THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center®

Leukemia insights

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Chronic Lymphocytic Leukemia: Evolution of Non-Chemotherapy Based Approaches

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in the Western world. Approximately 16,060 men and women were diagnosed with CLL and approximately 4500 patients died from CLL in 2012 in the US. Chemoimmunotherapy (CIT) is the current standard of care therapy for patients with CLL. MD Anderson pioneered CIT with development and testing of the FCR (fludarabine, cyclophosphamide, rituximab) regimen. In the first-line setting, treatment with the FCR regimen results in complete remission (CR) in 72% of treated patients with a median progression-free survival (PFS) of 6.6 years. Patient subgroups can be identified where improved outcomes are still needed. Subgroups include elderly patients (>65 yrs old), those with high-risk genetic abnormalities [del(17p), del(11q), complex karyotype, unmutated IGHV gene] and those who develop relapsed, refractory disease. Elderly and patients with comorbidities do not tolerate FCR as well as young fit patients with CLL, due to myelosuppression.

Indeed, standard first-line therapy for elderly is CIT with combined chlorambucil and obinutuzumab, a type II CD20 monoclonal antibody (mAb), which does not achieve the high complete remission rate and durable remissions as FCR, but is less myelosuppressive and better tolerated by the elderly population. Del(17p) by FISH is associated with loss of the TP53 gene, which confers resistance to standard chemotherapy such as purine analogues and alkylating agents. As such, poor outcomes are seen with standard CIT regimens in patients with del(17p). Based on efficacy and durable disease control, the Bruton's Tyrosine Kinase (BTK) inhibitor, ibrutinib has become standard first-line monotherapy for patients with del(17p), regardless of patient age.

We have undertaken many developmental approaches to improve outcomes for patients with CLL, including incorporation of drugs such as lenalidomide, ofatumumab, alemtuzumab, and bendamustine. Small molecule inhibitors of intracellular kinases and other proteins are new categories of drugs with novel mechanism of action that have fundamentally changed treatment for patients with CLL. Multiple lines of data point to the critical role of B cell receptor (BCR) signaling in the pathogenesis in CLL. There are several

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kinases comprising the BCR, chemokine, and cytokine receptor signaling pathways being pursued as therapeutic targets in CLL including, Bruton's Tyrosine Kinase (BTK), Lyn, Spleen tyrosine kinase (Syk), and PI3 kinases. Furthermore, CLL is characterized by over-expression of the anti-apoptosis protein Bcl-2, which is being targeted with an orally bioavailable, small BH-3 mimetic molecule, as another novel therapeutic strategy in CLL. These oral non-chemotherapeutic agents are proving to be highly effective at managing CLL and are well tolerated with minimal toxicity.

Early Stage Symptomatic or High-Risk CLL

Currently, the standard approach for all patients with early stage (Rai stage 0-II) asymptomatic CLL is to watch and wait. Treatment is initiated when patients develop active disease with indications for treatment according to IWCLL 2008 guidelines. Prognostic factors such as IGHV gene mutation status, ZAP-70 expression status, and chromosome abnormalities by FISH, can identify patients at high-risk for early progression to first therapy.

Ofatumumab (Phase II)

We are currently evaluating early intervention with ofatumumab, a CD20 monoclonal antibody (mAb), for high-risk patients, with the goal to delay time to first CIT. In this trial, patients receive ofatumumab monotherapy as 8 weekly infusions and are then monitored for time to progression. To be considered high-risk, and therefore eligible for the trial, patients must have one or more of the following characteristics: unmutated IGHV gene, del(17p) or del(11q) by FISH, ZAP-70 or CD38 expression, Beta-2 microglobulin ≥3 mg/L, or absolute lymphocyte count ≥25 K/μL. In addition, they may not have any of the standard indications for first-line treatment. Ofatumumab is provided at no charge to the patients on this study.

Ruxolitinib (Phase II)

Patients with CLL often have disease-related symptoms, even at an early stage of the disease. Preclinical work showed that patients with CLL have activated JAK-STAT pathway and increased levels of inflammatory cytokines. Ruxolitinib blocks JAK-STAT signaling, reduces levels of inflammatory cytokines, and is FDA approved for treatment of patients with myelofibrosis. We are currently evaluating ruxolitinib for patients with CLL who have disease-related fatigue but do not otherwise have an IWCLL 2008 indication for treatment. Eligible patients may be treatment-naïve or previously treated, should have only disease-related fatigue and not have any of the other criteria used to initiate standard treatment for CLL. Ruxolitinib is provided at no charge to the patients on this study.

Lenalidomide

Lenalidomide is an immune-modulating agent that has immune-restoring activity and monotherapy activity in treating CLL. We are currently evaluating lenalidomide for patients with CLL who have low immunoglobulin level (IgG <400) but do not otherwise have an IWCLL 2008 indication for treatment. Patients will also be studied for immune response to influenza and pneumococcal vaccination. Patients may be previously untreated or may have received prior treatment. Lenalidomide is provided at no charge to the patients on this study.

First-line Therapy for CLL

First-line CIT was shown in randomized trials to result in improved outcomes, including overall survival, and is well tolerated by younger patients with no significant comorbidities. The FCR combination is considered standard first-line treatment for these patients. Patients who are older tend to have comorbidities and do not tolerate the myelosuppression of FCR as well as their younger counterparts. Obinutuzumab (GA-101) is a new, type II CD20 mAb recently approved by FDA in combination with chlorambucil for first-line treatment of patients with CLL who have comorbidities, which typically includes those in the elderly age group. This type II CD20 mAb appears superior to rituximab, the standard type I CD20 mAb, and is being incorporated in the new CIT and non-CIT regimens and treatment strategies in development.

FCR Combination Chemoimmunotherapy

For patients who are able to tolerate CIT, FCR remains the standard chemotherapy of choice for first-line treatment of patients with non-del 17p CLL. For patients with mutated IGHV gene, 10-year progression-free survival after FCR CIT is close to 60%. We are currently working on refining the FCR regimen to incorporate a BCR-inhibitor and to replace rituximab with the more effective type II CD20 mAb obinutuzumab.

Ofatumumab Monotherapy for Elderly, Unfit Patients (Phase II)

We are currently investigating first-line ofatumumab (type I CD20 mAb) monotherapy for elderly patients who are deemed unfit for CIT. This includes patients with CLL age >65 and either ECOG performance status of 2-3 or ECOG performance status 0-1 with CIRS or Charlson co-morbidity score of 2 or higher. Ofatumumab is given weekly IV at a dose of 300 mg during week 1, then 2000 mg in weeks 2, 3 and 4, then monthly during months 2-12. Ofatumumab is provided at no charge for patients on this study.

ACP-196 (BTK-Inhibitor) (Phase I)

ACP-196 is a novel oral BTK-inhibitor in clinical development. This trial is open for first-line treatment of patients with CLL. ACP-196 is provided at no charge for patients on this study.

Ibrutinib ± Rituximab for Patients with del(17p) (Phase II)

Ibrutinib is the new, irreversible small molecule inhibitor of BTK (see below) with significant monotherapy activity in first-line and in treatment of relapsed and refractory CLL, including del(17p) disease. Ibrutinib is FDA approved first-line for patients with del(17p) CLL and for treatment of relapsed disease. Early phase trials were initiated combining ibrutinib with CD20 mAb and CIT, but it is unclear if combinations significantly improve patient outcomes compared to ibrutinib monotherapy. Therefore, we initiated a randomized phase II clinical trial of ibrutinib ± rituximab. This trial is enrolling treatment-naïve patients with del(17p) (high-risk) CLL and previously treated patients. This trial will study the effects of the addition of CD20 mAb to ibrutinib. Ibrutinib is provided at no charge to the patients on this study.

Relapsed or Refractory CLL

Many agents with novel mechanisms of action are being evaluated in clinical trials for patients with relapsed or refractory CLL.

B Cell Receptor (BCR) Pathway Inhibitors

BCR signaling plays a crucial role in the pathogenesis in CLL and many kinases in the BCR signaling pathway are now being pursued as therapeutic targets including, Bruton's tyrosine kinase, PI3 kinase isoforms, and spleen tyrosine kinase (Syk).

Ibrutinib ± Rituximab (Phase II)

Ibrutinib showed promising monotherapy activity in patients with CLL with an ORR of 71% and additional 20% patients achieving PR with lymphocytosis. Importantly, responses are seen across all cytogenetic risk groups and in heavily pretreated fludarabine-refractory patients. In this randomized phase II trial, we are evaluating the benefit of adding rituximab to ibrutinib. All patients

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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)
- TG02 (2012-0912)
- GDC-0199 + Obinutuzumab (2013-0486)
- Ublituximab + TGR-1202 (2013-0566)
- Ibrutinib +/- Rituximab (2013-0703)
- PRT062070 (2013-0880)
- ACP-196 (2013-0907)
- ACP-196 + ACP-319 (2014-0419)

3. Minimal Residual Disease

- Revlimid (2007-0213)

4. Hairy Cell

- 2CDA + Rituximab (2004-0223)
- 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 (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)

E. Mixed Phenotype:

- Clofarabine + Idarubicin + Ara-C + Vincristine (2013-0073)

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)
- DAC vs DAC + Carboplatin vs DAC + Arsenic (2013-0543)
- Volasertib + DAC (2013-0583)
- ASP2215 (2013-0672)
- Brentuximab +/– Aza (2013-0706)
- RO 5503781 (2013-0746)
- IGN 523 (2013-0971)
- SL-401 (2013-0979)
- AC220 vs Salvage Therapy (2014-0058)
- AG-221 (2014-0408)
- ABT-199 + Aza or Dac (2014-0490)

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

- Deferasirox (2010-0041)
- DAC vs. Aza (2012-0507/2014-0112)
- Horse ATG (2012-0334)
- Sotatercept (2012-0428)
- Bortezomib (2012-0562)
- Rigosertib (2012-0598/2013-0324)
- 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)
- AZA +/– Birinapant (2014-0399)

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)
- Blinatumomab (2013-0602)

3. CNS Disease

- Intrathecal Rituximab (2011-0844)

CML Treatment Priorities

1. CML Chronic Phase

- Bosutinib vs Imatinib (2014-0437)

2. TKI Failures, T315I Mutations or Advanced Phases

- Nilotinib (2005-0048)
- Dasatinib + DAC (2011-0333)
- Ponatinib (2012-0074)
- Omacetaxine (2014-0229)

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)
- MEK 162 (2013-0116)
- GSK525762 (2013-0527)
- MRX34 (2014-0052)
- CB-839 (2014-0152)
- DS-3032B (2014-0565)

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will receive ibrutinib, and ibrutinib is provided at no charge to the patients on this study.

ACP-196 (BTK-Inhibitor) + ACP-319 (P13Kδ-Inhibitor) (Phase I)

This trial is evaluating a combination of two oral BCR pathway inhibitors for previously treated CLL. Each of these agents has monotherapy activity in treating CLL; the trial will evaluate tolerability and activity of the combination. Patients with relapsed or refractory CLL are eligible. Both drugs are provided at no charge to the patients on this study.

ACP-196 (BTK-Inhibitor) (Phase I)

This ACP-196 monotherapy trial is open for patients with relapsed or refractory CLL. ACP-196 is provided at no charge for patients on this study.

TGR-1202 (P13Kδ-Inhibitor) + Ublituximab (novel CD20 monoclonal antibody) (Phase I)

TGR-1202 is a novel oral P13Kδ-inhibitor. Ublituximab is a third generation CD20 monoclonal antibody with enhanced antibody dependent cellular cytotoxicity (ADCC). Patients with relapsed or refractory CLL are eligible. Both drugs are provided at no charge to the patients on this study.

PRT062070 (Phase I)

PRT062070 is an orally available, dual inhibitor of Syk and the JAK family of tyrosine kinases. Patients with relapsed or refractory CLL are eligible. The drug is provided at no charge to the patients on this study.

Bcl-2-Inhibitors

CLL cell survival depends on presence of the anti-apoptotic protein Bcl-2. High levels of Bcl-2 are found in CLL cells and thus, Bcl-2 is a therapeutic target.

ABT-199 + Obinutuzumab (Phase I/II)

ABT-199 (GDC-199) is an oral, small molecule inhibitor of Bcl-2. Previously, a related compound, navitoclax (ABT-263), was studied in phase I/II monotherapy trials in CLL and NHL. There was therapeutic activity in relapsed/refractory CLL with navitoclax; however, since it also inhibited Bcl-xL, it had the dose-limiting toxicity of thrombocytopenia. ABT-199 does not inhibit Bcl-xL and therefore does not have thrombocytopenia as the dose-limiting toxicity (Souers et al. Nature Medicine 2013). ABT-199 monotherapy is highly active in treatment of CLL with an ORR of 84% (20% CR/CRi, 64% PR). ABT-199 can be associated with significant tumor lysis syndrome and must be initiated at a low dose (20 mg) and dose-escalated gradually and cautiously. This trial combines ABT-199 with the highly active type II CD20 mAb, obinutuzumab. Patients with relapsed or refractory CLL are eligible, with a cohort of treatment-naïve patients to open when the phase II dose is identified. Both drugs are provided at no charge to the patients on this study. We will soon be opening trials with ABT-199 for patients with deletion 17p and for patients who have failed tyrosine kinase inhibitors such as ibrutinib.

Lenalidomide + Obinutuzumab (Phase II)

Lenalidomide is an immunomodulatory drug and has monotherapy activity in CLL. We previously reported encouraging activity of lenalidomide combined with rituximab (ORR 66% in R/R CLL). Obinutuzumab is more potent at directly inducing apoptosis in CLL cells (type II), was glyco-engineered to enhance ADCC, and was shown to be a superior CD20 mAb to rituximab when combined with chlorambucil. Lenalidomide enhances NK cell function, therefore, this combination is expected to be more effective than lenalidomide and rituximab. Patients with relapsed or refractory CLL are eligible. Both drugs are provided at no charge to the patients on this pending study.

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Cyclin-Dependent Kinase (CDK) Inhibitor

The CDKs are serine/threonine kinases, are bound by various cyclins, and regulate progression of the cell through specific phases of the cell cycle. There are nine known CDKs (CDK1 to CDK9) and numerous cyclins (cyclin A to cyclin T). In addition to their role in cell cycle progression, CDKs also play an important role in transcriptional regulation by phosphorylating the carboxy terminal domain of the large subunit of ribonucleic acid (RNA) polymerase II. Inhibition of RNA polymerase II potentially leads to the down-regulation of several important intracellular proteins in CLL including Mcl-1 and XIAP, which can induce apoptosis in CLL cells.

TG02 (Phase I)

TG02 is a small molecule oral multi-kinase inhibitor that blocks the actions of a spectrum of oncogenic kinases. These include CDK1 and CDK2, which specifically control cell cycle progression, CDK7 and CDK9, which are responsible for activation of transcription, the signal transducers JAK2 and TYK2, and FLT3 and TYR03 which promote survival. Inhibition of CDK9 (and CDK7) by TG02 in CLL cells drives effective cell killing. Patients with relapsed or refractory CLL are eligible. The drug is provided at no charge to the patients on this study.

Adoptive Immunotherapy with Genetically Modified T cells (CAR therapy)

We have an active protocol with our collaborators in the Department of Stem Cell Transplantation for patients with relapsed/refractory CLL that examines the feasibility of administering autologous ex vivo expanded genetically modified T cells expressing a CD19-specific chimeric antigen receptor (CAR). Patients' autologous T cells are collected via venipuncture or leukapheresis. The CAR-T cell product is manufactured in the Cell Therapy GMP Facility at MD Anderson. Patients receive lymphodepleting chemotherapy with fludarabine and cyclophosphamide prior to their CAR-T cell infusion. This protocol is active and currently accruing patients. We will open soon a ROR1-specific CAR protocol for patients with relapsed/refractory CLL. ROR1 is selectively expressed on malignant B cells and thus ROR1-CAR should spare normal B cells (unlike CD19-specific CAR).

Richter's Transformation of CLL

Richter's transformation (RT) refers to transformation to an aggressive NHL, and is seen in approximately 5-10% of patients with CLL over the course of their disease. The most common variant is transformation to a diffuse large B cell lymphoma histology. Patient with RT have poor outcomes with a median survival of less than 1 year with standard chemoimmunotherapy such as OFAR (oxaliplatin, fludarabine, cytarabine, rituximab). Novel therapies are needed for this group of patients.

Selinexor (KPT-330) (Phase II)

Selinexor is an oral selective inhibitor of nuclear export (SINE) and is currently being studied in patients with NHL. Patients with relapsed or refractory RT are eligible. The drug is provided at no charge to the patients on this study.

ACP-196 (BTK-Inhibitor) (Phase I)

ACP-196 is a novel oral BTK-inhibitor. This trial is open for patients with newly transformed Richter's. ACP-196 is provided at no charge for patients on this study.

Conclusion

In addition to the currently active treatment trials outlined above, we are in the process of opening several other clinical trials for patients with CLL and RT, including combination therapies with BCR-inhibitors, chimeric antigen receptor trials, and trials targeting immune checkpoint inhibitors.
The CLL Section of the Leukemia Department welcomes and will facilitate referrals, and would like to work with you to make novel therapies available to your patients.

For information about our program and any of these options, contact Nitin Jain, William Wierda, or any Leukemia physician.

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