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CLINICAL TRIALS AND OBSERVATIONS

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A new era in the treatment of acute lymphoblastic leukemia

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In this issue of *Blood*, Brivio et al show that inotuzumab ozogamicin is safe and effective in pediatric relapsed-refractory (R-R) acute lymphoblastic leukemia (ALL) with a phase 2 recommended dose of 1.8 mg/m².[1]

Major advances have been made in the last decade toward a better understanding of the disease pathogenesis and the development of novel therapies for ALL.[2] Targeted therapies toward specific transcripts and specific leukemic cell surface antigens are major breakthroughs in the management of ALL.[2] Historically, R-R ALL is associated with dismal prognosis, with a cure rate of <10% in adult ALL and 30% in pediatric ALL.[3,4] In adult ALL, the complete remission (CR) rate with standard chemotherapy regimen is 30% to 40% in the first relapse and 20% to 25% in the second relapse.[3]

Brivio and colleagues report the results of a phase 1 study of inotuzumab ozogamicin in pediatric R-R ALL. This treatment was found to be safe and effective, with an overall response rate of 80% and 12-month survival rate of 40% in heavily pretreated patients (median number of courses given, 2; range, 1-4). Two of 23 patients (9%) experienced hepatic sinusoidal obstruction syndrome (SOS). The recommended phase 2 dose was 1.8 mg/m², as in adults. These results were similar to those reported by the COG ALL0232 in 48 patients.[5] The objective response rate was 62%, and the 12-month survival rate was 40%. The hepatic SOS rate was 10.4% (26% in patients who received subsequent allogeneic stem cell transplantation [ASCT]).

Several comments are worth addressing.

First, the results obtained with inotuzumab in pediatric population are better than the ones observed in adult patients.[6] The median survival at the phase 2 recommended dose has not been reached compared with 7.7 months in the adult population. The same observation was noted with blinatumomab in salvage 1 in children and young adults.[4] In a randomized phase 3 study, blinatumomab induced 2-year disease-free survival and overall survival rates of 59% and 79% compared with 41% and 59% with standard-of-care chemotherapy.[4] This is in contrast with blinatumomab in the salvage 1 setting in adult patients, where the median overall survival was 11.1 months compared with 5.5 months with standard-of-care chemotherapy.[7] The improvements in outcomes with both antibody constructs and chemotherapy observed in pediatric compared with adult patients indicate a better disease biology.

Second, the results of inotuzumab and blinatumomab in pediatric ALL compare favorably with those with the chimeric antigen receptor (CAR) T-cell therapy. In the Eliana trial, the 3-month CR rate was 67% and the estimated 2-year survival rate was 66% among evaluable patients.[8] The grade 3 to 4 rate of cytokine release syndrome was 49%, with a rate of hospitalization in the intensive care unit of 48%.[8]

Third, while these results are encouraging, further improvement can be accomplished in order to improve survival and reduce hepatic SOS. In adults with R-R ALL, the use of low-intensity chemotherapy in combination with a fractionated lower dose of inotuzumab (0.9 mg/m² during course 1 and 0.6 mg/m² during courses 2-4), followed sequentially with blinatumomab, improved the rate of minimal residual disease (MRD) negativity and distanced the timing of ASCT from the last dose of inotuzumab.[9] Among 96 patients treated, the overall response rate was 80%, the MRD negativity rate was 83%, and median overall survival was 13.4 months (2-year survival rate, 33%). These results compare favorably with single-agent inotuzumab and single-agent blinatumomab in a similar patient population (median survival, 6-8 months).[9] The sequential addition of blinatumomab and the distancing of ASCT from the last dose of inotuzumab led to a decrease in the rate of hepatic SOS to 3%. This strategy may be important in the setting of pediatric regimens, where combinations of asparaginase and anthracyclines with inotuzumab may result in a high risk of liver toxicities and SOS.

Fourth, current studies are exploring the use of inotuzumab in the frontline setting. Inotuzumab in combination with low-dose chemotherapy and blinatumomab is being evaluated in older ALL, where strategies to deintensify treatment regimens are needed. Among 64 patients treated with this regimen, the median age was 68 years (range, 60-81 years), and 42% of patients were ≥70 years.[10] The CR rate was 98%, and the MRD negativity rate by flow cytometry rate was 95%. The 3-year CR duration and survival rates were 76% and 54%, respectively. A propensity matched analysis showed that this regimen significantly improved survival compared with the historical results with hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin,

and dexamethasone on courses 1, 3, 5, and 7 alternating with high-dose methotrexate and cytarabine on courses 2, 4, 6, and 8) in this older population (3-year survival rates of 63% vs 34%; $P = .007$).[10]

In summary, the encouraging results achieved with monoclonal antibodies, bispecific antibody constructs, and CAR T cells provide important therapeutic tools to improve outcomes of patients with ALL. These treatment modalities are not competitive but complementary. They can be administered sequentially to produce the deepest and best remission rates possible. Their rational combination in the frontline setting is ongoing and may reduce the need for long-term intensive chemotherapy and ASCT in many patients.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Song et al, page 1591

Quicker and digital: the way on protein biomarkers?

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In this issue of *Blood*, Song et al[1] report the development of a new biomarker assay for the continuous monitoring of systemic immune disorders based on single-molecule digital detection of proteins. The technique is very rapid, multiplexed, and easy to handle.

For most chronic diseases, biomarker assays should be highly reproducible, with high sensitivity and specificity. The tradeoff for these advantages is usually the time of execution of the assays (blood draw-to-answer time), which can be hours or days.[2] In the case of acute, lethal conditions, such as septic shock or various types of cytokine release syndrome (CRS), including post-chimeric antigen receptor T-cell (post–CAR-T) therapy[3] or COVID-19–related cytokine storm,[4,5] the quickness of diagnosis is critical for patient survival. Therefore, for such conditions, rapidity is crucial.

In line with this, Song et al report a very interesting advance of the classics assay of enzyme-linked immunosorbent assay (ELISA) that they named, suggestively, PEdELISA (pre-equilibrium digital ELISA). This assay is based on 2 principles: the instantaneous single-molecule binary counting of nonequilibrium protein-binding events (the "digital" part, to achieve simultaneously speed and sensitivity) and the intentional stopping of the immunologic reaction with a washing buffer in its pre-equilibrium state (the "pre-equilibrium" part, to achieve the single-molecule counting condition). This produces a result in minutes (approximately half an hour) from the sample collection (and the authors have a clear plan to further reduce this interval) vs hours to days for the classic ELISA test or mass spectroscopy assays, respectively. The disease state used for testing was profiling of multiple plasma cytokines in patients manifesting post–CAR-T therapy CRS. This is a deadly complication for one of the most expensive nonsurgical therapies (yet rapidly expanding in applications) in the entire medical field.

The research behind is solid, wise, and simple. First, the authors developed the PEdELISA platform by combining the microarray biosensor design with the microfluidic chip for multiplex analysis. Then, they developed the theoretical basis of the method by prediction of "quench-and-snapshot" measurement, which includes accounting for mass transport and surface reaction for a theoretical "reaction volume" with a bead placed in its center, followed by the kinetics of the antibody-antigen antibody immune complex formation. They continued with the analytical validation of the assay based on 10 representative cytokine biomarkers and identified the signal-to-noise ratio. The linearity of the assay was confirmed over a three-order-of magnitude concentration range regardless of the cytokine and was well maintained even for the ultrafast (15 seconds only) PEdELISA interleukin-6 assay. Importantly, the authors demonstrated close concordance between the