

Updates Of New Strategies in Chronic Myelogenous Leukemia (CML)

Introduction

Approximately 80% to 85% of patients with CML in early chronic phase achieve a complete cytogenetic response with standard-dose imatinib mesylate therapy (Gleevec). With a median follow up of 7 years, the overall survival is 90%.¹ The estimated 5-year survival considering only CML-related deaths is 95%. However, resistance to imatinib occurs in up to 4% to 7% per year, at least for the first 3-4 years. The most common mechanism of resistance is point mutations of the Bcr-Abl kinase domain (40% to 60% of resistant cases). Over 50 different mutations have been reported which vary in their extent of resistance to imatinib.² Other mechanisms of resistance include BCR-ABL-dependent (e.g., overexpression and amplification) and BCR-ABL-independent mechanisms (e.g., overexpression of Src-related kinases).³ This led to developing new agents/strategies which may overcome or prevent resistance. Targeted approaches such as second generation tyrosine kinase inhibitors (TKIs) have been favored, e.g. dasatinib (Sprycel), nilotinib (Tasigna) and bosutinib (SKI606). Dasatinib and nilotinib are now FDA approved for the treatment of CML post imatinib failure. Other non-TKIs are in development. T315I mutations are emerging

with increasing frequency, and patients with this mutation do not respond to current TKIs. Several studies with tyrosine kinase inhibitors with activity against T315I are ongoing with positive results. Homoharringtonine is also under investigation for patients with T315I inhibitors and those whose CML is resistant to 2 or more TKIs. These will be discussed in this update.

Imatinib

The standard dose of imatinib for patients in chronic phase is 400 mg daily.⁴

Approximately 40% of patients in chronic phase who fail to respond to the standard dose may respond when their dose is increased to 800 mg daily. Some single-arm phase II studies have suggested that higher doses of imatinib (i.e., 600 to 800 mg daily) used as the starting dose for patients in chronic phase may result in improved responses.⁵⁻⁸ Using this higher dose, over 90% of patients have achieved a complete cytogenetic response and approximately 50% have achieved undetectable levels of Bcr-Abl by PCR (i.e., "complete" molecular response). Responses occur significantly faster with higher doses. Higher doses are well tolerated in most patients and over 80% of patients have continued receiving high dose imatinib after 12 months of therapy. In the most recent update of our experience with high-dose imatinib, the rate of complete cytogenetic responses was significantly higher with high-dose compared to a historical population treated with standard-dose imatinib (91% vs 78%; $p=0.03$). The rate of major and complete molecular responses was also significantly

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higher with high-dose imatinib. Most important, event-free survival and survival free from transformation to accelerated or blastic phases were significantly superior with high-dose imatinib as initial therapy. Randomized studies of high-dose versus standard dose imatinib are ongoing and early results have confirmed the earlier achievement of cytogenetic and molecular responses. Currently imatinib 400 mg daily is the standard of care; high-dose imatinib should be considered for patients with suboptimal response, and could also be considered for patients with cytogenetic relapse on standard dose imatinib.

Management of Myelosuppression

During the course of treatment with imatinib and other tyrosine kinase inhibitors, 30% to 50% of patients develop grade 3 or 4 anemia, thrombocytopenia or neutropenia. Cytopenias most frequently occur during the first 2 to 3 months of therapy and in many instances they do not recur. This early myelosuppression is managed with a temporary treatment interruption if there is grade 3 or greater neutropenia (absolute neutrophil count $<1 \times 10^9/L$) or thrombocytopenia (platelets $<50 \times 10^9/L$). Upon recovery, the tyrosine kinase is restarted at the same dose if counts recover within 2 weeks or at a lower dose if recovery takes more than 2 weeks.¹⁰ For the occasional patient with prolonged and recurrent grade 3 or higher myelosuppression, hematopoietic growth factors have been used. Filgrastim (G-CSF) has been reported to improve the neutropenia, allowing uninterrupted therapy with imatinib, and frequently improving response to therapy.¹¹ Erythropoietin and darbepoetin have also been reported to improve anemia associated with tyrosine kinase therapy but the impact on survival is uncertain.¹² These are all investigational uses of these growth factors.

New Tyrosine Kinase Inhibitors and Other Agents to Treat CML Post Imatinib Failure

More potent Bcr-Abl and dual Src/Abl kinase inhibitors are being developed. At least four of

them are already in phase II trials or have been approved: nilotinib (AMN107; Tasigna), dasatinib (BMS-354825; Sprycel), bosutinib (SKI-606), and INNO-406.

Nilotinib

Nilotinib was developed following a rational drug design with nilotinib as the lead compound. Imatinib fits into the canonical ATP-binding site of the kinase domain and captures a specific inactive conformation of the activation loop of Abl. This close interaction made changes in the core of imatinib prohibitive. However, the N-methylpiperazine group of imatinib was more amenable to modifications. Nilotinib was developed through replacements of this ring and proved to be approximately 30 times more potent than imatinib in vitro against BCR-ABL, while maintaining similar activity against other kinases.¹³ Nilotinib inhibits the kinase activity of most BCR-ABL mutants tested, except T315I. A phase I study of nilotinib in patients with CML in all phases of the disease who had failed prior imatinib therapy showed efficacy.¹⁴ The phase II dose selected was 400 mg twice daily with dose limiting toxicities being myelosuppression, and transient bilirubin

Table 1. Response in Phase 2 studies of nilotinib after imatinib failure.

Response	Chronic	Accelerated	Myeloid Blastic	Lymphoid Blastic	Ph+ ALL
Patients (N)	321	129	105	31	39
Hematologic:					
Any (%)	70	54	22	19	29
Complete (%)	77	26	11	13	26
Cytogenetic:					
Complete (%)	42	19	32	32	34
Major (%)	58	31	38	48	51

elevations.¹⁵ Phase II studies have confirmed the high response rates and favorable toxicity profile of nilotinib after imatinib failure (Table 1).^{15,16} In the phase II study in chronic phase CML post imatinib failure, 321 patients received nilotinib 400 mg P.O. BID. The CHR rate was 77%, the major cytogenetic response rate was 58%, the complete cytogenetic response rate was 42%. The estimated 18-month survival rate was 91%. This resulted in the FDA approval of nilotinib for CML post imatinib failure in chronic and accelerated phases.

Based on this experience, we have initiated a

study of nilotinib as first line therapy for patients with CML in early chronic phase with the objective to improve the overall molecular response and to achieve responses earlier, since early achievement of response has been correlated with improved long-term outcome. The preliminary data in the first 50 patients suggest that indeed nilotinib may be better than imatinib: 97% of patients were in complete cytogenetic response after only 3 months of therapy, and 100% at 6 months. This compares favorably with rates at 6 months of 82% and 54% with high- and standard-dose imatinib, respectively (p=.0001). This study continues accrual.

In addition, we are exploring earlier intervention with nilotinib in patients who have not met the criteria for failure but have a suboptimal response as defined by the recommendations of a panel of CML experts. (Baccarani. Blood 2004). Ongoing studies with nilotinib in CML at our institution include:

- Single-arm, phase II study of nilotinib in patients with newly diagnosed Ph-positive CML in chronic phase – protocol 2005-0048.
- Randomized trial of Nilotinib versus standard dose imatinib in patients with newly diagnosed Ph-positive CML in chronic phase – protocol 2007-0545.

Dasatinib

Dasatinib is an ATP-competitive, dual-specific Src- and Abl-kinase inhibitor. Src activation may play a role in the development and progression of many tumors. Dasatinib is structurally unrelated to imatinib and is 300 times more potent inhibitor of Bcr-Abl kinase activity. It induces significant inhibition of the kinase activity of cells transfected with the wild-type Bcr-Abl as well as all mutants of Bcr-Abl, the exception being T315I. Phase II studies of dasatinib in CML post imatinib failure were very encouraging and led to the FDA approval of dasatinib post imatinib failure in all CML phases.^{17,18} In chronic phase, 91% achieved CHR and 62% achieved a major cytogenetic response, which was complete in 53%. The estimated 2-year survival rate was 94%. Responses were observed in patients with a wide variety of mutations. DLTs are myelosuppression (in approximately 50%) and

pleural effusions (severe in 10%). The summary of phase II studies is shown in Table 2.

Based on these favorable results we have initiated a trial of dasatinib in newly diagnosed CML in chronic phase. Preliminary results in the first 50 patients suggest that approximately 80% of patients achieve a complete cytogenetic response after 3 months of therapy and 94% after 6 months of therapy; results compare favorably to those achieved with imatinib at standard- or high-dose.

Table 2. Response in Phase 2 studies of dasatinib after imatinib failure.

Response	Chronic	Accelerated	Myeloid Blastic	Lymphoid Blastic	Ph+ ALL
Patients (N)	387	174	109	48	46
Hematologic:					
Any (%)	91	64	50	39	49
Complete (%)	91	50	26	29	35
Cytogenetic:					
Complete (%)	53	33	27	52	54
Major (%)	62	40	47	46	56

Ongoing studies with dasatinib are as follows:

- Dasatinib as front-line therapy in patients with newly diagnosed Ph-positive CML in chronic phase – protocol 2005-0422.
- Dasatinib in combination with chemotherapy (Hyper-CVAD) for patients with Ph-positive ALL – protocol 2006-0478.

Bosutinib (SKI-606)

Bosutinib is another orally available, potent dual Src/Abl kinase inhibitor. Bosutinib is 100-fold more potent than imatinib as an inhibitor of Bcr-Abl phosphorylation, and is active against mutant lines except T315I. Unlike imatinib, nilotinib and dasatinib, bosutinib exhibits no significant inhibition of c-kit and PDGFR. This could reduce problems of myelosuppression and pleural effusions. Phase I-II studies of bosutinib have shown high efficacy and minimal side effects (rash 7%, diarrhea 9%, myelosuppression 19%). No pleural effusions were seen.

Ongoing studies with bosutinib include:

- A phase II study of bosutinib for patients with CML resistant to prior therapy with imatinib – protocol 2005-0813.
- A randomized phase III study of bosutinib versus imatinib as frontline therapy for newly-diag-

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nosed CML – protocol 2007-0709.

T315I Inhibitors

T315I mutations represent approximately 20% of all mutations. Patients with T315I mutations do not respond to imatinib, dasatinib, nilotinib or bosutinib. New “T315I inhibitors” are available to treat such patients with favorable responses being observed. Studies at MD Anderson ongoing include XL228 (IV once or twice weekly; protocol 2007-0502), PHA739358 (IV daily x 7 every 2 weeks; protocol 2007-0939), and AP 24534 (orally daily; protocol 2008-0046). A study with DCC-2036 will open soon. These agents are also under study for patients with resistance to 2 or more TKIs.

Homoharringtonine (HHT)

HHT is active in patients with CML as a single agent or in combinations.^{19,20} HHT may be additive or synergistic with imatinib. In addition, there is *in vitro* evidence of activity of HHT in CML cells carrying the T315I obtained from patients who have failed imatinib therapy. A study by Marin et al included 10 patients with CML who had achieved at least a cytogenetic response with imatinib but had reached a plateau in transcript levels. In addition to continuing imatinib, SQ HHT 1.25 mg/m² twice daily for 5 days was given every 28 days. Seven patients had a decline in Bcr-Abl transcript levels which was greater than 1-log in 5. Two patients not in complete cytogenetic remission at the start of therapy became 100% Ph-negative.²¹ Recent studies investigated an easier subcutaneous (SQ) HHT schedule. Two studies at MD Anderson are studying SQ HHT in patients with CML and 1) T315I mutations, or 2) failure on 2 or more TKIs. The preliminary data (multi-institutional) are shown in Table 3. There is evidence of synergy between imatinib and HHT and this is currently being explored in the clinic. Patients with CML in any stage of the disease who have failed imatinib (or imatinib-naïve if they are in blastic phase) receive therapy with HHT intravenously combined with imatinib. Over 60% of patients treated achieve a hematologic response in all phases of the disease even in the presence of T315I, and complete cytogenetic responses have

been observed in some patients. In addition, the T315I clone is eliminated in approximately half of the patients.

The following ongoing studies with HHT are available:

- Intravenous HHT plus imatinib in patients who have failed imatinib therapy. Patients in any phase of the disease (chronic, accelerated or blastic) are eligible, and patients in blast phase can be imatinib-naïve – protocol 2005-0067.
- Subcutaneous HHT for patients with CML in any stage who have failed imatinib therapy and carry the T315I mutation – protocol 2006-0192.
- Subcutaneous HHT for patient with CML in any stage who have failed 2 or more TKIs – protocol 2006-0926.

Immune modulation

Immune modulation may be partially responsible for the favorable results with IFN- α . Immunomodulation is an attractive way to try to eliminate the leukemic stem cell which is insensitive to all available tyrosine kinase inhibitors. If successful, this strategy could lead to a safe permanent discontinuation of therapy in patients with a good response. Different types of antigens may be used in CML vaccines. One approach is to use tumor-specific antigens. The Bcr-Abl fusion creates a new sequence of amino acids only expressed in leukemic cells. Short peptides containing 8 to 12 amino acids, derived from the fusion region, have been tested.^{22,23}

A different peptide used for immune stimulation is PR1, a nona-peptide derived from proteinase 3 and presented through HLA-A2.1. Proteinase 3 is expressed in myeloid cells during normal neutrophil maturation and is overexpressed in myeloid malignancies. Cytotoxic T-lymphocytes (CTL) specific for PR1 inhibit colony formation in an HLA-restricted manner. PR1-specific CTL is iden-

Table 3. Homoharringtonine results.

CML Chronic Phase	No.	Response (%)		
		Complete Hematologic	Cytogenetic	T315I Suppression
T315I Mutation	19	90	30	50
Failure \geq 2 TKIs	9	50	11	N/A

tified in most patients with CML who responded to IFN- α or allogeneic SCT, but not in non-responding patients or in patients treated with chemotherapy. In one study, 10 patients with CML were treated with PR1: 1 achieved a complete cytogenetic response, and 3 had cytogenetic improvement.²⁴

Other approaches can also be used to stimulate an immune response against the leukemic clone. One approach is to use anti-CTLA-4 monoclonal antibodies. These have been shown to stimulate an anti-tumor immune response in patients with melanoma and other solid tumors.

Studies with vaccines and other immunomodulatory approaches for patients with CML at M.D. Anderson, some in collaboration with many other centers in the USA, include:

- Phase II study of PR1 vaccine in patients with Ph-positive CML who are HLA-A2 positive who have received at least 12 months of therapy with imatinib and are in complete cytogenetic remission but have stable or increasing levels of BCR-ABL as determined by real-time PCR – protocol 2006-0360.
- A phase II study of ipilimumab (an anti-CTLA4 monoclonal antibody) in combination with dasatinib for patients with CML in any stage that have minimal residual disease (molecular in chronic phase, cytogenetic or molecular in advanced stages) while on treatment with dasatinib – protocol 2008-0157.

Monitoring Response and Resistance to Therapy in CML

Several monitoring methods are available to assess response and resistance to therapy in CML: 1) cytogenetics, 2) FISH, 3) qualitative PCR, and 4) mutational studies. Advantages and disadvantages of each are detailed in a recent review.²⁵

A simple way of monitoring patients outside the context of a protocol is as follows;

Bone marrow for morphology and cytogenetics should be done pretreatment then at 6 and 12

months (to assess imatinib response), then every 1-2 years if stable complete cytogenetic response. Cytogenetic karyotyping is the only routinely available assessment of all chromosomes.

FISH can help assess the cytogenetic response and can be done in peripheral blood. It can be easily used for long-term monitoring (e.g. every 6-12 months) although it would not allow for detection of chromosomal abnormalities in Ph-negative metaphases.

In cytogenetic CR, monitor with QPCR every 6 months. Aim for a BCR-ABL/ABL ratio of <0.1% in the international scale (i.e., 3-log reduction from standardized baseline). In a patient in cytogenetic CR, do not react drastically to rises in transcript levels unless consistent with loss of major molecular response (BCR-ABL/ABL ratio >0.1% in the international scale) and with a 1-log increase. Still, resort to lower-risk treatment changes, (e.g. increase imatinib dose), but not to higher-risk ones (e.g. allogeneic transplant).

In standard practice, do not do mutational analysis pretreatment or in patients responding to imatinib. Mutational studies are best done only in patients with cytogenetic or hematologic relapse on imatinib. About 50% will show mutations. A T315I mutation should lead to consideration of allogeneic stem cell transplant. The mutation IC50 to a particular agent is a better guide to select therapy. For example, most P-loop mutations respond well to dasatinib, while mutations V299L and F317L respond well to nilotinib. Please consult with a CML expert in such situations.

For QPCR and mutational studies, you may contact the MD Anderson Molecular laboratory at 713-794-4780, Dr. Luthra Raja.

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CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytosan + Rituximab (FCR) (2008-0431)
- FCR + Ofatumumab (2006-0839)
- Lenalidomide (2006-0715)
- CFAR (2005-0269)

2. Prior Therapy

- Fludarabine + Cytosan + Rituximab (ID99-338)
- FCR + Bevacizumab (2005-0992)
- HuMax-CD20 (2006-0314)
- Dasatinib (2005-0497)
- OFAR2 (2006-1026)
- FCR ± Lumiliximab (2006-0789)
- 5-aza (2006-0428)
- CNF2024 (2005-0452)
- SNS-032 (2006-0843)
- Alemtuzumab (2007-0626)
- ABT-263 (2007-0096)

- GS-9219 (2007-0087)
- Enzastaurin (2006-0868)
- 8-Chloro-adenosine (2004-0144)

3. Other

- T-cell LPD: Alemtuzumab + Pentostatin (2004-0408)
- Hairy Cell: 2CDA + Rituximab (2004-0223)

AML/MDS Treatment Priorities

1. Newly Diagnosed

- Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17): ATRA + Arsenic Trioxide +/- Gemtuzumab (2006-0706)
- Cytogenetic feature: Inv16 or t(8;21): Fludarabine + Ara-C + Gemtuzumab (2007-0147)

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C. Younger Patients:

- IA + Sorafenib (2006-0977)
- IA + SAHA (2007-0835)

Older Patients:

- Ida + Ara -C (2006-0813)
- IV Clofarabine (2005-0535)
- Low Dose Decitabine +/- Valproic Acid (2006-0686)
- DAC vs low-dose Ara-C (2005-0647)
- Obatoclax (2008-0037)
- SNS-595 (2007-0965)
- Vidaza ± MGCD0103 (2007-0763)
- Low dose Ara-C ± Lintuzumab (2008-0065)

2. Salvage Programs

- Clofarabine+Ida+Aa-C (ID03-0181)
- Tamibarotene (2007-0512) in APL
- Mitoxantrone + Etoposide + Ara-C +CEP-701 (2003-0719)
- Lenalidomide (2006-0293)
- HuM195/rGel (DM98-342)
- Ara-C ± Clofarabine (2006-0069)
- Ida + Ara-C + AEG (2005-0384)
- Oral Clofarabine (2005-0536)
- 5-aza + Ara-C (2005-0291)
- AZD1152 (2006-0285)
- AC220 (2006-0850)
- IA + Sorafenib (2006-0977)
- FAO (2006-1089)
- Azacitidine (2007-0405)
- DAC + Mylotarg (2007-0882)
- Sapacitabine (2007-0727)
- IA + SAHA (2007-0835)
- CP-4055 (2006-0132)
- LY2181308 (2007-0707)

3. Low Risk MDS and CMML with <10% Blasts

- Azacitidine (2007-0405)
- Thymoglobulin + Cyclosporin (2005-0115)
- SAHA (2007-0201)
- PR1 vaccine (2005-0913)
- AMG531 (2005-0577)
- Gimatecan (2006-0943)
- CC-11006 (2007-0528)
- Revlimid + Darbepoetin alfa (2006-0657)

ALL Treatment Priorities

1. Newly Diagnosed or Primary Refractory (one non-hyper-CVAD induction)

- A. Modified Hyper CVAD (ID02-230)
- B. Burkitt's: Hyper CVAD + Rituximab (ID02-229)
- C. PH+: Hyper CVAD + Dasatinib (2006-0478)
- D. Age <31: Augmented BFM (2006-0375)
- E. T cell: Hyper CVAD + Nelarabine (2006-0328)

2. Salvage Programs

- IMTOX 19 + 22 (2005-0271)
- Clofarabine + Cytosine (2005-0552)
- 5-aza + Hyper CVAD (2005-0895)
- Marquibo (2006-1109)
- Augmented Hyper CVAD (ID03-0166)

CML Treatment Priorities

1. CML Chronic Phase

- BMS-354825 (2005-0422)
- Bosutinib vs. Imatinib (2007-0709)
- Oral AMN107 (2005-0048)
- Imatinib vs. Nilotinib (2007-0545)
- SKI-606 (2005-0813)
- Dasatinib (2007-0606)
- HHT (2006-0926/2006-0192)

2. CML Accelerated Phase

- HHT (2006-0926/2006-0192)
- SKI-606 (2005-0813)

3. CML Blastic Phase

- HHT (2006-0926/2006-0192)
- SKI-606 (2005-0813)

4. Minimal Residual Disease

- PR1 Vaccine + Gleevec (2006-0360)
- Dasatinib + Ipilimumab (2008-0157)

5. Philadelphia-negative Myeloproliferative Disorders (MF, ET, PV, CEL/HES, Ph-neg CML)

- CC-4047 (2006-0817)
- Pegasys (DM03-0109)
- INCB018424 (2007-0169/2008-0241)
- ST571 (ID01-167) (HES only)
- XL019 (2007-0373)
- 2CDA + Ara-C (DM97-232) (HES only)
- RAD001 (2006-0759)
- TG101348 (2007-0837)

Phase I/II Agents for Hematologic Malignancies

- BAY-43-9006 (2004-0702)
- SAHA + DAC (2005-0723/2006-1096)
- AT9283 (2006-0177)
- Triciribine (2006-0249)
- SJG-136 (2005-0607)
- INNO-406 (2006-0278)
- Sapacitabine (2005-0768)
- AZD4877 (2007-0287)
- XL228 (2007-0502)
- INCB018424 (2007-0925)
- PHA-739358 (2007-0939)
- RO5045337 (2007-0408)
- OPB-31121 (2007-0488)
- ARRY-520 (2007-0879)
- SB1518 (2008-0032)
- AP24534 (2008-0046)

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