Leukemia insights

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In this month's Leukemia Insights newsletter, written by Elias Jabbour, M.D. and sponsored in part by the Charif Souki Cancer Research Fund, we describe clinical trials available at our institution for patients with ALL, including Philadelphia chromosome (Ph)-negative and positive disease, and in both the frontline and salvage settings. Learn more about our Leukemia program.

Novel Approaches for the Treatment of ALL in Adults in 2023

Acute lymphoblastic leukemia (ALL) is characterized by clonal proliferation of lymphoid progenitors. In the last decade, significant advances have been made in understanding the disease pathogenesis, refining prognostic groups and developing novel therapies that target specific subsets. Therapies targeting either specific transcripts (e.g. Bcr-Abl tyrosine kinase inhibitors) or specific leukemic cell surface antigens (e.g. CD20, CD22, and CD19 monoclonal antibodies) are major breakthroughs. These novel therapies and combinations are transforming treatment strategies for adults with ALL and are beginning to result in significant improvements in survival. In this newsletter, we describe clinical trials available at our institution for patients with ALL, including Philadelphia chromosome (Ph)-negative and positive disease, and in both the frontline and salvage settings. Many of these approaches focus on decreasing or eliminating the role of chemotherapy, with the goal of making these regimens more tolerable in older adults and also decreasing the morbidity and mortality associated with myelosuppression-related infections and other complications of intensive chemotherapy.

When referring a patient for these trials, remember that most allow up to 2 previous cycles of therapy; therefore, patients are eligible 1-2 months after diagnosis. Furthermore, the monoclonal and bispecific antibody constructs (e.g. inotuzumab ozogamicin and blinatumomab) are provided free of charge as part of the trials.

1. Frontline Ph-Negative ALL

- **Hyper-CVAD + blinatumomab + inotuzumab** – Hyper-CVAD is the standard of care for adults able to tolerate intensive chemotherapy. Blinatumomab, the CD3-CD19 bispecific T-cell engager, has also shown significant

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promise in the treatment of ALL, with recent FDA approval based on a survival advantage for patients with relapsed or refractory ALL compared with combination chemotherapy. Blinatumomab has also shown efficacy in eliminating minimal residual disease (MRD). In this study, only 4 (rather than 8) courses of chemotherapy are given, followed by 4 cycles of blinatumomab incorporated into an 18-month maintenance regimen (half the duration of standard POMP maintenance). With the addition of blinatumomab, the goal is to both decrease the amount of intensive chemotherapy received and deepen responses. In the first 38 adult patients treated with Hyper-CVAD plus blinatumomab, the CR rate was 100%, the MRD negativity rate by flow cytometry (FCM) was 97%, and the estimated 3-year survival was 81% (compared to 66% with the historical HCVAD-ofatumumab). This protocol was amended to add the CD22 antibody-drug conjugate inotuzumab ozogamicin, thereby incorporating all of the most active agents in B-cell ALL into our frontline regimen. Thirty-seven patients were so far enrolled and treated with very encouraging results. The CR rate was 100%, the MRD negativity rate by FCM and by next generation sequencing (NGS) rate was 92% and 76%, respectively, and the estimated 2-year survival was 100%. The estimated 3-year overall survival of the whole population treated was 86%. The 3-year survival rates in patients with poor and favorable baseline features were 78% and 90%, respectively. By 3-month landmark analysis, there was no difference in outcome whether an allogeneic stem cell transplantation was performed or not. The 3-year overall survival rates were 86% in patients who received allogeneic stem cell transplantation and 84% in those who did not. This is the best outcome reported so far.

If the data mature with similar results in a larger cohort of patients, this may open a new form of therapy in adult ALL.

- **Hyper-CVD + inotuzumab ozogamicin + blinatumomab –** Because many older patients with ALL are not able to tolerate intensive chemotherapy, we have designed a low-intensity chemotherapy regimen (hyper-CVD) combined with the two most active monoclonal antibodies in ALL: inotuzumab ozogamicin and blinatumomab. Inotuzumab is given at lower, fractionated doses in an attempt to decrease the rate of veno-occlusive disease while maintaining efficacy. Blinatumomab was added to deepen the level of response. In the most recent update of 80 treated patients, the overall response rate is 99%, and no early deaths were observed. Overall, 94% of patients achieved MRD negativity. The 5-year overall survival rate is 46%, which compares favorably to historical data in which similar populations had a cure rate of only 20%. These data are the best reported thus far in this population. This regimen is also available for patients with relapsed/refractory Ph-negative ALL of any age. In order to improve the safety of this regimen in patients who are 70 years and older, the regimen was amended. Patients are receiving a chemotherapy-free regimen with inotuzumab and blinatumomab induction (4 cycles) followed by blinatumomab consolidation (4 cycles). No maintenance is offered. The early results are promising. All first 6 patients treated achieved MRD negative (by NGS) remission.

- Other regimens include **hyper-CVAD plus nelarabine** and the Bcl-2 inhibitor venetoclax (for T-cell ALL) **and low-intensity chemotherapy plus venetoclax** and **navitoclax** (for older patients with Ph-negative ALL). Pre-clinical studies have demonstrated activity of venetoclax and navitoclax in B-cell and T-cell ALL cell lines. Preclinical data suggests as well significant synergy with chemotherapy. Preliminary results of the combination of venetoclax with low-intensity chemotherapy in newly diagnosed older patients unfit for intensive

chemotherapy are promising with objective response and MRD negativity rates of 91% and 100%, respectively. The study provides venetoclax and navitoclax free of charge and is open for accrual. This regimen is open as well for patients with relapsed-refractory ALL, including mainly T-cell ALL.

2. Frontline Ph-Positive ALL

- **Hyper-CVD + ponatinib + blinatumomab** – Ponatinib is a potent third-generation Bcr-Abl tyrosine kinase inhibitor (TKI) that also suppresses the T315I mutation, which confers resistance to all other commercially available TKIs. A study of hyper-CVAD plus ponatinib resulted in a 6-year overall survival rate of 74%, the best so far described in Ph-positive ALL (long-term survival is 40-50% with earlier-generation TKIs). When compared to hyper-CVAD plus dasatinib in a propensity score matching analysis, the combination of H-CVAD and ponatinib had a significantly higher CMR rate (82% versus 65%) and higher 3-year survival rate (83% versus 60%). Given previous experience that full-intensity hyper-CVAD results in significant toxicity in many patients, there is a rationale to combine ponatinib with a less intensive chemotherapy backbone. Given its activity in Ph-positive ALL, blinatumomab is also added to this regimen. The goal is that by reducing toxicity from intensive chemotherapy and incorporating the most active agents in Ph-positive ALL (blinatumomab and ponatinib), we will reduce treatment-related morbidity and mortality and further increase the cure rate. This regimen is open to patients of all ages with newly diagnosed Ph-positive ALL, in particular patients with Ph-positive ALL transformed from chronic myeloid leukemia. The CMR rate was 82% and the estimated 2-year survival rate was 81% among 17 patients treated. Ponatinib and blinatumomab are provided free of charge.

- **Blinatumomab and ponatinib –** **B**linatumomab was evaluated in the Phase II ALCANTARA trial in patients with relapsed/refractory Ph-positive ALL. In this study, 36% of patients achieved complete remission (CR) or CR with incomplete hematologic response and was active in patients with T315I mutations. The median overall survival was 7.1 months. We have treated 8 patients with relapsed/refractory Ph-positive leukemias with the combination of ponatinib and blinatumomab, 6 of whom (75%) achieved CMR. With a median follow-up of 10 months, the 1-year overall survival rate was 75%. We are therefore evaluating this combination blinatumomab and ponatinib, a chemotherapy-free combination in patients with newly diagnosed and relapsed-refractory Ph-positive ALL. So far 83 patients (66 with newly diagnosed disease) were enrolled and treated. In the frontline treatment, 91% have achieved a complete molecular response (89% by NGS) within 3 months (64% at 4 weeks). Only one patient with newly diagnosed disease received allogeneic stem cell transplantation. The estimated 2-year survival rate is 96%. This is a paradigm shift and will potentially become a new standard of care.

3. Minimal Residual Disease

Persistence or reappearance of minimal residual disease (MRD) after induction chemotherapy is the most important adverse prognostic factor in patients with ALL and identifies chemo-refractory disease. More than 90% of patients who have persistent MRD after chemotherapy experience a clinical relapse, despite continued chemotherapy, with a median time to relapse of 4-5 months.

- **Blinatumomab** – Blinatumomab was assessed in 116 patients with ALL in CR but with MRD positivity. Approximately 78% achieved MRD negativity after one cycle. With a median follow-up of 29 months, the median survival was 36 months. The median OS for those who achieved MRD-negative status was 40 months versus 12 months for those who remained MRD-positive.

A Phase II study of blinatumomab in patients with B-cell ALL in first or second/third CR with positive MRD (≥0.01%) is active at our institution. Patients with Philadelphia-positive disease are eligible and will receive blinatumomab in combination with TKI. Thirty-seven patients have been treated so far. The MRD negativity rate is 73%, with 3-year survival rate of 67%.

- **Inotuzumab ozogamicin** – Inotuzumab has shown significant activity in R/R ALL with higher efficacy observed in patients with minimal disease and in those treated in Salvage 1 compared to Salvage 2 and beyond. Inotuzumab is currently being assessed in patients with both Ph-negative and Ph-positive ALL with positive MRD. Patients with Ph-positive disease can also receive a TKI. So far, 27 patients were treated, 67% achieved MRD negativity. The estimated 2-year survival was 62%.

Inotuzumab is provided free of charge.

4.Salvage treatments

Ph-negative ALL

- **Hyper-CVD + inotuzumab ozogamicin + blinatumomab –** This regimen combines low-intensity chemotherapy with the two most active monoclonal antibodies in ALL (inotuzumab ozogamicin and blinatumomab). To date, 110 patients have been treated. The overall response rate is 83%, with particularly efficacy in patients in first salvage (response rate: 89%). The 3-year overall survival rates for the entire cohort and for patients in first salvage are 40% and 49%, respectively. A historical comparison with patients who received inotuzumab ozogamicin as a single agent shows a significant benefit to the combination regimen (median overall survival: 17 months versus 6 months), strongly suggesting that combination therapies should be offered to patients with Ph-negative ALL with relapsed/refractory disease. Delivering inotuzumab and blinatumomab in combination with low dose chemotherapy concomitantly from the first cycle may further improve the results by eradicating measurable residual disease from Day 28 (assessed by NGS; MRD negativity by NGS of 87%). The addition of sequential blinatumomab and the weekly admiration pf low-dose inotuzumab reduced the rate of VOD from 13% to 2%; this change translated into survival improvement from a median of 14 months to a median of 37 months (3-year survival rates of 34% and 55%, respectively). The study was amended into a dose-dense mini-HCVD-inotuzumab-blinatumomab given for 6 cycles followed by POMP maintenance for 12 cycles with one cycle of blinatumomab after every 3 cycles of POMP. The overall doses of blinatumomab and inotuzumab remain the same as previously. Furthermore, patients responding are offered consolidation with chimeric antigen receptor T-cells therapy. Early results are promising; 8 of the 9 patients enrolled achieved MRD negative remission by NGS.

- **Hyper-CVD + venetoclax + navitoclax –** Venetoclax is an oral Bcl-2 inhibitor that has activity across a wide variety of hematologic malignancies. Preclinical data suggests significant synergy with chemotherapy and particular efficacy in patients with T-cell ALL. We have therefore designed a Phase I/II study of the combination of hyper-CVD plus venetoclax for patients with relapsed/refractory ALL. This regimen is particularly promising for patients with T-cell ALL, which is an unmet need as there are currently no approved monoclonal antibodies this ALL subtype. Early results are encouraging with an objective response rate of 67% obtained in patients with refractory disease with a median survival of 10.7 months. The study was amended and current patients are receiving the combination of low dose chemotherapy and venetoclax and navitoclax. Fifteen patients were treated. The overall response rate was 57% and MRD negativity rate among responders 86%. The study is ongoing and accruing patients.

- **Sub-cutaneous (SQ) blinatumomab –** In order to improve the compliance and the administration of blinatumomab, continuously 4 weeks, every 6 weeks, we are evaluating the pharmacokinetic of a SQ formulation of blinatumomab. We are leading the Phase I study. The drug is given daily during the first week, then 3 times per week subsequently. So far 20 patients were treated. Fourteen patients responded; of them, 9 patients achieved MRD negative remission. The treatment was well tolerated with no dose limiting toxicities encountered. The study is open and accruing patients.

- **Hyper-CVD + ponatinib + venetoclax – Outcome of patients with relapse** T-cell acute lymphoblastic leukemia is poor, and novel therapeutics are much needed. The developmental arrest in T-ALL drives differential activation of preTCR-LCK (sensitive to tyrosine kinase inhibitors) and BCL2 signaling, thus providing unique opportunities for targeted therapy. Therefore, following this rational, we just launched a phase II trial evaluating mini-HCVD plus ponatinib and venetoclax in patients with relapsed-refractory T-ALL.

- **ADCT-602** – ADCT-602 is an antibody drug conjugate composed of a humanized monoclonal antibody directed against CD22, conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. ADCT-602 is being assessed at our institution in a Phase I/II trial. The hope is that this agent will be a potent anti-CD22 therapy, without the hepatic toxicity associated with inotuzumab ozogamicin. This trial is currently open in the Phase I part. Patients with R/R B-ALL are eligible. Prior allogeneic stem cell transplant is allowed. This drug is given IV weekly. The drug is provided free of charge. At the recommended phase 2 dose, the rate of MRD-negative CR is 33%. The study is open and accruing patients.

- **CAR T-cells –** CAR T-cells directed at CD19 have emerged as an effective approach for patients with aggressive B-cell lymphomas and pediatric ALL. With this therapeutic approach, autologous T-cells are engineered to express a receptor directed at CD19, which mediates cytotoxicity. These cells have been noted to expand and persist *in vivo*, which may lead to more durable responses. The most notable toxicities encountered with CAR T-cell therapies include cytokine release syndrome (CRS), neurological toxicity (called ICANS) and B-cell aplasia. Two FDA approved CAR T-cells therapies are currently available. In a global study of CAR T-cell therapy, a single infusion of tisagenlecleucel provided durable remission with long-term persistence in 75 pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects. The 3-month overall remission rate was 81%, with all responding patients found to be negative for minimal residual disease. The 12-month event-free survival (EFS) and overall survival (OS) rates were 50% and 76%, respectively. KTE-X19 (Tecartus) showed a high objective response rate of 71% (CR 56%) in adult patients with R/R ALL, among them 47% having failed 3 or more previous therapies including blinatumomab (45%), inotuzumab (22%), and allo-SCT (42%). The median overall survival was 25.4 months. Similar outcomes were observed regardless of patients age. In contrast, patients with pre-infusion high-disease burden had less favorable outcome. Cytokine release syndrome of grade 3 or higher occurred in 13 (24%) patients and neurological events of grade 3 or higher occurred in 14 (25%) patients.

- **Autolus CD19 CAR T-cells (Obi-cell)** - Obi-cell is a second-generation CD19-CAR (CAT19-41BB-Z) with a fast off rate, designed for more physiologic T-cell activation to reduce toxicity and improve engraftment. Among 20 evaluable patients (25% had prior blinatumomab, 50% prior inotuzumab ozogamicin, and 65% prior allogeneic stem-cell transplantation)

infused, 17 (85%) achieved minimal residual disease-negative complete response. The 12-months event-free survival was 48%. No patients experienced ≥ grade 3 cytokine release syndrome; 3 of 20 (15%) experienced grade 3 neurotoxicity that resolved to ≤ grade 1 within 72 hours with steroids. With a longer follow-up, 40% of the patients remain in an ongoing CR. The Phase II study open at our institution has completed accrual; we are awaiting the results. The study is being amended for patients with positive MRD.

We have trials of both CD19 and CD22-directed CAR T-cells, as well as allogeneic CAR T-cells. Allogeneic CAR T-cells offer an "off-the-shelf" approach, in which the cells are derived from sources other than the patient such as from healthy-volunteer donors, or iPSC (induced pluripotent stem cell) line. Hence there is no requirement to leukopherese patients and then wait for the cells to be manufactured. Finally, we will be opening soon a CD7-directed CAR T-cells therapy for patients with relapsed-refractory T-cell. Below are the current CAR T-cell studies at MD Anderson:

Target	Product	Autologous vs. Allogeneic
CD19	Fate Therapeutics	Allo (derived from iPSC line)
	Autolus	Auto (low-affinity CD19)
	TCR2	Auto
	Precision Bio	Allo (derived from healthy donors)
CD22	UCART22	Allo (derived from healthy donors)

Ph-positive ALL

- **Blinatumomab and ponatinib –** In addition to being tested in older adults with newly diagnosed Ph-positive ALL (see above), the chemotherapy-free combination of blinatumomab and ponatinib is being evaluated in patients with relapsed/refractory Ph-positive ALL. This regimen combines two of the most active agents in Ph-positive ALL, both of which are capable of overcoming the T315I resistance mutation, which is the dominant mechanism of relapse in Ph-positive leukemias.

- **Inotuzumab and bosutinib –** A randomized trial comparing inotuzumab with physician's choice of chemotherapy in patients with relapsed/refractory ALL in first or second salvage showed a significant improvement in response rates and survival with inotuzumab. Bosutinib is a second-generation TKI and dual Abl and Src kinase inhibitor that is active in Ph-positive leukemias. A Phase I-II trial assessing the combination of inotuzumab and bosutinib in patients with newly diagnosed and relapsed/refractory ALL is enrolling. Eighteen patients with relapsed/refractory disease have been treated. The CR/CRi rate is 83%, and CMR rate 56%. The median overall survival is 13.5 months

The Leukemia Department welcomes and will facilitate referrals and would like to work with you to make novel therapies available to your patients. For referrals, please contact any of the Leukemia faculty listed.

Leukemia Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. View our faculty roster.

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