RESEARCH perspectives

Analysis of Recently Published Acute Lymphoblastic Leukemia Articles / Studies

OVERVIEW

In this CME activity Elias Jabbour, MD, reviews some of the recent clinical developments in advanced acute lymphoblastic leukemia. We invite you to learn more about the current and emerging standards of care, as well as safety and efficacy data from the selected clinical trials, in patients with acute lymphoblastic leukemia.

CONTENT AREAS

- CD19-positive ALL
- A bispecific T-cell engager antibody
- Philadelphia chromosome-positive ALL
- Tyrosine kinase inhibitor
- Complete remission with full hematologic recovery
- Minimal residual disease
- Allogeneic stem-cell transplantation

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CE STATEMENT

Target Audience

This activity is intended for hematologist-oncologists and other clinicians interested in the management of patients with Acute Lymphoblastic Leukemia (ALL).

Learning Objectives

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

- Summarize the latest research developments in the treatment of Acute Lymphoblastic Leukemia
- Describe how new data and recommendations can impact clinical practices to improve care
- Incorporate evidence-based research into clinical practice

FACULTY

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Editor's Note

This is a transcript of the Elias Jabbour, MD, presentation "Analysis of Recently Published Acute Lymphoblastic Leukemia Articles / Studies."

Introduction

Elias Jabbour, MD

I will review some of the recent clinical developments in advanced acute lymphoblastic leukemia (ALL). I'll be discussing 3 studies: Blinatumomab versus chemotherapy for advanced ALL, the TOWER trial, published by Dr. Hagop Kantarjian and his colleagues in *New England Journal of Medicine* in March of 2017.

The second study is: Blinatumomab for minimal residual disease in adults with B-cell precursor ALL, published by Dr. Nicola Gökbuget and her colleagues in *Blood*, in April of 2018.

And the third study is the report of a phase 2 trial: Combining hyper-CVAD with ponatinib in a frontline therapy of patients with Philadelphia chromosome-positive ALL, published by myself and my colleagues in *Lancet Oncology* in November of 2015, with an update to be published this fall.

The adoption of pediatric-inspired regimens significantly improved outcomes of adult patients with ALL and, currently, around half of them get cured. The most important prognostic indicator that drives treatment algorithms, which include allogeneic stem cell transplantation (allo-SCT), is the evaluation of minimal residual disease (MRD). For patients with high-risk disease, allo-SCT should be pursued as soon as possible. On the other hand, in light of raised toxicity, and lack of significant benefits in patients with standard-risk disease, this procedure should be avoided.

Furthermore, characterization of the underlying molecular genetic events can drive therapeutic decisions. An example, in this regard is the use tyrosine kinase inhibitors (TKIs) in Philadelphia chromosome (Ph)-positive (Ph+) ALL. In the near future, however, TKIs might be used also in other patient subgroups, such as breakpoint cluster region/Abelson 1-like cases and others with deregulated tyrosine kinases.

Lately, however, the greatest progress has been achieved with new immunotherapies targeting frequently expressed surface antigens in ALL, an approach that may also benefit elderly patients with ALL who are ineligible for intensive chemotherapy and allo-SCT. Finally, while the advent of targeted therapies treats the different algorithm, the greatest challenge, currently, is to find optimal sequence of the extended therapy options in an individual patient.

Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia.

Kantarjian H, Stein A, Gökbuget N, et al.

In summary, blinatumomab was shown to be superior to standard of care (SOC) chemotherapy in patients with relapsed/refractory (R/R) Ph-negative (Ph-) ALL. There was an improvement in overall response rates (ORR) and overall survival (OS), which was the primary endpoint of the study. The importance of this study is that it established a new SOC for patients with R/R ALL.

In this multi-institutional phase 3 trial, adults (N=405) with R/R, Ph- ALL were randomly assigned, in a 2:1 ratio, to receive either blinatumomab (n=271), which is a bispecific antibody construct that enables CD3+ T cells to recognize and eliminate CD19+ ALL blasts, or SOC chemotherapy (n=134) such as fludarabine, high-dose cytarabine, and G-CSF with or without anthracycline; a high-dose cytarabine-based regimen; a high-dose methotrexate-based regimen; or a clofarabine-based regimen.

The 2 arms had similar demographic and disease characteristics at baseline. I must mention that the primary endpoint was met early enough, due to the survival benefits obtained in the blinatumomab arm. The key secondary endpoints included achievement of complete remission (CR) with full hematologic recovery within 12 weeks after initiation of treatment; achievement of CR with full, partial, or incomplete hematologic recovery within 12 weeks after initiation of treatment; and event-free survival (EFS), defined as the time from randomization until relapse after achieving a CR with full, partial, or incomplete hematologic recovery, or death.

Other secondary endpoints included the duration of CR, minimal residual disease (MRD) remission, the rate of allo-SCT, and adverse event (AE) rates. The median OS, which, as I mentioned, was the primary endpoint, was 7.7 months in the blinatumomab group compared with 4 months in the chemotherapy group, with a highly significant hazard ratio of 0.71.

Estimated median survival at 6 months, among all patients who underwent randomization was 54% in the blinatumomab group and 39% in a chemotherapy group. The treatment benefit with respect to OS was generally consistent across key subgroups. The remission rates within 12 weeks after initiation of therapy, were significantly higher in a blinatumomab

group compared with the chemotherapy group. The CR rate was 34% in the blinatumomab vs 16% in the SOC arm.

And if you consider all responses together, including CR and CR without full hematologic recovery, the rates of responses were 44% with blinatumomab compared with 25% with SOC -- this difference being significant.

If you look at the patients who achieved CR, with or without full hematologic recovery, 76% of them achieved MRD-negative status in the blinatumomab arm compared with 48% in the SOC arm. Among the patients who achieved CR, with or without full hematologic recovery, the median duration of remission was 7.3 months in the blinatumomab arm compared with 4.6 months in the SOC arm. Let's look now at the key secondary efficacy endpoint of EFS. A 6-month EFS estimate was 31% in blinatumomab arm compared with 12% in the SOC arm, with a hazard ratio for relapse of 0.55 being significant.

Overall, the treatment was well tolerated. The rate of serious AEs in the blinatumomab arm was 62% compared with 45% in the SOC arm. However, the fatal AEs reported were 19% in the blinatumomab arm compared with 17% in the SOC arm.

Investigators considered fatal AEs to be related to the treatment with blinatumomab in 3% of patients and to the SOC chemotherapy in 7% of patients. The incidence of grade 3 or higher AEs such as neutropenia or infection was lower with a blinatumomab than with SOC. In contrast, neurologic events of grade 3 or higher occurred at a similar rate in the 2 arms.

The rates of treatment discontinuation due to any AE were 12% in the blinatumomab arm and 8% in the SOC arm, including 4% and 1%, respectively, due to a neurologic event and 1% and 0% due to the cytokine release syndrome (CRS). In the blinatumomab arm, CRS was reported as serious AE in 4% of the patient and as grade 3 or higher in 5% of the patients. However, after adjustment for treatment exposure between the 2 arms, the rate for serious AEs was lower overall in the blinatumomab arm compared with the SOC arm.

I think the TOWER trial is a very important landmark trial that established blinatumomab as the new SOC for patients with R/R disease. The study has shown that the blinatumomab can induce higher response rates and improve OS. At the same time, this treatment was found to be safe and effective compared to SOC chemotherapy.

How is the drug used? It is given over 4 weeks by continuous infusion, with the escalation of the dose from 9 mg per day, for the first week, to 28 mg per day for subsequent days of treatment. When you look at the outcome of patients in the salvage-1 setting, the OS was 11.1 months in the blinatumomab arm compared with 5.3 months for SOC arm.

I think blinatumomab has been established as the SOC for patients with R/R disease. The advantage of blinatumomab is mainly seen in the salvage-1 setting and not so in the more advanced disease setting. Importantly, not only do patients respond to blinatumomab, but they respond and achieve a deep response. That is very important because, in the long run, if you want to see improved survival in these patients you need to have as deep response as possible and then consolidate that response with either blinatumomab or transplantation.

With regard to blinatumomab-associated AEs, 2 common ones are neurologic events and CRS. Let me start with second one. Essentially, we see the CRS early on in patients with high disease burden. The protocol of the TOWER trial specified to use a debulking approach with steroid and low-dose chemotherapy followed by blinatumomab. This approach effectively minimizes the occurrence of the CRS. And whenever they occur, we usually hold therapy. If it is grade 3, we wait for the recovery, and then resume blinatumomab, while giving steroids, at a lower dose and later escalate.

Another type of AEs encountered, as I mentioned, are neurologic events. However, if you consider the exposure to the drug, the rates are not significantly higher than what is seen with the SOC. In fact, the rates are similar or less. But, nevertheless, one should be careful about this side effect. In case of a grade 3 event, we give steroids and, once we resume, we do it at a lower dose. In addition, when you look at the patient for the quality of life (QoL), we see an improvement of the QoL in patients who received blinatumomab compared with those who received SOC.

That was as seen in the TOWER trial. Blinatumomab is also effective in a Ph+ disease. There was a separate study called ALCANTARA trial that established blinatumomab as the SOC for patient with Ph+ ALL. Now where (are) we going with these data? In Ph+ ALL, we combine blinatumomab with TKI further to improve this outcome. For Ph- ALL we're moving blinatumomab to earlier disease settings, including with the ongoing clinical trials which are exploring it in a frontline setting.

The drug was also shown to be effective in pediatric patients with R/R ALL. One last comment about the TOWER trial is that there was a concern that patients who fail blinatumomab may lose CD19 expression, which would compromise their chance of getting subsequent chimeric antigen receptor (CAR) T cells. We have shown that more than 92% of the patients retain the CD19 expression and can be candidates for a treatment with CAR) T cells down the road.

How does this information impact my practice? I think today blinatumomab is the SOC for patients with R/R ALL. I think blinatumomab should be used earlier in the course of disease rather than later as a bridge to transplantation or as a blinatumomab

maintenance strategy with, if transplant is not considered. Blinatumomab is also being already approved for MRD and I will discuss that in a moment, but, moving forward, blinatumomab is also finding its way into the frontline setting. There are several ongoing randomized, phase 2, trials assessing its role in the frontline setting. What are the unanswered questions today?

I think that, logistically, administration of blinatumomab is cumbersome, because we have to give it over 4 weeks. Having in the clinic something similar to blinatumomab but with a longer half-life, so that we give it as weekly infusions, would really help a lot. And then, the frontline setting move for blinatumomab will hopefully allow us to use less chemotherapy and less transplantation.

Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia.

Gökbuget N, Dombret H, Bonifacio M, et al.

In summary, blinatumomab was found to be effective in patients with MRD positive disease, as 80% of them were able to convert to the MRD negative status and subsequently get transplantation. The importance of this study resides in the fact that we know that patients with MRD+ disease do not do well. They can go for transplant, but they have higher rates of relapses. However, blinatumomab is effective in converting the MRD+ disease into the MRD- one and improving the outcome of these patients in the long run. Do we still need a transplantation? The answer is, yes, today. So, today, nobody should get transplant while having the MRD+ disease, before being able to receive blinatumomab and convert into MRD negativity.

In this open-label, single-arm, phase 2 study, 116 patients, age 18 or older with B-cell precursor ALL in first or later CR, with persistent MRD after a minimum of 3 rounds of intensive chemotherapy, were eligible to receive a blinatumomab at a dose of 15 µg/m2 by infusion for up to 4 cycles. Each cycle comprised a 4-week blinatumomab infusion followed by 2-week treatment-free period. Patients could undergo allo-SCT after cycle 1 at the discretion of the investigator. The central nervous system (CNS) prophylaxis was recommended before cycle 1 and after cycle 2 and 4. Overall, 76 patients underwent transplantation in continuous CR after cycle 1 (n=27), cycle 2 (n=36), or cycle 3 or 4 (n=13).

The primary endpoint was the rate of complete MRD response after cycle 1 among patients in the primary endpoint full analysis set, or 113 patients. The key secondary endpoint was hematologic relapse-free survival (RFS) at 18 months after initiation of blinatumomab, and that was evaluated among patients in a key secondary endpoint full analysis set of 110 patients.

What are the key findings of the study? Of 113 patients with evaluable MRD markers, 88, or 78%, achieved a complete MRD response after cycle 1, which was the primary endpoint. So, essentially, 80% of the patients did achieve this endpoint which is MRD- status after cycle 1.

Two additional patients achieved the complete MRD response after cycle 2. No additional patients achieved the complete MRD response after cycle 3 or 4. That means responses do happen usually after 1 course of treatment or maximum 2. So, patients who do not respond after cycle 1 or 2 should not get further therapy. Among 5 patients with a Ph+ disease who had MRD evaluations, 3 patients, or 60%, had an MRD response during cycle 1. Now, of 103 patients in hematologic CR, with MRD>10^{-3} at baseline, 91, or 88%, achieved any MRD response, including 82, or 80%, with a complete MRD response after cycle 1.

Complete MRD response rates were similar between patients with MRD≥10^{-2} at the baseline, and those with MRD<10^{-2} at baseline, and between patients with first and later remission at baseline. So, the responses were seen across the board. Among 110 patients who had Ph- disease and <5% blasts at baseline, the Kaplan-Meier estimate for RFS at 18 months was 54%. Median RFS was 18.9 months with a median follow up of 29.9 months. Median RFS was 11 vs 26.4 months among patients treated within later CR vs first CR. Patients in first CR also had improved OS compared with those in later CR.

Of 110 patients, 48 remain in CR (36 after subsequent transplantation), 38 relapsed in CR, and 24 died in CR (20 after subsequent transplantation). The median duration of hematologic remission was not reached, and the median OS was 36.5 months after a median follow-up of 30 months. Among the entire study population of 116 patients, the median OS was also 36.5 months. In landmark analysis (the landmark of 45 days was used to represent the latest day of first MRD response assessment) the median RFS was 20.6 months vs 5.7 months, the value highly significant, and the median OS of 38.9 months vs 12.5 months, again highly significant, in patients with and without MRD response after cycle 1, respectively.

Of 110 patients in the key secondary endpoint analysis, 74, or 67%, underwent transplantation in CR after blinatumomab (55 in the first CR, and 19 in the second CR). Of 36 patients without transplantation or chemotherapy after blinatumomab 9, or 25%, remain in continuous CR with a median follow-up of 24 months, whereas, 36, or 49%, of 74 patients who underwent transplantation remain in remission.

Overall, 30% and 27% of patients had 3 and 4 AEs, respectively, including 20% and 18%, respectively, in cycle 1, and 11% each in cycle 2. Investigators

considered grade 3 and 4 AEs to be treatment-related in 29% and 22% of patients, respectively. Four patients, or 3%, had CRS, grade 1 in 2 patients and grade 3 in 2 patients, all during cycle 1. Sixty-one patients, or 53%, had neurologic events of any grade with decreasing incidents over cycle 1, 2, and 3, and 4, of 47%, 24%, 15% and 15%, respectively. Neurologic events resolved in 59 patients, or 97%, with any grade AEs, and in all patients with a grade 3 and 4. Most patients who had grade 3/4 neurologic events, resumed blinatumomab treatment after the event resolved. Two fatal AEs were reported during the treatment both in cycle 1: atypical pneumonitis with H1N1 influenzae, considered treatment-related by the investigator, and subdural bleeding, considered unrelated to the treatment by the investigators.

What does this all mean? What are the important features, or important elements, of this study? I think we all know that assessment of MRD should be part of our SOC today. Patients with MRD+ disease usually have a poor outcome.

In fact, MRD is not a biomarker, MRD means somebody has a residual disease and therefore we call it, measurable disease, not only minimal—it's measurable. We know that if you have an MRD+ status today the outcome is poor, and you go for transplant because it's better than chemotherapy, but we know that the transplant does not improve the outcome of these patients to the level observed in patients who have MRD- status. Blinatumomab is the first drug to show the capability of converting MRD+ to MRD-; 80% of the patients were able to get to MRD- status, eventually going for transplant.

The study had its limitation because it's (a) phase 2 study, it's not randomized. Although I doubt very much that you could get a randomized study today for patient with MRD+ disease. And then the question of transplant remains unanswered. Do we need a transplant for these patients or do we not need a transplant? The SOC is transplantation, although we do see that patients who received blinatumomab without transplant remained free of disease down the road. Therefore, there will be a subset of patients who can be cured with blinatumomab alone without transplantation. I think the SOC for somebody who is remaining MRD+ after 12 weeks of chemotherapy should be to get blinatumomab before considering transplantation, 1 or 2 courses and then going for transplant.

Also, exploring the role of blinatumomab maintenance with or without transplantation is important. Furthermore, we need to improve the MRD essays and we need to have the MRD assessment part of our treatment algorithm and have blinatumomab offered if they have MRD+ status. Moving forward, what are the unanswered questions today? Again, is transplant needed, yes or no? Second, what is the best tool to assess for MRD? Ultimately, we need to improve the cure rates for these patients.

First report of a phase II prospective study of combination of hyper-CVAD with ponatinib in frontline therapy of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia.

Jabbour E, Kantarjian H, Ravandi F, et al.

I will be discussing the result of this study as first published in *Lancet Oncology* in 2015, with an update recently accepted for publication in *Lancet Haematology*, with more than 75 patients enrolled. In summary, hyper-CVAD and ponatinib combination induced high rate of complete molecular remission (CMR), exceeding 80% in patients with Ph+ ALL. At the time of initial reporting, the OS was 80% at 2 years. At follow-up, an estimated 5-year OS was 71%, which is the best we ever had. When the study was designed, we allowed patients to receive a transplant subsequently. However, with the positive results we obtained, the need for transplant is now debatable; going forward, we may need less transplantation. So, again, in summary, high efficacy and less need for transplantation. The importance of this study is that is setting a new SOC for this patient population today with a Ph+ disease, improving the cure rate to 70%, 75%, which has never been achieved before.

What do I think are the 3 most important findings of the study? We know that TKIs should be part of the SOC for patients with Ph+ ALL, should be combined with chemotherapy and given continuously. How much chemotherapy we need, that is unanswered. We know as well that in Ph+ ALL we have a high rate of emergence of a T315I mutation. This particular kinase domain mutation leads to resistance to imatinib, nilotinib, dasatinib, and bosutinib, and it's only suppressed by ponatinib.

We also know that, if we want to improve the outcomes in this disease, we need to improve the rate of CMR. Ponatinib does that, improving the rate of CMR from 50% to 80% or higher. Therefore, I think the importance of this study resides in 3 things. Number 1, suppression of the emergence of T315I mutation that causes resistance to TKIs. Number 2, improvement of the CMR rate, and (3) by improving the CMR rate and eradicating the T315I mutation, we improve OS and subsequently need less transplantation down the road. Based on these findings I think ponatinib should be the SOC for patients with Ph+ ALL. Moving forward, we're exploring different combinations with the low-dose chemotherapy and blinatumomab, so that, eventually, hyper-CVAD and transplantation may not be needed.

What we have today is high response rate, great survival, and less need for transportation. So, let's focus on a study description and the key findings. The study regimen was a combination of intensive chemotherapy, what we call the hyper-CVAD, given for 8 cycles, in 3 week or 4 week blocks, and then followed by 2 years of maintenance and ponatinib indefinitely. When the study was designed, we used ponatinib at the labeled dose, which is 45 mg/d given for 2 weeks during induction, and from cycle 2 and beyond, we gave it at a dose of 45 mg/d continuously. For the 8 cycles, during the maintenance phase we did give vincristine, prednisone, and ponatinib continuously for 2 years, and after that a single agent ponatinib. At any time, patient can go for transplant after discussions with the investigator or treating physician. When we had all 37 patients enrolled, we had 2 vascular events encountered, essentially related to the drug. One young man and the woman who had sudden deaths from cardiac arrest. That led us (to) amend the study and modify the regimen so the study was qualified, where ponatinib was used at 45 mg/d during the first 2 weeks, and then 30 mg from cycle 2 and beyond, and with further reduction to 15 mg once CMR is achieved.

After this amendment of the study, we had 80 patients treated and we did not see any serious vascular AEs. We now know that there is a good correlation between the dose given and AEs and that lower dose is being effective.

We published originally on 37 patients, that's originally the paper published in *Lancet Oncology*. We now have updates, with 76 patients treated, and the data will be published in *Lancet Haematology* this year. The CR rate was 100%, the complete cytogenetic response was 100% as well. The CMR, or what we call 4.5 log reduction, we are at 83% of the patient population, and we have seen no heart attacks. At the median follow-up of 39 months, the 3-year OS was 76% and an estimated 5-year OS was 71%. We had only 3 patients relapse on ponatinib, and none of them developed T315I mutation.

There was 1 case of E255V mutation, known not to be sensitive to ponatinib. Of note, patients received 12 doses of intrathecal prophylaxis chemotherapy, and we did not see any central nervous system (CNS) relapses. Patients had a donor for transplantation, and we had 15 patients who underwent transplantation. Interestingly, we did the landmark analysis at 4 months and then at 6 months with a whole set of patients treated and observed that transplant did not seem to improve outcome compared with patients who did not get transplantation.

Among the 15 patients, a few of them had an MRD+ disease at the time of transplantation, but transplant did not seem to improve outcome of these patients and that let us think the transplant may not be needed down the road. With regard to the safety profile, we did see hypertension and pancreatitis, but highly manageable. As I mentioned, we did see 2 vascular events occurring at the high dose of 45 mg/d, and 30 mg/d, but not at 15 mg/d, which is quite reassuring. Today we have a long follow-up and we think ponatinib is becoming the SOC for patient with a Ph+ ALL.

Here are my thoughts on this study. It's a single arm trial, it's single situation, and, of course, these findings need to be confirmed by other prospective trials that can validate our point. But, nevertheless, this is the best result ever reported, superior to the hyper-CVAD and dasatinib combination. We've shown as well that having a CMR does improve the long-term outcome and essentially obviates the need for transplant. Therefore, if you get the CMR, you can essentially put transplant on hold. And today we have an option of adding blinatumomab to this regimen, mainly for patients who have an MRD+ disease, and improve their outcome.

What do we do, moving forward? We need a confirmation of our findings. There is an ongoing randomized study comparing low-dose chemotherapy and ponatinib with low-dose chemotherapy and imatinib, primary endpoint being MRD- CR. The second question that is being addressed is whether we still need intensive chemotherapy, if ponatinib is so effective. Maybe we can simplify the chemotherapy and that is being explored today with either low-dose chemotherapy and ponatinib or moving fully to a chemotherapy-free regimen, using blinatumomab and ponatinib.

One thing I like to highlight is that we still need CNS prophylaxis, and with 12 cycles of methotrexate and cytarabine, we are not seeing any more CNS relapses. In summary, ponatinib is the best TKI for this patient population by suppressing the emergence of T315I mutation and improving the CMR rate, and validation of these findings are still ongoing. So, what are the other questions for the future? Do we still need intensive chemotherapy? The answer is I don't know, prospective studies are ongoing, addressing this question. Do we still need transplantation? I think we can say that with the data we have today, if you have CMR, transplant may not be needed—it should be placed on hold. And the new era coming is to go into what we call chemotherapy-free regimen and that is being explored prospectively, as well. Thank you very much for your attention.