymphocyte infusions in patients with Philadelphia-positive acute leukemias. Leukemia 2003;17:290-7.
40. Deininger MWN, Schleuning M, Sayer HG, et al. Allografting after imatinib therapy: no evidence for increased transplant-related mortality and favorable results in patients transplanted in remission. A retrospective study by the EBMT. Blood 2002;100:783a[abstract].
41. Or R, Shapira MY, Resnick I, Amar A, Ackerstein A, Samuel S, et al. Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase. Blood 2003;101:441-5.
42. Crawley C, Szydlo R, Lalancette M, Bacigalupo A, Lange A, Brune M, et al. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Chronic Leukemia Working Party of the EBMT. Blood 2005; 106:2969-76.