

This issue of the newsletter updates investigational studies available in the Leukemia program at M. D. Anderson Cancer Center which may be relevant to patient care in the community practice. Novel agents and approaches continue to be introduced clinically with the potential to change treatment opportunities. We will divide the issue into disease specific programs and present brief updates of the existing strategies in our overall approach to treatment of Leukemia.

Chronic Myeloid Leukemia (CML)

Newly diagnosed CML

The second generation tyrosine kinase inhibitors (TKIs) have demonstrated significant activity in all phases of CML post imatinib failure. Dasatinib (Sprycel), a dual Src-Abl inhibitor was approved by the FDA for this indication in June 2006. Nilotinib (Tasigna), a 50x more potent Bcr-Abl was approved by the FDA in July 2007. We have implemented frontline studies with both of these second generation TKIs for patients with newly diagnosed CML. The preliminary analyses show the superior activity of both agents compared with standard- and high-dose imatinib and a reasonable safety profile. Dasatinib is now given as 100 mg single oral daily dose. Nilotinib is given as 400 mg PO bid. The preliminary findings of both studies have been updated at the ASCO 2008 (JCO 26:abst. 7009 and 7010, 2008)

- a. Dasatinib in newly diagnosed CML
– protocol 2005-0422.
- b. Nilotinib in newly diagnosed CML
– protocol 2005-0048.

Both studies provide free drug supply and require a minimum initial stay (3-5 days) at M. D. Anderson with 1 day visits q 3 months in year 1 and q 6 months thereafter.

CML post imatinib failure

We are investigating a new dual Src-Abl 200x more potent inhibitor in this setting, bosutinib (SKI-606). The experience with bosutinib is very encouraging. Among patients in chronic phase CML post imatinib failure treated with bosutinib 500 mg daily the CHR rate is 89% and the major cytogenetic response rate is 40%, complete in 30%, after a median duration of treatment of only 3 months. Side-effects are minimal including grade

3-4 thrombocytopenia in only 14% and rash in 7%. No pleural effusions or significant myelosuppression have been noted. This was updated at ASCO 2008 (JCO 26:abst 7001, 2008). The study of bosutinib in CML post imatinib failure in all phases is open.

Bosutinib in CML post imatinib failure
– protocol 2005-0813.

CML with T315I mutations

This mutation is notorious for its resistance to current TKIs including imatinib, nilotinib and dasatinib.

Aurora kinase inhibitors with potent T315I and JAK2 inhibitory activities include: 1) AT9283 (IV infusion for 3-6 days); 2) XL228, and 3) PHA 739358. In addition homoharringtonine, an old drug with significant anti-CML activity, has shown activity in the setting of CML T315I. In CML chronic phase with T315I, HHT produced a CHR rate of 45% and a cytogenetic response rate of 27%. It is currently under investigation in this setting as well as in patients with failure to at least 2 TKIs (updated at ASCO 2008; JCO 26: abst. 7021, 2008)

- a. AT9283 in refractory hematologic malignancies – protocol 2006-0177.
- b. XL228 – protocol 2007-0502
- c. Homoharringtonine in CML with T315I mutations – protocol 2006-0192.

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Vaccine and other immune modulating strategies in CML

Vaccines in CML may be helpful in the setting of minimal residual disease to augment the host immunity and eradicate residual disease resistant to TKIs. This may provide the future hope for cure of CML without the need for continued therapy. We are testing 2 vaccines in CML in the setting of significant minimal residual disease (complete cytogenetic response but no major molecular response, i.e. QPCR >0.1 and stable). The two vaccines include the synthetic peptide vaccine and the PR1 vaccine (if HLA A2 positive). The latter study is ongoing.

Acute Myeloid Leukemia (AML)

Several studies have confirmed the superiority of idarubicin over daunorubicin, and the value of high dose ara-C as consolidation in younger patients. A meta-analysis of different induction studies also indicated that high-dose ara-C induction improved remission duration in AML (Kern and Estey, Cancer 107:116, 2006). Therefore, in younger AML (age < 60 years) our frontline studies incorporate idarubicin and high-dose cytarabine as the backbone standard of therapy. We are currently investigating the potential value of adding sorafenib (a FLT3 / RAF inhibitor) or vorinostat (histone deacetylase inhibitor) to induction-consolidation therapy.

In elderly AML, intensive chemotherapy is associated with a high induction mortality. Investigations focus on low-intensity targeted strategies in patients who are not candidates for intensive chemotherapy. These include clofarabine (adenosine nucleoside analog), decitabine (a hypomethylating agent), and sapacitabine (oral cytosine analogue).

- a. Idarubicin + cytarabine + sorafenib in AML < 60 years – protocol 2006-0977.
- b. Idarubicin + cytarabine + vorinostat in AML < 65 years – protocol 2007-0835.
- c. Clofarabine + low dose ara-C in elderly high risk MDS/AML – protocol 2007-0039 (pending).
- d. Decitabine vs. low-dose ara-C in elderly AML – protocol 2005-0647.
- e. Decitabine + valproic acid in high risk MDS/AML – protocol 2006-0686.

- f. Sapacitabine in age ≥ 70 yrs
– protocol 2007-0727

In our studies of APL, we identified the combination of ATRA plus arsenic trioxide (+ mylotarg for high risk APL) to produce excellent results in APL. This is the basis for our ongoing study (Estey, Blood 107:3469, 2006). In AML with favorable karyotypes such as t(8;21) and inversion 16, our FLAG regimen has shown favorable results and continues as our frontline strategy.

- a. ATRA + arsenic trioxide + mylotarg in APL – protocol 2006-0706.
- b. T(8;21), inversion 16 – protocol 2007-0147.

For AML in CR (any age), 2 maintenance strategies are being investigated, decitabine and PR1 vaccines.

- a. Decitabine vs. Best standard of care as maintenance for AML in CR1 and for subsequent CRs – protocol 2006-0358.
- b. PR1 vaccine maintenance for AML in CR1 and HLA-A2 positivity – protocol 2006-0904.

Myelodysplastic Syndrome (MDS)

Approved treatments for MDS and CMML include: 1) hypomethylating agents (decitabine, azacitidine) for MDS/CMML; and 2) lenalidomide (a thalidomide analog) for low risk MDS transfusion dependence and 5q abnormality. We are investigating several strategies to improve the results beyond the standard of care. These are based on the IPSS/ general risk of the MDS.

Lower risk MDS (IPSS low – intermediate-1; blasts < 10%)

Approaches under investigation include combinations of growth factors, immune therapy (rabbit ATG), GX15070 (a Bcl 2 inhibitor shown to stimulate multilineage hematopoiesis), vorinostat (a histone deacetylase inhibitor shown also to stimulate multilineage hematopoiesis), and low doses of decitabine – azacitidine. In lower risk MDS as well as higher risk MDS with 5q abnormality, lenalidomide based regimens are under investigation.

Higher risk MDS (IPSS intermediate-2 – high; blasts > 10%)

To improve the results of hypomethylating agents we are combining them with histone deacetylase inhibitors. Programs in these MDS subtypes include decitabine + valproic acid, decitabine + vorinostat, azacitidine + MGCD.

For patients who fail on hypomethylating strategies, investigational strategies include clofarabine, PO and IV, sapacitabine (an oral cytosine analog), gimatecan (an oral topoisomerase I inhibitor), and other phase I/II agents.

Chronic Lymphocytic Leukemia (CLL)

Significant success and advance has been made with combination therapies for patients with CLL, particularly chemoimmunotherapy. Fludarabine, cyclophosphamide, and rituxan (FCR) has produced excellent results and is our backbone of CLL therapy. Efforts are now focused on developing active and well tolerated regimens for patients over 65 years old. Current or planned clinical trials for patients with CLL are indicated below.

Previously Untreated (treatment indicated)

- a. Age > 65 yrs - Single-agent Lenalidomide – protocol 2006-0715.
- b. Age < 70, beta-2 microglobulin > 3.9 mg/L (high risk) - Fludarabine, Cyclophosphamide, Rituximab, Alemtuzumab (CFAR) – protocol 2005-0269.
- c. Any age - Fludarabine, Cyclophosphamide, Rituximab + GM-CSF (FCR+GM-CSF) – protocol 2006-0267.

Previously Treated (treatment indicated) Chemoimmunotherapy

- a. Randomized FCR +/- Lumiliximab (anti-CD23 mAb) – protocol 2006-0789.
- b. Fludarabine sensitive - FCR + Bevacizumab – protocol 2005-0992.
- c. Oxaliplatin, Fludarabine, Cytarabine, Rituximab (OFAR2) – protocol 2006-1026.

Single-Agent Phase I or II

- a. Fludarabine and Alemtuzumab refractory (or bulky nodes) - Ofatumumab (HuMax CD20; anti-CD20 mAb) – protocol 2006-0314.
- b. 5-Azacitidine (Phase II) – protocol 2006-0428.
- c. Anti-CD40 mAb (Phase I) – protocol 2005-0025.
- d. Oral CNF2024 (Hsp90 inhibitor) (Phase I) – protocol 2005-0452.
- e. SNS-032 (cyclin-dependent kinase inhibitor - Phase I) – protocol 2006-0843.
- f. Oral Enzastaurin (protein kinase C inhibitor) (Phase II) – protocol 2006-0868.

Minimal Residual Disease

- a. Revlimid – protocol 2007-0213.

Richter's Transformation

- a. Oxaliplatin, Fludarabine, Cytarabine, Rituximab (OFAR2) – protocol 2006-1026.

Acute Lymphocytic Leukemia (ALL)

With the hyper-CVAD regimen, the CR rate in adult ALL is 90% with a 5-10 year survival rate of 40-50% (Kantarjian.Cancer 101:2788, 2004). We are now treating adult ALL based on its subtype with protocol specific modifications.

1. In Ph+ ALL, the hyper-CVAD + imatinib regimen has shown encouraging data with 3 year survival rates of 60% (Thomas.Blood 103:4396, 2004). We are currently attempting to improve these results using the combination of hyper-CVAD + dasatinib (dual Src-Abl inhibitor; 300 times more potent than imatinib).
2. In Burkitt ALL, hyper-CVAD + rituximab has produced event-free-survival rates of 80-90%. This continues to be our current frontline regimen (Thomas.Cancer 106:1569, 2006).
3. In T-cell ALL, we have incorporated nelarabine (an active anti-T-All agent) with hyper-CVAD to improve on the previous positive results (Thomas.Blood 104:1624, 2004).
4. In adolescent-young adults (age 12-30) with ALL, pediatric dose intensive regimens appear to produce better results than standard adult

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ALL regimens, although no direct comparisons have been made to the hyper-CVAD regimen. Because of the literature experience, we have initiated a frontline study of augmented BFM (the pediatric protocol for high risk ALL) in our adolescent-young adult patients.

- a. Hyper-CVAD + dasatinib in Ph+ ALL – protocol 2006-0478.
- b. Hyper-CVAD + rituximab in Burkitt ALL – protocol ID02-229.
- c. Hyper-CVAD + nelarabine in T-Cell ALL – protocol 2006-0328.
- d. Augmented BFM regimen in adolescent-young adults (age 12-30) – protocol 2006-0375.

- b. Obatoclax (pan bcl-2 inhibitor) in MF – protocol 2006-0411
- c. Pomalidomide (CC-4047) – protocol 2006-0817
- d. CEP-701 in MF – protocol 2007-0070
- e. INCB018424 in MF – protocol 2007-0169
- f. XL019 in MF – protocol 2007-0373
- g. TG101348 in MF – protocol 2007-0837

For additional information about the therapies for MPD at M.D. Anderson Cancer Center, visit website at <http://www.mdanderson.org/diseases/mpd/> or contact Srdan Verstovsek, MD, PhD, MPD Program Leader, at (713) 745-3429; e-mail sverstov@mdanderson.org.

Myeloproliferative Disorders (MPD)

The development of novel therapies for patients with MPD has been historically hampered by limited understanding of the abnormal processes and molecular causes of these diseases. The discovery of JAK2 mutation in most MPD patients is a first step in this direction. Agents potentially able to interfere with identified abnormalities in MPD are becoming available. Available programs are listed below.

- a. Pegylated interferon (Pegasys) for ET and PV – protocol DM03-0109

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WebMaster: *Charles A. Koller, M.D.*
Associate Editor: *Sherry Pierce, R.N.*
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CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytosan + Rituximab (FCR) + GM-CSF (2006-0267)
- 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)
- Anti CD40 MoAb (2005-0025)
- Dasatinib (2005-0497)
- Forodesine HCL (2005-0290)
- 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)

3. Other

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

AML/MDS Treatment Priorities

1. Newly Diagnosed

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

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- C. Others: Ida + Ara -C (2006-0813)
- IV Clofarabine (2005-0535)
 - Low Dose Decitabine +/- Valproic Acid (2006-0686)
 - DAC vs low-dose Ara-C (2005-0647)
 - IA + Sorafenib (2006-0977)
 - IA + SAHA (2007-0835)
 - Obatoclox (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)
- MGCD0103 (2006-0474)
- AZD1152 (2006-0285)
- AC220 (2006-0850)
- IA + Sorafenib (2006-0977)
- FAO (2006-1089)
- Azacitidine (2007-0405)
- DAC + Mylotary (2007-0882)
- Sapacitabine (2007-0727)
- IA + SAHA (2007-0835)
- CO-4055 (2006-0132)

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

- Cytokine Immunotherapy (2004-0253)
- Azacitidine (2007-0405)
- Thymoglobulin + Cyclosporin (2005-0115)
- SAHA (2007-0201)
- PR1 vaccine (2005-0913)
- AMG531 (2005-0577)
- Obatoclox Mesylate (2006-0688)
- Gimatecan (2006-0943)
- CC-11006 (2007-0528)
- Revlimid + Darbepoetin alfa (2007-0657)

ALL Treatment Priorities

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

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

2. Salvage Programs

- IMTOX 19 + 22 (2005-0271)
- Clofarabine + Cytosan (2005-0552)
- 5-aza (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)
- TALL-104 + Gleevec (2004-0837)

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

- CEP-701 (2007-0070)
- CC-4047 (2006-0817)
- Pegasys (DM03-0109)
- INCB018424 (2007-0169)
- ST571 (ID01-167) (HES only)
- XL019 (2007-0373)
- GX15-070MS (2006-0411)
- 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)
- Fenretinide (2005-0690)
- SAHA + DAC (2005-0723/2006-1096)
- SNS-595 (2005-0295)
- CP-4055 (2006-0132)
- MK-0457 (2005-0330)
- AT9283 (2006-0177)
- SAHA+ Ida (2005-0031)
- Triciribine (2006-0249)
- KW-2449 (2006-0275)
- SJG-136 (2005-0607)
- INNO-406 (2006-0278)
- Sapacitabine (2005-0768)
- MGCD0103 + Aza (2005-0659)
- AVN-944 (2005-0609)
- AZD4877 (2007-0287)
- XL228 (2007-0502)
- INCB018424 (2007-0925)
- PHA-739358 (2007-0939)

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M. D. Anderson Cancer Center
1515 Holcombe Boulevard
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