THE UNIVERSITY OF TEXAS
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Leukemia insights

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Innovative Treatment Approaches for Patients with Acute Lymphoblastic Leukemia (ALL)

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is characterized by clonal proliferation of lymphoid progenitors. Significant advances have been made in the last decade toward understanding the disease pathogenesis, refinement of prognostic groups and development of novel therapies that target specific subsets. These risk-adapted therapies are transforming the treatment strategies for adults with ALL and are beginning to result in significant improvements in overall survival (OS). With the current treatment regimens, long-term survival is achieved in approximately 50% of patients with B-cell ALL, 50%-60% with Philadelphia-chromosome-positive ALL, and around 80% with Burkitt's leukemia. In this newsletter we describe clinical trials available for patients with ALL at our institution.

In This Issue

Frontline Treatment

PRECURSOR B-CELL

Augmented BFM in combination with ofatumumab

For AYA patients, the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) tested the concept of a pediatric-inspired regimen in patients up to the age of 60. When compared to historical data, this regimen was found to significantly improve OS (66% versus 44%; $p < 0.001$) mainly in patients up to the age of 45. At our institution, augmented BFM has induced a complete response (CR) rate of 94%, with MRD negativity in 69% and a 3-year CR duration and survival of 71% and 75%, respectively. These results were comparable to R-HCVAD in a similar population. Ofatumumab is a second generation anti-CD20 monoclonal antibody that binds to a different site than rituximab. Ofatumumab targets a membrane proximal small-loop epitope on the CD20 molecule and is more potent than rituximab. The combination of HCVAD with ofatumumab was found to be highly effective. Therefore we are about to initiate a clinical trial testing the combination of the augmented Berlin-Frankfurt-Munster (Augmented BFM) regimen with ofatumumab. This trial allows patients with precursor B-cell ALL up to age 40.

Hyper-CVAD + Ofatumumab

Currently twenty-five patients with de novo pre-B CD20 positive ALL have been treated on this clinical trial. Ofatumumab was given as 2 grams twice per course in the first 4 courses. The rates of CR and minimal residual disease negativity were both 96%. With a median follow-up of 14 months, the one-year progression-free and overall survival rates were 94% and 92%, respectively. This trial allows patients with precursor B-cell ALL Philadelphia negative CD20 positive (regardless of the level of expression).

Hyper-CVAD + Liposomal Vincristine

Eleven patients have been treated so far on our current protocol, 6 of them

continued on page 2

coninued from page 1

Philadelphia-positive. The CR rate was 82%. The MRD negativity rate was 88%. The 6-month CR duration and survival rates were 100% and 90%, respectively. This trial allows patients with precursor B or T-lymphoblastic leukemia or lymphoblastic lymphoma. Patients with CD20 expression above 20% can receive additional rituximab. Patients with Philadelphia-positive ALL can receive additional tyrosine kinase inhibitors. The protocol continues to accrue.

T-CELL

Nelarabine is a prodrug of ara-G and produces cytotoxic levels of ara-GTP in circulating leukemia cells. It has been demonstrated that ara-GTP is accumulated at higher levels in T-lymphoblasts than in myeloblasts or B-lymphoblasts.

Hyper-CVAD + Nelarabine

To try to improve remission duration and long-term disease-free survival, we have developed a hyper-CVAD and nelarabine regimen where two cycles of nelarabine are given during consolidation and two cycles are given during maintenance. Thirty-six patients have been treated so far with a CR rate of 92% and an additional 5% patients achieving PR. This trial is ongoing.

ELDERLY (≥ 60 YEARS)

Among patients 60 years or older with ALL, hyper-CVAD chemotherapy results in a CR rate of 80%, but the regimen can be toxic. One-third of patients achieving CR may die of myelosuppression-associated complications, and many relapse. The long-term cure rate among such patients is only 15% to 20%. The goal with these regimens is to maintain efficacy but reduce toxicity in the elderly ALL population.

Mini-hyper-CVD + Inotuzumab

CD22 expression occurs in >90% of patients with ALL. Inotuzumab is a CD22 monoclonal antibody bound to a toxin, calecheamicin, and has shown single-agent activity in relapsed/refractory ALL. Patients ≥60 years with newly-diagnosed B-cell ALL are eligible for this protocol. The chemotherapy is low-intensity hyper-CVAD (cyclophosphamide and dexamethasone at 50% dose reduction, no anthracycline, methotrexate at 75% dose reduction, ara-C at 0.5 g/m2 x 4 doses). Inotuzumab is given on Day 3 of each of the first 4 courses. Twenty-six patients (median age of 67 years; range, 60 to 79) have been treated so far. The objective response rate was 96% with CR 79% and CR with incomplete platelet recovery (CRp) 17%. All patients achieving response also had a negative MRD status, 75% of them after one cycle. The one-year progression-free and overall survival rates were 86% and 81%, respectively. The one-year survival rate was superior to previous results obtained with HCVAD +/- rituximab in similar patient populations (one-year survival rates 81% and 60%, respectively). This trial continues to accrue.

Marqibo (liposomal vincristine) vs. Standard Vincristine in combination with standard chemotherapy

Vincristine is an active vinca alkaloid antineoplastic agent widely used in many neoplasms including ALL. But neurological effects are the dose-limiting toxicity of the drug. Marqibo is a vinca alkaloid indicated for the treatment of adult patients with Philadelphia chromosome-negative ALL whose disease has progressed following two or more anti-leukemia therapies. Patient's age ≥ 60 years are eligible for this phase III randomized trial comparing Marqibo or standard vincristine in combination with multi-agent chemotherapy.

BURKITT'S

Burkitt's Leukemia/Lymphoma is an aggressive mature B-cell neoplasm characterized by translocation of the MYC gene. The addition of rituximab to standard chemotherapy has been shown to improve outcomes in patients with Burkitt's leukemia with a CR rate of 86% and a 3-year survival of 89%.

Dose adjusted EPOCH + Ofatumumab/ Rituximab

In a pilot trial in 30 patients treated at the NIH, dose adjusted EPOCH in combination with rituximab was found to be safe and highly effective. All patients achieved a CR/CRu. The survival and progression-free survival rates (OS and PFS) were both 100% at a median follow-up of 28 months. Significant toxicities included tumor lysis syndrome in only one patient and fever/neutropenia in 16% of cycles. There were no treatment related deaths. This trial will open soon and allow patients with de novo and relapsed/ refractory Burkitt's leukemia.

Hyper-CVAD + Ofatumumab

We are currently investigating ofatumumab in combination with Hyper-CVAD chemotherapy for patients with Burkitt's leukemia. Ofatumumab is given for a total of 8 doses (2 doses each in the first 4 chemotherapy cycles).

PHILADELPHIA CHROMOSOME POSITIVE

The combination of cytotoxic chemotherapy with imatinib or dasatinib is effective in the treatment of Philadelphia-positive ALL. Ponatinib is a more potent BCR-ABL inhibitor. It also suppresses the T315I clones, a common cause of relapse in patients with Philadelphia-positive ALL. Clinical trials of ponatinib have demonstrated its high activity in Philadelphia-positive leukemias. The combination of chemotherapy and ponatinib may be associated with better response rates and higher likelihood of eradication of minimal residual disease than those reported with imatinib or dasatinib and chemotherapy.

Hyper-CVAD + Ponatinib

We have designed a phase II study combining hyper-CVAD and ponatinib. This study is open for newly diagnosed Ph-positive ALL, including patients who have received one cycle of chemotherapy. To date, 37 patients have been treated. The CR, CCyR, MMR, and CMR rates were 100%, 100%, 95%, and 70%, respectively. With a median follow-up of 16 months, the 1-year progression-free and survival rates were 100% and 86%. Two deaths due to vascular events potentially related to ponatinib were observed. Subsequently the study was amended: ponatinib was reduced to 30 mg after the first course and further reduced to 15 mg once a complete molecular response is achieved. Furthermore, risk factors will be optimized including the use of baby aspirin and low-dose statins if no contra-indications. Patients will receive additionally 12 intrathecal therapies (2 per courses for the first 6 courses) to minimize the risk of late CNS relapse. This trial is ongoing and accruing both newly diagnosed and previously treated patients with Philadelphia-positive ALL.

MIXED PHENOTYPE ACUTE LEUKEMIA (MPAL)

Throughout the years, these leukemias have been referred to by a number of names, including mixed lineage leukemia, biphenotypic leukemia, bilineal leukemia, hybrid leukemia, undifferentiated leukemia, or leukemia of ambiguous lineage. This terminology has been used to describe leukemias with a single population of cells expressing markers from multiple lineages, as well as leukemias exhibiting two distinct blast populations each belonging to a distinct lineage. In 2008, the World Health Organization grouped these processes together under the heading MPAL. There is very little reported in the literature on adults with MPAL, and as a referral center, we may encounter these patients more often than many other institutions. A contemporary regimen employing drugs active against both myeloid and lymphoid leukemias may be the optimal approach.

Clofarabine, idarubicin, cytarabine, vincristine, and corticosteroid +/- rituximab

We are proposing to use a hybrid regimen, with components of both AML and ALL therapy, to treat patients diagnosed with MPAL at MDACC. The backbone of the regimen will be our standard induction for AML, clofarabine, idarubicin, and cytarabine administered at attenuated doses. Importantly, all three of these drugs also have activity against ALL. In addition, we will add vincristine and corticosteroids to the regimen for enhanced lymphoid activity. These are ideal candidates for addition to the regimen for a number of reasons. First, the toxicity profiles do not overlap,

coninued on page 6

Leukemia *insights*

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CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytoxan + Rituximab (FCR) (2008-0431)
- Ofatumumab (2010-0241/2011-0520)
- Lenalidomide + Rituximab (2011-0509)
- CAL-101 + Rituximab (2011-0612)
- TRU-016 + Rituximab (2012-0626)

2. Prior Therapy

- Sapacitabine + Cytoxan + Rituximab (2010-0516)
- ABT-199 (2011-0164/2013-0315)
- CD19 CAR (2011-1169)
- Ublituximab + TGR-1202 (2013-0566)
- Ibrutinib +/- Rituximab (2013-0703)
- ACP-196 (2013-0907)
- ACP-196 + ACP-319 (2014-0419)

3. Minimal Residual Disease

- Revlimid (2007-0213)

4. Hairy Cell

- 2CDA + Rituximab (2004-0223)
- Moxetumomab (2013-0302)
- PCI-32765 (2013-0299)

AML/MDS Treatment Priorities

1. Newly Diagnosed

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

- ATRA + Arsenic +/- Gemtuzumab (2010-0981)

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

C. Younger Patients:

- CIA vs FAI (2010-0788)
- 3 + 7 vs IA+Vorinostat (S1203)
- PF-04449913 with 3 + 7 (2012-0062)
- Cladribine + IA + Sorafenib (2012-0648)

D. Older Patients:

- Sapacitabine (2007-0727)
- SGI-110 (2010-0615/2013-0843)
- Sapacitabine vs. DAC vs. Both (2010-0727)
- Omacetaxine + LD Ara-C (2010-0736)
- Cladribine + LD Ara-C/DAC (2011-0987)
- PF-04449913 with LD Ara-C or DAC (2012-0062)
- LD Ara-C + Lintuzumab (2012-0434)
- CPX-351 vs. Ara-C + Dauno (2012-0980)
- DAC 5 vs. 10day (2012-1017)
- Vosaroxin + DAC (2013-0099)
- LD Ara-C +/- Volasertib (2013-0416)
- Pracinostat + Aza (2013-0596)

2. Salvage Programs

- Clofarabine + LD Ara-C (2011-0660)
- Crenolanib (2012-0569)
- BL-8040 (2012-1097)
- AC220 + Aza or Ara-C (2012-1047)
- DAC + CIA (2012-1064)
- Trametinib + GSK2141795 (2013-0001)
- Rigosertib + Aza (2013-0030)
- Birinapant + Aza (2013-0141)
- Eltrombopag (2013-0225)
- Pracinostat + Aza (2013-0321)
- DAC vs DAC + Carboplatin vs DAC + Arsenic (2013-0543)
- Volasertib + DAC (2013-0583)
- ABT-199 (2013-0656)
- ASP2215 (2013-0672)
- IGN 523 (2013-0971)
- AC220 vs Salvage Therapy (2014-0058)
- AG-221 (2014-0408)

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

- Deferasirox (2010-0041)
- DAC vs. Aza (2012-0507)
- Horse ATG (2012-0334)
- Sotatercept (2012-0428)
- Bortezomib (2012-0562)
- Rigosertib (2012-0598/2013-0324)
- Oral Aza vs. Placebo (2012-0733)
- Ruxolitinib (2013-0012)
- MK-3475 (2013-0531)
- Eltrombopag + DAC (2013-0590)
- Pracinostat + DAC or Aza (2013-0873)
- MEDI 4736 (2013-1041)
- FF-10501-01 (2014-0014)
- ASTX 727 (2014-0089)

4. MDS/MPN

- Ruxolitinib + Aza (2012-0737)

5. Maintenance/MRD

- Oral Aza vs. Best Care (2012-0866)

ALL Treatment Priorities

1. Newly Diagnosed or Primary Refractory

(one non-hyper-CVAD induction)

A. Age <40:Augmented BFM (2006-0375)

B. Age >60: Marquibo (2011-1071)

- Low dose Hyper CVD + CMC-544 (2010-0991)

C. Hyper CVAD + Ofatumumab (2010-0708)

D. Hyper CVAD + Liposomal Vincristine (2008-0598)

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

F. Ph+: Hyper CVAD + Ponatinib (2011-0030)

2. Salvage Programs

- A-dmDT390-bis Fv (2008-0077)
- Low Dose Hyper CVAD + CMC-544 (2010-0991)
- Rituximab (2011-0844)
- BMS-906024 (2011-0382)
- Inotuzumab Ozogamicin (2012-0151/2013-0144)
- MOR 00208 (2012-0904)
- DAC + CIA (2012-1064)
- Moxetumomab (2012-1143)
- Blinatumomab vs SOC (2013-0161)
- Ibrutinib (2013-0459)

3. CNS Disease

- Intrathecal Rituximab (2011-0844)

CML Treatment Priorities

1. CML Chronic Phase

- Nilotinib (2005-0048)
- Ponatinib (2012-0074)

2. TKI Failures, T315I Mutations or Advanced Phases

- Dasatinib + DAC (2011-0333)

3. Minimal Residual Disease

- Ruxolitinib (2012-0697)

Myeloproliferative Disorders

1. Myelofibrosis

- NS-018 (2011-0090)
- Sotatercept (2012-0534)
- Ruxolitinib + Aza (2012-0737)
- PRM-151 (2013-0051)
- Momelotinib vs. Ruxolitinib (2013-0741)
- Oral Pacritinib vs Best Available Therapy (2013-1001)
- Momelotinib (2014-0145)

2. Systemic Mastocytosis

- Masatinib (2008-0275)
- Brentuximab (2012-0734)

3. ET and PV

- Momelotinib (2013-0977)
- Anagrelide CR (2014-0354)

Phase I/II Agents for Hematologic Malignancies

- L-Grb2 Antisense (2003-0578)
- Nelarabine (2009-0717)
- KB004 (2010-0509)
- BKM120 (2010-0874)
- CWP232291 (2011-0253)
- PM01183 (2010-0965)
- AMG900 (2011-0369)
- PRI-724 (2011-0527)
- DFP-10917 (2012-0262)
- KPT-330 (2012-0372)
- EPZ-5676 (2012-0374)
- GSK525762 (2013-0527)
- MRX34 (2014-0052)
- CB-839 (2014-0152)

coninued from page 3

allowing us to safely give all five agents during the same course of therapy. Second, corticosteroids are routinely used as a premedication to prevent toxicity induced by moderate to high doses of cytarabine, albeit at lower doses. The trial is approved to open soon allowing patients with de novo and relapsed MPAL.

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Salvage Treatment

NEW MONOCLONAL ANTIBODIES IN PRE-B ALL

Almost all pre-B ALL leukemic cells express CD19 and CD22. Several monoclonal antibodies target CD19 and CD22, and have shown high activity in refractory and relapsed ALL.

Inotuzumab Ozogamicin (anti-CD22 monoclonal antibody conjugated to calecheamicin)

Calecheamicin is a natural product of micromonospora echinospora, and is significantly more toxic than chemotherapy. It binds to the minor DNA groove and causes double-strand DNA breaks resulting in cell apoptosis. Inotuzumab binds to CD22 with subnanomolar affinity, is rapidly internalized and delivers the conjugated calecheamicin intracellularly.
We conducted two studies of inotuzumab in refractory or relapsed ALL, one with 1.3-1.8 mg/m2 single dose every 3-4 weeks (n=49), and a second with a weekly dose (0.8 mg/m2 D1, 0.5 mg/m2 day 9 and day 15; every 3 weeks) (n=41). In the 90 patients treated, the marrow CR rate was 55%. The median survival was 6.3 months.

Inotuzumab vs. Standard Chemotherapy

Encouraging results with single-agent inotuzumab have led to an ongoing international study comparing weekly inotuzumab to standard ALL chemotherapy (FLAG at MD Anderson) in first or second ALL salvage. This study is ongoing and open at MD Anderson and other centers.

Mini-hyper-CVD + Inotuzumab

Inotuzumab in combination with lower intensity hyper-CVD chemotherapy is also available for patients with relapsed ALL. Thirty-two patients were treated so far. The observed objective response rate was 70% (CR in 50%). The 6-month progression-free and overall survival rates were 81% and 65%. The protocol continues to accrue.

BLINATUMOMAB

The Bispecific T-cell Engaging (BiTE) antibody blinatumomab represents the first agent in a class that redirects host T-cells to cell surface antigen-expressing cancer cells. Blinatumomab contains the variable domains of a CD19 antibody and a CD3 antibody which are joined by a non-immunogenic linker. Upon binding to CD19, the cytotoxic T cells become activated and induce cell death via the pore-forming perforin system. Based on the short half-life of the drug and the mechanism of action, continuous infusions over several weeks were investigated. This drastically improved the activity of the drug, particularly in ALL, and minimized adverse effects.
The first study with blinatumomab used as continuous infusion evaluated its potential role in eradicating MRD. MRD conversion after one cycle was observed in 16 of 20 evaluable patients (80%). In a long-term follow up update (median observation time 33 months), 12 of the 20 patients remained in CR. The estimated 3-year relapse-free survival was 60%. Blinatumomab was subsequently studied in patients with active systemic ALL relapse.
In a confirmatory open-label, single-arm, multicenter phase II study in 189 patients with relapsed-refractory disease, the overall response rate was 43% with 80% of the responses occurring within cycle 1. The median response duration and overall survival were 9 and 6 months, respectively.

Blinatumomab vs. Standard Chemotherapy

Blinatumomab is currently being assessed in a phase III trial in patients with ALL in first or second relapse who

are randomized to either blinatumomab or an investigator's choice chemotherapy regimen. This study is ongoing and open at MD Anderson and other centers.

MOXETUMOMAB

BL22 (CAT-3888) is an anti-CD22 immunotoxin composed of a variable fragment (Fv) derived from a monoclonal antibody directed toward CD22 and fused to a 38-kDa fragment of Pseudomonas aeruginosa exotoxin A (RFB4 [dsFv]-PE38). Following preclinical studies demonstrating the cytotoxic effect of BL22 against CD22+ cell lines and leukemic cells from patient samples, BL22 was also found to be highly active in phase I/II human studies in hairy cell leukemia. To improve the efficacy of BL22 in non-HCL malignancies, further mutagenesis analysis was performed and resulted in the selection of an Fv with a higher binding affinity to surface CD22 by virtue of a slower off-rate. This new compound, initially named high-affinity BL22 (HA22), was later renamed moxetumomab pasudotox. In a phase I study, 21 children and young adolescents with relapsed-refractory ALL received moxetumomab pasudotox every other day for six doses. Cycles were repeated every 3 weeks. Of 17 evaluable patients, 24% achieved CR, 6% had partial response, and 47 % had hematological improvement for an overall activity rate of 77%. Treatment was well tolerated. Moxetumomab pasudotox is currently being assessed in a Phase I/II study in patients with relapsed/refractory ALL. The trial is open to accrual.

Other Novel Treatment Strategies

NELARABINE (SINGLE-AGENT) CONTINUOUS INFUSION

Pharmacodynamic studies have shown that continuous infusion of nelarabine (as opposed to short infusions) leads to higher intracellular ara-GTP levels and thus may lead to improved clinical outcomes. In the present trial, patients receive a 5-day continuous infusion of nelarabine which is repeated every 4-6 weeks. This trial is open to accrual in a variety of lymphoid malignancies.

BMS-906024 (NOTCH-INHIBITOR)

The Notch pathway plays a critical role in the development of normal lymphocytes, and aberrant activation of Notch plays an important role in lymphoid malignancies. In this trial, BMS-906024 is administered intravenously on a weekly schedule. Patient with relapsed or refractory T-cell ALL or T-cell lymphoblastic lymphoma are eligible. This trial is open to accrual.

IBRUTINIB

BTK is expressed in B-ALL cell lines but not in T-ALL. The function of BTK in B-ALL is controversial. Generally, pre-B cells undergo apoptosis unless they are rescued by pre-BCR-dependent survival signals, and BTK is an integral part of the BCR signaling cascade, suggesting that BTK inhibition with ibrutinib would thwart pre-BCR-derived survival signals. In vitro, ibrutinib reduced primary pre-B ALL cells viability with variable efficacy and inhibited pre-B ALL cell proliferation and metabolism, providing a rationale for clinical testing of this novel, well-tolerated targeted agent in patients with relapsed B-ALL. Patients with relapsed or refractory B-ALL in first, second or third salvage, and Philadelphia-positive ALL who have failed treatment with at least 1 second generation tyrosine kinase inhibitor are eligible. This trial is open to accrual.

INTRATHECAL RITUXIMAB IN PATIENTS WITH LYMPHOID MALIGNANCIES INVOLVING THE CENTRAL NERVOUS SYSTEM

CNS relapse is common in ALL. Patients who develop CNS disease have historically a poor prognosis. Phase I studies have established the safety of intraventricular rituximab in patients with primary CNS and intraocular lymphoma. An ongoing phase I/II study is testing the effectiveness of intraventricular rituximab in patients with ALL CD20-positive with CNS relapse. This trial is open to accrual.

Conclusion

Our ALL program continues to build on the advances made in therapy and the ever expanding knowledge of the disease and it's subsets in order to offer more therapeutic strategies for our patients. For information about our program and any of these options, contact Elias Jabbour, Susan O'Brien, or any Leukemia physician.

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Leukemia insights

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