

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 outline clinical trials offered for patients with myeloproliferative neoplasms. Learn more about our [Leukemia program](#).

Novel Approaches for the Treatment of Adult Acute Lymphoblastic Leukemia (ALL) in 2024

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 of decreasing the morbidity and mortality associated with myelosuppression-related infections and other complications of intensive chemotherapy.

When referring patients 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 promise in the treatment of ALL, with a recent FDA approval based on a

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survival advantage for patients with relapsed or refractory ALL compared with combination chemotherapy alone. 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 75 adults treated (38 patients treated with Hyper-CVAD plus blinatumomab and 37 patients treated with Hyper-CVAD plus blinatumomab plus Inotuzumab), the complete remission (CR) rate was 100%, the measurable residual disease (MRD) negativity rate by flow cytometry (FCM) was 95%, and 73% by next-generation sequencing (NGS). The estimated 3-year survival rate was 89% (compared with 66% with the historical HCVAD-ofatumumab). The 3-year survival rates in patients with poor and favorable baseline features were 78% and 90%, respectively. By a 3-year landmark analysis, there was no difference in outcome whether an allogeneic stem cell transplantation was performed. The 3-year overall survival rates were 86% in patients who received transplant 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. The study was amended recently into a Phase 2 randomized trial comparing Hyper-CVAD plus blinatumomab and inotuzumab to Hyper-CVAD plus blinatumomab (2-to-1 randomization).

- **Hyper-CVD + inotuzumab + 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 response. In the most recent update of 83 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 49%, 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 of any age with relapsed/refractory Ph-negative ALL. To improve the safety of this regimen, it was amended so that patients 70 years and older receive 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.

- 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). Preclinical studies demonstrated the activity of venetoclax and navitoclax in B-cell and T-cell ALL cell lines, and preclinical data suggest 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 rate of 91% and MRD negativity rates of 100%. The study provides venetoclax and navitoclax free of charge and is open for accrual. It is open as well for patients with relapsed-refractory ALL, including 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 of hyper-CVD plus ponatinib plus blinatumomab 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 78% and the estimated 2-year survival rate was 83% among 20 patients treated. Ponatinib and blinatumomab are provided free of charge.

- **Blinatumomab and ponatinib** – Blinatumomab was evaluated in the Phase II ALCANTARA trial in patients with relapsed/refractory Ph-positive ALL. In this study, 36% of patients achieved CR or CR with incomplete hematologic response, and the regimen 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 chemotherapy-free combination in patients with newly diagnosed and relapsed-

refractory Ph-positive ALL. So far, 62 newly diagnosed patients were treated, with 84% achieving a complete molecular response by RT-PCR within 3 months (64% at 4 weeks) and 94% becoming negative by NGS. Only two patients received allogeneic stem cell transplantation. The estimated 2-year survival rate is 91%. This is a paradigm shift and will potentially become a new standard of care.

3. Minimal Residual Disease

Persistence or reappearance of 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.

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 with 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, and 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 + blinatumomab** – This regimen combines low-intensity chemotherapy with the two most active monoclonal antibodies in ALL (inotuzumab ozogamicin and blinatumomab). To date, 125 patients have been treated. The overall response rate is 83%, with particular 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 as a single agent shows a significant benefit of the combination regimen (median overall survival: 17 months versus 6 months), strongly suggesting that combination therapies should be offered to patients with relapsed/refractory Ph-negative ALL. Delivering inotuzumab and blinatumomab in combination with low-dose chemotherapy concomitantly from the first cycle may further improve the results by eradicating MRD from Day 28 (assessed by NGS; MRD negativity by NGS of 87%). The addition of sequential blinatumomab and the weekly administration of low-dose inotuzumab reduced the rate of VOD from 13% to 2%; this change translated into a 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 to treat with a dose-dense regimen of 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; 10 of the 11 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 suggest significant synergy with chemotherapy and particular efficacy in patients with T-cell ALL. We have therefore designed a Phase I/II study 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 for this ALL subtype. Early results are encouraging with an objective response rate of 67% in patients with refractory disease and a median survival of 10.7 months. The study was amended, and current patients are receiving low dose chemotherapy and venetoclax plus navitoclax. Fifteen patients have been treated. The overall response rate was 57% and MRD negativity rate among responders 86%. The study is ongoing.

- **Sub-cutaneous (SQ) blinatumomab** – Blinatumomab is currently administered via continuous infusion for 4 weeks on, 2 weeks off. To improve compliance and convenience, we are evaluating the pharmacokinetics of a SQ formulation and have completed the Phase I study. The drug is given daily during the first week, then 3 times per week subsequently. So far, 27 patients have been treated in the 2 arms (Arm A=250µg QD/500µg TIW; Arm B=500µg QD/1000µg TIW) expanding phase. The CR/CRh rates were 86% and 92%, respectively. The MRD negativity rates were 75% and 100%, respectively. The study is open.
- **Hyper-CVD + ponatinib + venetoclax** – The outcome of patients with relapsed T-cell ALL is poor, and novel therapeutics are needed. The developmental arrest in T-ALL drives differential activation of pre-TCR-LCK (sensitive to tyrosine kinase inhibitors) and BCL2 signaling, thus providing unique opportunities for targeted therapy. Therefore, following this rationale, we launched a Phase II trial evaluating HCVD plus ponatinib and venetoclax in patients with relapsed-refractory T-ALL. The study is open.
- **ADCT-602** – ADCT-602 is an antibody-drug conjugate composed of a humanized monoclonal antibody directed against CD22, conjugated to SG3199, a pyrrolobenzodiazepine dimer cytotoxin. We are assessing ADCT-602 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. Patients with relapsed/refractory B-ALL are eligible. Prior allogeneic stem cell transplantation is allowed. This drug is given IV weekly and is provided free of charge. At the recommended Phase 2 dose, the rate of MRD-negative CR is 33%. The study is open.

- CAR T-cells** – CAR T-cells directed at CD19 have emerged as an effective treatment for patients with aggressive B-cell lymphomas and pediatric ALL. With this 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-cell products are available. The cytokine release syndrome and neurologic events of grade 3 or higher occurred in one-quarter of patients. The toxicity was more pronounced in patients with high disease burden, and they had less favorable outcomes. Obe-cel, not yet approved by the FDA, is a second-generation CD19-CAR T (CAT19-41BB-Z) with a fast off-rate, which is designed for more physiologic T-cell activation to reduce toxicity and improve engraftment. In 127 patients treated, the objective response rate was 75%, and the MRD negativity rate was 95%. The 12-months EFS was 50%. Of interest, the grade 3 cytokine release syndrome rate was 2% and the neurologic event rate was 7%. Obe-cel may be approved in the near future.
- 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 such as healthy-volunteer donors or iPSC (induced

pluripotent stem cell) lines. 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 ALL. Below are the current CAR T-cell studies at MD Anderson:

Target	Product	Autologous vs. Allogeneic
CD19	Fate Therapeutic	Allo (derived from iPSC line)
	TCR2	Auto
	Precision Bio	Allo (derived from healthy donors)
CD22	UCART22	Allo (derived from healthy donors)

Since, the best outcome post CAR T-cell infusion is observed in patients with no/or minimal disease before the lymphodepletion, we are launching a Phase II trial testing CAR T-cell therapy as a consolidation strategy in patients in Salvage 1 post mini-HCVD-inotuzumab-blinatumomab and in the frontline setting post HCVAD-inotuzumab-blinatumomab in patients with high-risk disease. Of note, all immunotherapies including Inotuzumab, blinatumomab, and CAR T-cells are offered free of charge as part of this trial.

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.

Launching soon:

- Blinatumomab and asciminib
- Blinatumomab and olverembatinib