Leukemia INSIGHTS
VOL. 17 • NO. 1 SPRING 2012

Slow Motion Breakthroughs in Adult ALL Therapy

With a recent wave of new, highly active monoclonal antibodies and of a new BCR-ABL tyrosine kinase inhibitor (ponatinib), we are at the brink of therapeutic breakthroughs which will significantly improve survival of adult acute lymphocytic leukemia (ALL).

Adult ALL encompasses a heterogeneous group of lymphoid malignancies. The two predominant subtypes are B-ALL and T-ALL, based on expression of B-lineage or T-lineage markers. Prognosis is related to age, karyotype, molecular profile, immunophenotype, and other disease features. Prognosis for pediatric ALL has improved significantly in the past several decades; the current long-term survival rate is greater than 80 percent. Long-term survival in adult ALL is 35 percent to 40 percent. The most common reason for failure is disease recurrence.

The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine) has demonstrated significant activity in the front-line setting, producing a complete remission (CR) rate of 90 percent and a cure rate of about 50 percent. Outcome of salvage chemotherapy for ALL is poor, however, with complete response rates of 20 percent to 30 percent, depending on prior therapy and duration of first remission. Median disease-free survival ranges from 2 to 7.5 months. Long-term survival after ALL salvage therapy is less than 10 percent. In this issue of Leukemia Insights, we focus on newer investigational strategies in adult ALL.

In This Issue

New Monoclonal Antibodies in Pre-B ALL

The targeting of CD20 in ALL with combinations of rituximab and chemotherapy has improved survival in Burkitt leukemia and in CD20+ ALL. In the same light, several conjugated and unconjugated monoclonal antibodies targeting CD22 and CD19 are under study as almost all ALL leukemic cells also express these markers. Currently, four of these antibodies are of interest.

Inotuzumab Ozogamicin

Inotuzumab ozogamicin is an anti-CD22 monoclonal antibody bound to calicheamicin. Calicheamicin is a natural product of micromonospora echinospora and is significantly more toxic than chemotherapy (1, 2). Calicheamicin causes cell apoptosis by binding to the minor DNA groove and causing double-strand breaks. Inotuzumab delivers the conjugated calicheamicin by binding to CD22 with subnanomolar affinity where it is then internalized by the cell. Phase I-II studies have shown encouraging activity in lymphomas (3, 4) with durable response rates ranging from 60 to 80 percent. Phase II of the study proposed a dose schedule of 1.8 mg/m2 IV every 3-4 weeks and showed dose-limiting toxicities of myelosuppression and reversible liver function abnormalities.

(continued on page 2)

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Based on these results, a Phase II study of inotuzumab at a dose of 1.3 – 1.8 mg/m2 IV every 2-4 weeks was conducted in patients with refractory-relapsed ALL. A total of 49 patients received treatment, 75% were at or beyond Salvage 2. Thirty percent were either Ph+ or t(4;11) ALL. The results of the study showed a total of 28 patients achieving a response: 9 patients achieved CR, 14 patients achieved marrow CR without recovery of platelet counts, and 5 patients achieved marrow CR without recovery of neutrophil or platelet counts. Of these 28 patients, 16 patients achieved a complete cytogenetic response after showing chromosomal abnormalities at the start of therapy. Additionally, multiparameter flow cytometry for minimal residual disease showed 17 patients converted to MRD negative status. Treatment was well-tolerated with only 2 deaths due to non-drug-related complications within the first 4 weeks of therapy. Side effects included liver function abnormalities, 31% of which were severe but reversible.

The study results demonstrated a median survival rate of 4.5 months across all patients. The refractory nature of the study group is the likely cause of the shortened duration of response (5). However, among the patients achieving marrow CR, the median survival rate was shown to be 6.7 months while the 9-month survival among the patients achieving CR was 78%. Furthermore, 22 of the 49 patients receiving treatment proceeded to allogeneic stem cell transplant.

This experience indicates that inotuzumab is a highly active single agent for the treatment of refractory-relapsed ALL. We are currently evaluating a weekly schedule of inotuzumab, which appears to be equally effective and less toxic than the single dose every 3-4 weeks. The study is open for accrual.

Blinatumomab

Blinatumomab is a bispecific, single chain antibody that invokes cell death in CD19- expressing ALL cells. Blinatumomab first engages the T-cell through an anti-CD3 arm. Once engaged, the T-cell is re-directed to bind to CD19-expressing ALL cells via its anti-CD19 arm. Within minutes after the T-cell and ALL cell are in contact, the T-cell becomes active and induces perforin-mediated death of the targeted ALL cell.

Topp et al. treated 21 ALL adult patients in first complete remission but with persistent minimal residual disease (MRD). Blinatumomab was given at a dose of 15 mcg/m2 daily by continuous infusion over 24 hours daily for 1 month with possible repeat of courses. Past experience indicated a very poor outcome of patients with ALL in first complete remission and persistent MRD unless they undergo allogeneic stem cell transplant promptly (6). However, of the patients receiving treatment, 16 patients became MRD negative, 12 of which were molecularly refractory to prior chemotherapy. With a median follow-up of 15 months, the 1-year probability of relapse-free survival was 78% across all patients. For patients who did not undergo allogeneic stem cell transplant, the 1-year probability of relapse-free survival was 60% (7).

More recently, blinatumomab was investigated in 18 patients with active refractory ALL. Early analysis reported marrow complete responses, including 9 CRs, in 12 patients treated. Blinatumomab is currently undergoing pivotal trials in refractory ALL with the aim of potential approval of this treatment as single-agent therapy. The study is open for accrual.

SAR3419

SAR3419 is an anti-CD19 antibody conjugated to maytansine. Only after it has been bound and taken up by the tumor cells is the active drug released from the immunoconjugate. Targeted therapy like SAR3419 has the potential for high efficacy and low toxicity.

Phase II studies in lymphoma showed response rates of 30 to 40 percent. This has led to a Phase II study of SAR3419 in adult ALL. SAR3419 is given intravenously weekly for 4 to 8 weeks (until CR), then every other week for another 12 doses. Patients are required to have adequate liver and kidney functions, and expression of CD19 on leukemia cells. The study is open for accrual.

DT2219ARL

Monoclonal antibodies, when linked to toxic moieties, form highly specific and potent anti-cancer agents called immunotoxins. A mixture of immunotoxins targeting CD19 and CD22 was recently proven to be effective in killing pre-B

ALL cells in vitro (8). Diphtheria toxin fused to IL-2 (DAB386IL2) or IL-3 (DT388IL3) is being tested for the treatment of patients with CLL and ALL, respectively. DT2219ARL is a genetically engineered fusion toxin protein consisting of the enzymatically active portion of diphtheria fused to the Fv fragments of the antibodies targeting the CD19 and CD22 cell surface receptors. In vitro, studies have shown specific and reproducible cytotoxic activity (9).

We are participating in a Phase I multicenter study which is currently accruing. Patients will be treated with four every-other-day IV infusions.

Inotuzumab Combined with Mini-Hyper-CVAD in Older Patients with ALL

Among patients 60 years or older with ALL, hyper-CVAD chemotherapy results in a CR rate of 80 percent, but the regimen is toxic. One-third of patients achieving CR may die of myelosuppression-associated complications, and the long-term cure rate is only 15 to 20 percent. Because of the potency of inotuzumab and its low toxicity profile, we have designed a new regimen combining "mini-hyper-CVAD" with inotuzumab. The chemotherapy doses in mini-hyper-CVAD are 50 percent of the standard doses, and the methotrexate-cytarabine doses are 25 percent of the standard doses. Inotuzumab is added as a single short infusion with each of the first four courses of chemotherapy. It can also be given later for persistent minimal residual disease. This study is ongoing.

Ponatinib Combination with Hyper-CVAD in Ph-Positive ALL

Hyper-CVAD has good activity in Philadelphia-positive B-ALL, with CR rates of 90 percent. Despite improvement in CR rates and median CR durations compared with earlier published ALL regimens, three-year survival and disease-free survival are less than 10 percent. Thomas et. al. have reported CR rates of 94 percent using hyper-CVAD and imatinib. Long-term follow-up of patients who received the hyper-CVAD and imatinib regimen continue to demonstrate favorable disease- free survival rates compared with hyper-CVAD alone. Dasatinib is 325-fold more potent than imatinib in cells transduced with wild-type BCR-ABL, and has demonstrated preclinical activity against 18 of 19 imatinib-resistant BCR-ABL mutants. We are currently conducting a Phase II study to evaluate the clinical efficacy of an intensive short-term chemotherapy regimen (Hyper-CVAD program) given in combination with the tyrosine kinase inhibitor dasatinib for Philadelphia-positive acute lymphoblastic leukemia. Interim results from this study have been encouraging, with a CR rate of 94 percent, median disease-free survival and median overall survival have not been reached, and an estimated 2-year survival of 64% (10).

In several front-line studies of Ph-positive ALL, relapses were noted with a high incidence of T315I mutation. This mutation is sensitive to ponatinib, a third- generation pan-BCR-ABL inhibitor. Therefore, combining ponatinib and chemotherapy in Ph-positive ALL might enhance overall activity, reduce resistance resulting from T315I clones and improve cures. We have designed a study combining hyper-CVAD and ponatinib 45 mg orally daily. This study is open for newly diagnosed Ph-positive ALL, including patients who have received one cycle of chemotherapy.

T-cell ALL

Nelarabine was developed based on the success of cytarabine and fludarabine, the most important agents in the therapy of AML and CLL, respectively. Studies predicted that nelarabine might be most effective in T-cell malignancies. Nelarabine is currently administered as a short daily or every-other-day infusion. The dose-limiting toxicity was acute neurotoxicity. Recent studies have tried different dosing schedules of nelarabine including short versus long infusions (11). Neurologic toxicity was least common with slow infusion.

Based on this, we currently have a Phase I trial in which nelarabine is administered as a five-day continuous infusion via central catheter for patients with relapsed-refractory disease. The goal is to minimize neurotoxicity.

(continued on page 6)

CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytoxan + Rituximab (FCR) (2008-0431)
- Ofatumumab (2010-0241/2011-0520)
- CAL-101 + Rituximab (2010-0388)
- GA101 + Chemo (2010-0894)
- Lenalidomide + Rituximab (2011-0509)

2. Prior Therapy

- Ofatumumab (2010-0266)
- FBR (2009-0546)
- ABT-263 + FCR or BR (2009-0077)
- Revlimid (2007-0213)
- Bafetinib (2010-0175)
- Sapacitabine + Cytoxan + Rituximab (2010-0516)
- AVL-292 (2011-0513)

3. Other

- Hairy Cell: 2CDA + Rituximab (2004-0223)

AML/MDS Treatment Priorities

1. Newly Diagnosed

A. Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17):

- ATRA + Arsenic +/- Idarubicin (2006-0706)
- ATRA + Arsenic +/- Gemtuzumab (2010-0981)

B. Cytogenetic feature: Inv16 or t(8:21): Fludarabine + Ara-C + Idarubicin (2007-0147)

C. **Younger Patients:**

- Ida + Ara -C (2006-0813)
- Oral Panobinostat + IA (2010-0591)
- AC220 + 3 + 7 (2011-0041)

Older Patients:

- DAC +/- Clofarabine (2008-0092)
- Vorinostat + Aza (2007-0685)
- Plerixafor + Clofarabine (2009-0536)
- Azacitidine vs Conventional Care (2009-1001)
- Sapacitabine vs. DAC vs. Both (2010-0727)
- Sorafenib + Azacitidine (2010-0511)
- Omacetaxine + LD Ara-C (2010-0736)
- Cladribine + LD Ara-C/DAC (2011-0987)

2. Salvage Programs

- Tamibarotene (2007-0512) in APL
- Sapacitabine (2007-0727)
- IA + SAHA (2007-0835)
- Plerixafor + Sorafenib (2008-0501)
- GSK1120212 (2009-0239)
- Vidaza + Revlimid (2009-0467)
- Oral Panobinostat + Vidaza (2009-0619)
- MK-2206 (2010-0243)
- PKC 412 + Aza (2010-0374)
- SGI-110 (2010-0615)
- Ara-C +/- Vosaroxin (2010-0692)
- CIA vs FAI (2010-0788)
- MDX-1338 (2010-0825)
- Plerixafor + G-CSF (2011-0036)
- CWP232291 (2011-0253)
- Clofarabine + LD Ara-C (2011-0660)

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

- Oral Clofarabine (2005-0536)
- Lenalidomide (2009-0737)
- Azacitidine (2007-0405)
- Deferasirox (2010-0041)
- Alemtuzumab (2010-0187)
- ON 01910 (2010-0209)
- TXA 127 (2010-0805)
- Best Care +/- Siltuximab (2011-0548)
- ARRY-614 (2011-0827)

ALL Treatment Priorities

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

A. Modified Hyper CVAD (ID02-230)
B. Age <40:Augmented BFM (2006-0375)
C.Hyper CVAD + Ofatumumab (2010-0708)
D.Age >60: Low Dose Hyper CVAD + CMC-544 (2010-0991)
E. Burkitt's: Hyper CVAD + Rituximab (ID02-229)
F. Ph+: Hyper CVAD + Dasatinib (2006-0478/SW0G0805)
- Hyper CVAD + Ponatinib +/- Rituximab (2011-0030)

G. T cell: Hyper CVAD + Nelarabine (2006-0328)

2. Salvage Programs

- MOAD (2008-0267)
- DT2219ARL (2008-0519)
- RAD001 + Hyper CVAD (2009-0100)
- PF-03084014 (2010-0317)
- SAR3419 (2011-0287)
- BMS-906024 (2011-0382)
- Blinotumimab (2011-0784)

CML Treatment Priorities

1. CML Chronic Phase

- Dasatinib (2005-0422)
- Nilotinib (2005-0048)

2. TKI Failures, T315I Mutations or Advanced Phases

- DCC-2036 (2008-0732)
- Nilotinib (2009-0683)
- LDE225 + Nilotinib (2011-0394)

Myeloproliferative Disorders

1. Myelofibrosis

- Pomalidomide (2007-0199)
- LY2784544 (2010-0167)
- BMS-911543 (2010-0782)
- INC (2010-0964)
- AB0024 (2011-0016)
- NS-018 (2011-0090)
- INCB 018424 (2011-0213)
- Ruxolitinib + Revlimid (2011-0269)
- Ruxolitinib (2011-0359)
- IPI-926 (2011-0445)
- CYT387 (2011-0458)

2. Polycythemia Vera

- INC 424 (2010-0808)

3. Essential Thrombocythemia

4. Systemic Mastocytosis

- Masatinib (2008-0275)

Phase I/II Agents for Hematologic Malignancies

- L-Grb2 Antisense (2003-0578)
- RO5045337 (2007-0408)
- DT388IL3 (2008-0313)
- DCC-2036 (2008-0732)
- AS703026 (2009-0195)
- Nelarabine (2009-0717)
- PR104 (2009-0772)
- ABT348 (2009-0788)
- Thiarabine (2009-1000)
- PF-04449913 (2010-0078)
- TG02 (2010-0244)
- TH-302 (2010-0268)
- ON 01910.Na (2010-0303)
- INCB018424 (2010-0450)
- KB004 (2010-0509)
- Dasatinib + BMS-833923 (2010-0785)
- CA-18C3 (2010-0933)
- PM01183 (2010-0965)
- AMG900 (2011-0369)
- AZD1208 (2011-0816)

Other Phase I/II Investigational Agents for ALL

4'-Thio-araC (Thiarabine)

4'-Thio-araC is structurally related to cytarabine and, like other drugs in this class (cytarabine and gemcitabine), requires conversion to the active triphosphate by intracellular kinases. But 4'-thio-araC was found to be 10- to 20-fold more potent as an inhibitor of DNA synthesis than the 5'-triphosphate of cytarabine (12). In vitro studies have also shown potential anti-angiogenic effect. 4'-Thio-araC was more efficacious than cytarabine in nine of nine xenograft tumor models . Phase I studies in solid tumors have established the maximum tolerated dose, and a study is ongoing for salvage therapy in adult ALL.

INCB018424

The JAK-STAT signaling pathway is constitutively activated in a spectrum of human malignancies including AML and ALL. A series of studies has defined somatic alterations in JAK1, JAK2, and JAK3 in patients with ALL, including in Down syndrome-associated ALL and in patients with high risk and/or relapsed ALL (13). INCB018424 has been very effective in the treatment of symptomatic myelofibrosis. After two or more weeks of INCB018424 therapy, 44 percent to 79 percent of patients showed a reduction in individual symptom scores of at least 50 percent when all dose levels were combined and assessed together. Given the promising results in myelofibrosis, we are now conducting a Phase I/II prospective study to determine the safety and efficacy of INCB018424 in patients with refractory or relapsed acute lymphoblastic leukemia.

References

1. Thorson J, Sievers E, Ahlert J, et al. Understanding and exploiting nature's chemical arsenal: the past, present and future of calicheamicin research. Cur Pharm Des 6: 1841-79, 2000.
2. Ricart A. Antibody-drug conjugates of calicheamicin derivative: gemtuzumab ozogamicin and inotuzumab ozogamicin. Clin Cancer Res; 17(20) 6417-6427, 2011.
3. Advani A, Coiffier B, Czuczman M, et al. Safety, pharmacokinetics, and preliminary clinical activity of inotuzumab ozogamicin, a novel immunoconjugate for the treatment of B-cell non-Hodgkin's lymphoma: results of a phase I study. J Clin Oncol 28, 2085-93, 2010.
4. Di Joseph J, Dougher M, Kalyandrug L, et al. Antitumor efficacy of a combination of CMC-544 (inotuzumab ozogamicin), a CD22-targeted cytotoxic immunoconjugate of calicheamicin, and rituximab against non-Hodgkin's B-cell lymphoma. Clin Can Res 12: 242-249, 2006.
5. Kantarjian H, Jabbour E, Jorgensen J, et al. Inotuzumab ozogamicin, a CD22 monoclonal antibody conjugated to calicheamicin, shows significant antileukemic activity in patients with refractory-relapsed acute lymphocytic leukemia. Submitted, 2011.
6. Schultz K, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group study. Journ of Clin Onc 27 (31): 5175-5181, 2009.
7. Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. JCO 29:2493-8, 2011.
8. Herrera L et al. Immunotoxins against CD19 and CD22 are effective in killing precursor-B acute lymphoblastic leukemia cells in vitro. Leukemia 14:853-858, 2000 and Herrera L et al. Treatment of SCID/human B cell precursor ALL with anti-CD19 and anti-CD22 immunotoxins. Leukemia 17:334-338, 2003.

9. Vallera DA et al. A bispecific recombinant immunotoxin, DT2219, targeting human CD19 and CD22 receptors in a mouse xenograft model of B-cell leukemia/lymphoma. Clin Cancer Res. 11:3879-3888, 2005.
10. Ravandi F et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood 116(12):2070-7, 2010.
11. Gandhi V et al. Phase I trial of nelarabine in indolent leukemias. J Clin Oncol 26(7):1098-1105, 2008.
12. Tiwari KN et al. Synthesis of 4'-thio-beta-D-arabinofuranosylcytosine (4'-thio-ara-C) and comparison of its anticancer activity with that of ara-C. Nucleosides, Nucleotides, Nucleic Acids 19:329-340, 2000 and Parker WB et al. Proc Am Assoc Ca Res 40:297, 1999.
13. Bercovich D. et al. Mutations of JAK2 in acute lymphoblastic leukaemias associated with Down's syndrome. Lancet 372:1484-92, 2008 and Mullighan CG et al. JAK mutations in high-risk childhood acute lymphoblastic leukemia. Proc Natl Acad Sci U S A 106:9414-8, 2009.

List of Leukemia Service Attendings

ALVARADO, YESID	(713) 794-4364
ANDREEFF, MICHAEL	(713) 792-7260
BORTHAKUR, GUTAM	(713) 563-1586
BURGER, JAN	(713) 563-1487
CORTES, JORGE	(713) 794-5783
DAVER, NAVAL	(713) 794-4392
ESTROV, ZEEV	(713) 794-1675
FADERL, STEFAN	(713) 745-4613
FERRAJOLI, ALESSANDRA	(713) 792-2063
FREIREICH, EMIL	(713) 792-2660
GARCIA-MANERO, GUILLERMO	(713) 745-3428
ILIESCU, GLORIA	(713) 563-0502
JABBOUR, ELIAS	(713) 792-4764
KADIA, TAPAN	(713) 563-3534
KANTARJIAN, HAGOP	(713) 792-7026
KEATING, MICHAEL	(713) 745-2376
KOLLER, CHARLES	(713) 792-7747
KONOPLEVA, MARINA	(713) 794-1628
KORNBLAU, STEVEN	(713) 794-1568
NAQVI, KIRAN	(713) 745-6080
NGUYEN, KHANH	(713) 563-0295
O'BRIEN, SUSAN	(713) 792-7543
PEMMARAJU, NAVEEN	(713) 792-4956
QUINTAS-CARDAMA, ALFONSO	(713) 792-0077
RAVANDI, FARHAD	(713) 745-0394
RYTTING, MICHAEL	(713) 792-4855
THOMAS, DEBORAH	(713) 745-4616
VERSTOVSEK, SRDAN	(713) 745-3429
WIERDA, WILLIAM	(713) 745-0428

Leukemia Insights and other valuable information are now available via the World Wide Web.

Our address is: http://www.mdanderson.org/leukemia
or you may E-mail us at: ckoller@mdanderson.org

Editor: *Hagop Kantarjian, M.D.* WebMaster: *Charles A. Koller, M.D.*
Associate Editor: *Sherry Pierce, R.N.*
Assistant Editor: *Jeff Sarmiento*

For referrals, please call 713-563-2000 or 1-85-Leukemia (1-855-385-3642 toll free)

The University of Texas
MD Anderson Cancer Center
18013603
1515 Holcombe Blvd. - 428
Houston, Texas 77030-4009

Leukemia INSIGHTS

Funded in part by the Betty Foster Leukemia Fund