PosterPerspectives: Acute Lymphoblastic Leukemia Posters and Abstracts from San Diego

Elias Jabbour, MD

Overview: Elias Jabbour, MD, provides his perspectives on key posters presented at the American Society of Hematology's 60th Annual Meeting & Exposition held in San Diego, California, on the treatment of patients with acute lymphoblastic leukemia (ALL). We invite you to learn more about the current and emerging standards of care, as well as safety and efficacy data from the select clinical trials, in patients with acute lymphoblastic leukemia.

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Content Areas

- CD19-positive ALL
- A bispecific T-cell engager antibody
- Antibody drug conjugate
- Low-intensity chemotherapy
- Philadelphia chromosome-negative ALL
- Minimal residual disease
- Veno-occlusive disease
- Allogeneic stem-cell transplantation

Target Audience

This activity was developed for Hematologists, oncologists, and other healthcare professionals who manage patients with Acute Lymphoblastic Leukemia and other healthcare professionals who have an interest in Acute Lymphoblastic Leukemia.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Summarize the latest research and clinical trial developments in the treatment of acute lymphoblastic leukemia.
- Incorporate evidence-based research and clinical trial developments into clinical practice.

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Blinatumomab for Minimal Residual Disease (MRD) in Adults with B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL): Median Overall Survival (OS) Is Not Reached in Complete MRD Responders at a Median Follow-up of 53.1 Months (554)

Author(s): Gökbuget N, et al.
Link: http://www.bloodjournal.org/content/132/Suppl_1/554

Dr. Jabbour: We'll start with the first study that I would like to discuss today, which was presented by Dr. Nicola Gökbuget.

We know that having MRD-positive (MRD+) ALL is a bad milestone.

In fact there was a meta-analysis published by Dr. Berry (Berry DA, et al. *JAMA Oncol*. 2017 Jul 13;3(7):e170580) with ~13 000 patients, which showed that both pediatric and adult patients with MRD+ disease have worse outcomes. Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that targets the CD19+ B-cells.

In the BLAST study, 116 patients were treated, in the first complete remission (CR), or second CR and beyond, who were MRD+, with blinatumomab given [for] 4 weeks every 6 weeks.

The primary endpoint of the study was conversion into MRD-negativity (MRD-), defined as no target amplification with a minimum sensitivity of 10^{-4}. Patients were treated for 4 weeks every 6 weeks, and those who had a donor proceeded to have the transplantation. Eighty percent of patients responded, and those who responded had a better outcome.

The import of this presentation is that this was a long-term, follow-up [study]—the study was already reported and published (Gökbuget N, et al. *Blood*. 2018;131:1522-1531), and led to the approval of the drug—to see whether blinatumomab is long-term effective.

What's important in this study was...We know that historically median survival was 12 months. In this study, for responding patients, the median overall survival (OS) had not been reached at the median follow-up of more than 4 years, which is excellent. And if you look at the transplant, post-remission transplant did not seem to add much—although the study was not powered to show a difference in favor of transplant or not—while in second remission or beyond, patients who had a transplant did better.

Patients who responded had an improvement in OS compared to patients who did not respond,

for whom the median OS has been only 12 months.

So what's in it for me as a clinician today? I think it's really important to acknowledge, 1) that the MRD is a sign of refractoriness, not just a biomarker; 2) patients who are MRD+ have a very poor outcome, and we should not transplant them while they are MRD+. We should make every effort to attain MRD- status, and blinatumomab is highly effective in this regard.

So, in practice, I suggest check for MRD, whether due to a persistent disease or relapse, give them blinatumomab and, then, if MRD-, eventually go for transplant. Down the road, the role of transplant may become questionable; do we go for transplant or not? I would say, yes, today, but in the future, things may change.

The questions and issues that remain are, 1) we need the confirmation of this study and data; 2) as I said, the question of transplant is still debatable; today we'd go for transplant, but maybe future studies would address the question of whether the transplant is needed or not; and, finally, 3) those who became MRD-, do they have the same outcome as patients who are MRD- from the beginning? As blinatumomab negates the presence of MRD, I think so, but we have to wait for future studies to confirm these data.

Chemoimmunotherapy with Inotuzumab Ozogamicin Combined with Mini-Hyper-CVD, with or without Blinatumomab, for Newly Diagnosed Older Patients with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: Results from a Phase II Study (36)

Author(s): Short NJ, et al.

Link: http://www.bloodjournal.org/content/132/Suppl_1/36

Dr. Jabbour: I would like to review the phase 2 study from MD Anderson. It's a chemo-immunotherapy with inotuzumab ozogamicin, combined with mini-hyper-CVD, with or without blinatumomab, in older patients with Ph-negative (Ph-) ALL.

This study has shown good results and a good long-term outcome in this special population, with a 2-year survival of 51%. What does that mean?

So, let's go into the depth of this study. First of all, we know that elderly people typically have very poor outcome, because they have a very bad biology, and because they have a very poor response to chemotherapy.

Therefore, when you get them chemotherapy, some of them may respond, some of them may not respond. The ones that respond, eventually may suffer from various complications. The available data show that the survival of these patients is around 6 months on average, and therefore the outcome is poor.

We explored inotuzumab ozogamicin, and then we explored blinatumomab. As both are tolerable among older patients, we thought maybe it's a good idea to combine them with a low-dose chemotherapy. Here, the chemotherapy was cyclophosphamide and dexamethasone at 50% dose reduction, no anthracycline, methotrexate at 75% dose reduction, and cytarabine at 0.5 g/m^2. We added at the beginning inotuzumab ozogamicin on a monthly regimen, at the does on average of 1.3 to 1 mg/m^2.

And then, after that, in order to avoid veno-occlusive disease (VOD), we split the dose of inotuzumab ozogamicin into a weekly regimen, instead of monthly. As we know that VOD correlates with the loading dose, we reduced the dose of inotuzumab ozogamicin to a total of 2.7 mg/m^2.

Also, we know that age is a relevant factor for VOD. With a dose adjustment, we have less VOD, although it's not yet highly significant. What we've seen with this regimen is that it is highly tolerable among older patients, with the early mortality of 0%. We had everybody responding but 1 patient. And among responders, we had a high MRD-negativity, which is good.

In the long run, with a median follow-up of more than 3 years today, we see OS of at least of 54%, which is excellent, contrasting with historical data of 15%. These results are really promising for patients who are older, unfit for chemotherapy.

So, what is the main point of this study? I think we're making progress in older patients with ALL. The outcome has been bad because of the biology, and because of the patient comorbidities. With a very effective therapy that can overcome the biology, with lower safety profile concerns, we can improve the outcome; and this regimen has shown the good efficacy with high response rates and 0% rate of mortality.

I think this is really the best we have seen so far in this group of patients.

In the future, older patients with ALL will likely be able to benefit from this therapy, and we will not need to be sending them to hospice because we have nothing to offer them. The question that remains to be answered in the future is whether these data will be confirmed in the randomized trial so that this approach may become a new standard of care.

I think the study presented is likely to set the stage for a new standard of care for these patients.

Sequential Combination of Low-Intensity Chemotherapy (Mini-hyper-CVD) Plus Inotuzumab Ozogamicin with or without Blinatumomab in Patients with Relapsed/Refractory Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia (ALL): A Phase 2 Trial (553)

Author(s): Sasaki K, et al.
Link: http://www.bloodjournal.org/content/132/Suppl_1/553

Dr. Jabbour: Another study presented at the last ASH meeting, with the same regimen, was conducted by the team from MD Anderson.

We know that the combination of inotuzumab ozogamicin, blinatumomab and hyper-CVD is feasible. We know also that the inotuzumab ozogamicin and blinatumomab were both effective in a relapsed setting, they had improved OS by 7 months, compared to 4-5 months in a standard-of-care arm.

One could think, well, this improvement is not so great; it's significant but not so great. Maybe if we can combine them with chemotherapy, we can further improve the outcome.

Again, the rationale for the weekly schedule of inotuzumab ozogamicin was to reduce the rate

of VOD. By using low dose of inotuzumab ozogamicin at 2.7 mg/m^2, and by using blinatumomab subsequently, we were able to reduce VOD in a major way.

This study included patients in salvage 1, 2, or 3. Patients received low-dose of chemotherapy consisting of cyclophosphamide (150 mg/m^2 every 12 h on days 1-3), vincristine (2 mg flat dose on days 1 and 8), and dexamethasone (20 mg on days 1-4 and days 11-14) without anthracycline. Cycles 2, 4, 6, 8 included methotrexate (250 mg/m^2 on day 1) and cytarabine (0.5 g/m^2 given every 12 h on days 2 and 3).

Eighty-four patients were treated and high response rate, almost 80%, were seen -- higher in salvage 1 compared to salvage 2, though. Overall, the responding patients had high MRD- of 80%, and a median OS was 14 months, overall. And this OS was better in salvage 1 than in salvage 2 or 3.

So, in this study, the combination showed better results than a single agent inotuzumab ozogamicin or blinatumomab, with a median bump of 14 months; that is way better than 7 months seen with inotuzumab ozogamicin or blinatumomab alone. Better results were seen in salvage 1, where the median survival was 25 months, and the 2-year OS was 54%, which is the best ever observed in this population. Finally, almost half of the patients were able to go for transplant, which is potentially curable. And then, we also saw a significantly reduced VOD; we had 9 out of 61 in the beginning, and 0 out of 18, or 0%, in a weekly schedule.

So this is highly effective regimen. I think a relapsed patient can be cured. Historically we had a survival of 7% in the long run. Today, we can hope to have half of these patients alive at 2 or 3 years, by giving the best sequential regimen, attaining MRD- status, and proceeding with a transplant.

I think we were able to reduce the VOD rate in a significant way by getting lower dose of inotuzumab ozogamicin, and proceeding with the transplantations. So, this is a new standard of care for patients in relapsed/refractory setting.

Moving forward, what are the questions that remain to be answered? I think the role of CAR T-cell therapy is debatable. CAR T-cells may be the replacement for transplantation. I think we need longer follow-up for this regimen—where blinatumomab is used sequentially post-inotuzumab ozogamicin, that allows us to use lower dose of inotuzumab ozogamicin and reduce the rate of VOD in a major way. And finally, we're studying certain subsets, mainly highest risk patients to see whether this regimen can overcome the negative or the poor biology to start with.

A Phase II Study of the Hyper-CVAD Regimen in Sequential Combination with Blinatumomab As Frontline Therapy for Adults with B-Cell Acute Lymphoblastic Leukemia (B-ALL) (32)

Author(s): Richard-Carpentier G, et al.
Link: http://www.bloodjournal.org/content/132/Suppl_1/32

Dr. Jabbour: This study is in patients who are adults, with B-cell ALL up to the age of 60.

We know for these patients, hyper-CVAD has been our standard of care, although a pediatric regimen may be as good as a hyper-CVAD. We know that blinatumomab is effective in a relapsed setting, and better than standard of care chemotherapy. Therefore, the hypothesis was, if we incorporate blinatumomab upfront, we may need less chemotherapy, we can increase the rates of MRD- status and improve the outcomes. Therefore, investigators from MD Anderson designed this regimen with 4 cycles of hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone in cycles 1 and 3, and high-dose methotrexate/cytarabine in cycles 2 and 4), followed by 4 cycles of blinatumomab, and then they shortened the maintenance to almost a year and a half, where POMP (6-mercaptopurine, vincristine, methotrexate, prednisone) is given with blinatumomab as part of the maintenance regimen, in addition to the intrathecal chemotherapy given for a total of 8 cycles.

What was seen were high response rates, high MRD- rates, and the survival so far is 92% at 17 months. It's a very encouraging experience, and treatment was very well tolerated; cytokine release syndrome and ataxia were seen but were highly manageable.

This study is an attempt at the new way of combining therapy, where we're using inotuzumab ozogamicin and blinatumomab, in a frontline setting to minimize the use of chemotherapy and further improve the outcomes. In this study, most of the patients enrolled had bad features such as t(4;11), CRLF2+ and others. And blinatumomab was able to overcome the bad features. So, this study is still accruing patients for a total of 80 patients, and if it turns out positive, that may mean that we can get rid of the intensive chemotherapy.

So, it's about a proof of concept that we can get rid of chemotherapy; we are deepening the MRD- status of these patients. For the future, the question is, can we do better by adding maybe inotuzumab ozogamicin and blinatumomab to chemotherapy to fully overcome the impact of negative features, such as hypodiploidy, and require less transplant?

So, again, this is an example where we're moving into the frontline setting with these new drugs.

Results of SWOG 1318: A Phase 2 Trial of Blinatumomab Followed by POMP (Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine) Maintenance in Elderly Patients with Newly Diagnosed Philadelphia Chromosome Negative B-Cell Acute Lymphoblastic Leukemia (33)

Author(s): Advani AS, et al.

Link: http://www.bloodjournal.org/content/132/Suppl_1/33

Dr. Jabbour: There was another study in the older group of patients with B-cell ALL presented by Dr. Advani.

Again, I mentioned before, these older patients with ALL have a very poor outcome. In fact, they do not tolerate intensive chemotherapy. They die of complications, and they have a very aggressive biology.

The primary endpoint of this trial is 3-year OS, with patients who are unfit for chemotherapy, 65 years and older, with good overall function. Patients will receive induction treatment with blinatumomab, for 1 or 2 cycles, until achievement of CR/CR with incomplete count recovery (CRi). And then, patients will get 3 cycles of blinatumomab post-remission therapy, followed by 18 months of POMP maintenance. Patients will get intrathecal chemotherapy, as well. So far, in this study, we have 31 elderly (75 years) patients being enrolled.

Treatment was, on average, well tolerated. Although, one could think about, if you give the blinatumomab upfront to a patient with a high white blood cell count, they may end up having cytokine release syndrome. So, one should really decrease the disease burden and give blinatumomab thereafter. So far, the median follow-up is 1 year, and the median duration on study is 170 days, which is really early on. At this point, objective response rate was 66%, all CRs. We did not have trouble with thrombocytopenia, and of the 13 patients with MRD data available post-treatment, 12 became MRD-. The 1-year OS is 67%, disease-free survival being 58%.

What do I think of this trial? Again, investigators are exploring low intensity regimens in older patients with ALL, because older patients don't do well with chemotherapy. It's an example where the use of blinatumomab early on is effective. I think between this study and the MD Anderson study, we have the proof that we can move into low dose chemotherapy upfront. My comment is that maybe the use of blinatumomab upfront can be limited because of the tumor burden; therefore we may have to reduce the tumor burden before giving blinatumomab.

And then the questions that remain to be answered will require more patients and longer follow-ups.

That being said, I want to comment on these 2 studies in older patients. Namely, I think that the new drugs available to us will make a big difference in outcomes for these patients.

Disease Burden Subgroup Analysis of Health-Related Quality of Life of Blinatumomab Versus Standard-of-Care Chemotherapy in Patients with Relapsed or Refractory Philadelphia Chromosome-Negative B-Cell Precursor Acute Lymphoblastic Leukemia in a Randomized, Open-Label Phase 3 Study (TOWER) (3967)
Author(s): Stein AS, et al.
Link: http://www.bloodjournal.org/content/132/Suppl_1/3967

Dr. Jabbour: One last study I want to review has to do with the quality of life of our patients.

The TOWER trial was a randomized trial comparing blinatumomab to standard of care in patients with Ph- relapsed/refractory ALL, randomized 2:1, with a primary endpoint of OS. Blinatumomab was shown to be superior by inducing high response rates and meeting the primary endpoint of OS. By the way, the primary endpoint was met early, and the study was closed prematurely, because of the benefit induced with blinatumomab.

That being said, in this study, investigators did look at the quality of life (QoL), treatment effects of blinatumomab vs standard of care. And the study has shown that those who received blinatumomab had better functioning and had better outcomes. Patients received a questionnaire on different time points to assess their functionalities, the symptoms, and other parameters. Again, in this study, those patients who received blinatumomab had better QoL, better functioning, and better symptom control, compared to patients who received standard of care. And therefore, the global health status was improved with blinatumomab compared to standard of care, and the improvement was seen, across the board, regardless of how much prior therapy they had, whether it's salvage 1 or 2, and regardless of the white blood cell count.

What I take from this study and others is that: 1) blinatumomab is effective in several settings, although I think we should use it in salvage 1 more than in salvage 2. Regardless of whether we go for transplant or not; and I discussed, in the beginning, the role of blinatumomab in combination with chemotherapy, and in MRD+ disease. I think blinatumomab does improve the functioning of these patients, not only their survival and their response rates. And I think we don't have to be concerned with safety of blinatumomab.

I think that blinatumomab is set to be the standard of care, but I think its role should be earlier in the disease, mainly in the frontline, MRD+ disease, and in salvage 1 setting.

Conclusion

In conclusion, what we've seen from these abstracts and others presented at last year's ASH, we have new drugs that can be used in a frontline setting, and early on. I think today, we have all the tools to cure ALL, starting with TKIs, for example, in combination with chemotherapy. We have blinatumomab and inotuzumab ozogamicin. These are very potent tools used in the relapsed setting, but we can optimize their use early on. And these drugs are explored in a frontline setting to improve on efficacy, to deepen the responses, and eventually help us physicians, not use intensive chemotherapy anymore, avoiding the long-term complications, or even, patients dying from complications.

So I think the use of inotuzumab ozogamicin and blinatumomab, in combination with chemotherapy, they have their place in practice, and I think in the long run, they will improve the outcome across the whole disease spectrum, in adult patients to the level seen in pediatrics. I don't see the CAR T-cells as competing with blinatumomab, I think they're complementary. And the role of the newer generation CAR T-cells is to minimize the safety concern and to replace transplant. Or maybe, in the future, as part of the combination of short chemotherapy, inotuzumab ozogamicin, blinatumomab, and then CAR T-cells adding to the cure.

Moving forward, do I think we need to go for a massive randomized drug? I don't think so. I think we should think in a patient-dynamic way, where we need to adjust to what is the best regimen, pivotal trial. Once we get the best regimen, then we go forward for a larger, confirmatory trial of these findings.

A lot of things are evolving, a lot of great tools, and I think these are promising developments to reach the cure for patients with ALL.