Leukemia insights

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

Novel Approaches for the Treatment of ALL in Adults in 2020

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 or blinatumomab) are provided free of charge as part of the trial.

1. Frontline Ph-negative ALL

- **Hyper-CVAD + blinatumomab –** 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 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

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responses. To date, 34 patients were treated. The 2-year overall survival rate is 93% very favorable compared with a rate of 80% in patients treated with HCVAD and ofatumumab only. This protocol is being 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.

- **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 66 treated patients, the overall response rate is 98%, and no early deaths were observed. Overall, 95% 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 with relapsed/refractory Ph-negative ALL of any age.
- Other regimens include **hyper-CVAD plus nelarabine** and the Bcl-2 inhibitor venetoclax (for T-cell ALL) **and low-intensity chemotherapy plus venetoclax**(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 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 5-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. 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 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 older e patients (≥60 years) with newly diagnosed Ph-positive ALL and younger patients unfit for intensive chemotherapy, as well as in those with relapsed/refractory Ph-positive ALL of any age, with promising initial results. So far 15 patients were enrolled and treated. In the frontline treatment, 80% have achieved a deep molecular response within 3 months.

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 CR with positive MRD is active at our institution. Patients with Philadelphia-positive disease are eligible and will receive blinatumomab in combination with TKI. Twenty-seven patients have been treated so far. The MRD negativity rate is 78%, with 2-year survival rate of 72%.

- **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.

Both blinatumomab and inotuzumab are 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, 89 patients have been treated. The overall response rate is 79%, with particularly efficacy in patients in first salvage (response rate: 91%). The 2-year overall survival rates for the entire cohort and for patients in first salvage are 39% and 51%, 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: 14 months versus 6 months), strongly suggesting that combination therapies should be offered to patients with Ph-negative ALL with relapsed/refractory disease.

- **Hyper-CVD + venetoclax** – 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 74% obtained in patients with refractory disease.

- **ADCT-602 –** ADCT-602 is an antibody drug conjugate composed of a humanized monoclonal antibody directed against CD22, conjugated to the cross-linking cytotoxic agent tesirine (SG3249). 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 once every 3 weeks. The drug is provided free of charge.

- **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), encephalopathy and B-cell aplasia. The FDA recently approved tisagenlecleucel for the treatment of relapsed/refractory ALL in patients up to age 26. In clinical trials, the response rate is 59% (83% among patients who were evaluable for efficacy). The 12-month duration of response is 64%.

- 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 healthy-volunteer donor T-cells. Hence there is no requirement to leukopherese patients and then wait for the cells to be manufactured. Below are the current CAR T-cell studies at MD Anderson:

Target	Product	Autologous vs. Allogeneic
CD19	UCART19	Allo (derived from healthy donors)
	KTE-C19	Auto
	NK-CAR	Allo (NK cells derived from cord blood)
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.

- **Venetoclax and ponatinib** – The Bcl-2 inhibitor venetoclax has shown significant promise across multiple leukemias, with FDA approval for patients with relapsed/refractory CLL with 17p deletion and with excellent safety and efficacy when combined with low-intensity therapies in older patients with AML. There is significant preclinical rationale for the combination of venetoclax and ponatinib, with the combination showing synergistic activity in preclinical models. Ponatinib may also help to prevent venetoclax resistance by preventing upregulation of Mcl-1, an established resistance mechanism of venetoclax-based regimens. A Phase I/II trial of the oral, chemotherapy-free regimen is now accruing for patients of all ages with relapsed/refractory Ph-positive ALL.

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.

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.

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