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POINT Immunotherapy in adult acute lymphoblastic leukemia: the role of monoclonal antibodies

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Introduction

The past decade has witnessed major advances in the development of novel therapies that target specific subsets of adult acute lymphoblastic leukemia (ALL). Monoclonal antibodies (MoAbs) targeting specific leukemic cell surface antigens (eg, CD20, CD22, and CD19) represent a significant breakthrough in the ALL therapeutic armamentarium (Table 1). MoAbs bind to a specific target on leukemic cells that has relatively lower expression on normal cells. They work through a number of mechanisms, including antibody-dependent and complement-dependent cytotoxicity and direct induction of apoptosis. If a target is known to internalize upon binding, potent drugs or toxins can be conjugated to the antibody portion, producing an additional mechanism for leukemic cell–targeted elimination. The anti-CD20 antibody rituximab has produced encouraging results as a component of the initial B-cell ALL (B-ALL) therapy. Other MoAbs targeting CD19 and CD22 have been evaluated in clinical trials of refractory/relapsed ALL (Table 2). The promising results have led to combining these MoAbs with standard chemotherapy in ALL salvage and first-line regimens. With the recent development of CD19-direct chimeric antigen receptor (CAR) T cells that are capable of producing deep and lasting remissions in patients with multiply refractory ALL, the question arises: How should we best prioritize the use of these various tools against ALL to maximize efficacy? Herein, we review the clinical activity of MoAbs in adult ALL and discuss the relative roles of MoAbs and CAR T cells in modern ALL therapy.

Anti-CD20 antibodies

CD20 expression ≥20% is found on approximately 30% to 40% of precursor B-ALL leukemia blasts and in nearly 100% of mature B-ALL cells.[1,2] Rituximab is a chimeric human/mouse MoAb to CD20 with activity in several lymphoid malignancies.[3-5] Evaluation of the addition of rituximab to chemotherapy for ALL was based on the positive data in high-grade non-Hodgkin lymphoma, in which the addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (R-CHOP) improved overall survival by ≥20%.[3]

The addition of rituximab to chemotherapy has improved the cure rates in patients with mature B-cell or Burkitt ALL treated in phase 2 studies.[6-8] This observation is interesting in itself, because single-agent rituximab has no activity in ALL. The addition of rituximab to hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (hyper-CVAD) regimen (8 infusions) resulted in a 3-year survival rate of 89% compared with 53% with chemotherapy alone.[6] Ribrag et al[9] conducted an open-label randomized phase 3 trial comparing chemotherapy alone (n = 129) with chemotherapy plus rituximab (n = 128). Rituximab (375 mg/m^2) was given on days 1 and 6 during the first 2 courses of chemotherapy (total of 4 infusions). The addition of rituximab improved event-free survival, which was the primary end point of the study (3-year rate, 75% vs 62%; $P = .024$) and overall survival (3-year rate, 83% vs 70%; $P = .011$) without increasing the incidence and severity of adverse events. It is possible that more doses of rituximab might have produced even better results.

The benefit of adding rituximab to chemotherapy was also observed in patients with B-precursor ALL. The addition of rituximab to the hyper-CVAD regimen in newly diagnosed patients with Philadelphia chromosome–negative (Ph^-) $CD20^+$ ALL improved the complete remission (CR) duration (3-year rate, 70% vs 38%; $P < .001$) and survival (3-year rate, 75% vs 47%; $P = .003$) among patients younger than age 60 years.[10] The German Multicenter Study Group for ALL also reported an improvement in the incidence of minimal residual disease (MRD) negativity, as well as in the 5-year remission duration and survival rates with the addition of rituximab to standard chemotherapy in patients younger than age 55 years.[11] The addition of rituximab to chemotherapy was recently assessed in the GRAAL-R 2005

Table 1. Expression of antigens in B-cell lineage ALL for potential antibody therapy

Surface antigen	ALL subtype	Expression (%)	MoAb
CD20	Mature B-cell precursor	86-100 30-40	Rituximab, ofatumumab, obinituzumab
CD19	Mature B-cell precursor	95-<100 95-<100	Blinatumomab
CD22	Mature B-cell precursor	~100 93-98	Inotuzumab ozogamicin, epratuzumab, moxetumomab pasudotox

Adapted from Jabbour et al.[2]

randomized study: rituximab improved the 2-year event-free survival rate (the study primary end point) from 52% to 65% ($P = .038$) and the 2-year overall survival rate from 63% to 74% ($P = .018$) after censoring for allogeneic stem cell transplantation (SCT).[12]

Further improvements in outcomes may be achievable with newer more potent MoAbs targeting CD20. Both ofatumumab and obinutuzumab exhibit greater CD20 affinity than rituximab and are superior to rituximab in the treatment of chronic lymphocytic leukemia. Ofatumumab, a more potent second-generation anti-CD20 MoAb, is being tested in combination with hyper-CVAD following the same schema used with rituximab.[13] Among 59 patients treated, the 3-year CR duration and overall survival rates were 78% and 68%, respectively. No increase in the rates of relevant adverse events was observed. Obinutuzumab, a novel glyco-engineered type II CD20 MoAb, was superior to rituximab when combined with chlorambucil in untreated chronic lymphocytic leukemia, resulting in better progression-free survival and in higher duration rates of CR and molecular response.[14] Investigations of obinutuzumab in patients with $CD20^+$ ALL may be warranted.

Anti-CD19 bispecific T-cell engager blinatumomab

Blinatumomab is a bispecific T-cell engager antibody of CD3 and CD19 which is designed to direct cytotoxic T cells to CD19-expressing leukemic cells.[15] CD19 is nearly universally expressed on the cell surface of both precursor and mature B-ALL leukemic blasts and thus is a rational target for antibody-directed therapy for these diseases.[2]

Blinatumomab was first assessed in patients with positive MRD and subsequently studied in patients with relapsed/refractory ALL. Blinatumomab was evaluated in 116 patients with ALL in CR with positive MRD. Most patients had ≥3 courses of chemotherapy and ≥35% were in second CR.[16,17] Blinatumomab was given at 15 $\mu g/m^2$ per day continuous infusion for 28 days every 6 weeks for 4 cycles. Approximately 78% of patients achieved MRD negativity after 1 cycle, and 80% achieved MRD negativity after 4 cycles. With a median follow-up of 29 months, the median survival was 36 months and the relapse-free survival was 19 months. The median survival for patients who achieved MRD-negative status was 40 months compared with 12 months for those who remained MRD positive. Notably, allogeneic SCT did not confer a survival benefit for patients who achieved MRD-negative status in first remission. These results provide evidence that a strategy of MRD-directed therapy using MoAbs is useful in improving outcomes in ALL.

In a phase 2 study of 189 heavily pretreated patients with relapsed/refractory Ph^- ALL, blinatumomab given as continuous intravenous therapy over 4 weeks every 6 weeks was associated with a CR plus CR with partial hematologic recovery rate of 43%.[18] The median response duration and overall survival were 9 and 6 months, respectively. A phase 3 randomized trial compared blinatumomab to the chemotherapy regimen of the investigator's choice in patients with relapsed/refractory ALL. A total of 405 patients with relapsed/refractory Ph^- ALL were randomly assigned to either blinatumomab (n = 271) or standard-of-care chemotherapy (n = 134).[19] The overall response rates were 45% and 30% ($P = .007$), respectively. Molecular remission rates among responders, defined as $<10^{-4}$ blasts in the first 12 weeks, were 75% and 48%, respectively. Blinatumomab prolonged survival, the primary study end point: the median survival was 7.7 months (range, 5.6 to 9.6 months) with blinatumomab and 4.0 months (range, 2.9 to 5.3 months) with standard-of-care chemotherapy, respectively ($P = .012$)

Blinatumomab was evaluated in a phase 2 trial in 45 patients with relapsed/refractory Ph^+ ALL.[20] Thirty-six percent of patients achieved CR or partial hematologic response. With a median follow-up of 9 months, the median relapse-free survival and overall survival were 6.7 and 7.1 months, respectively. Among the 16 responders, the MRD negativity rate was 88%, and 44% of patients were able to receive allogeneic SCT. The combination of blinatumomab with tyrosine kinase inhibitors (TKIs) may further improve the complete molecular response and survival rates compared with a combination of chemotherapy and TKIs, with a significantly better safety profile.

Anti-CD22 antibody-drug conjugate inotuzumab ozogamicin

CD22 is expressed in 93% to 98% of precursor B-ALL and universally in Burkitt leukemia.[21] Inotuzumab ozogamicin is an immunoconjugate comprising an anti-CD22 antibody linked to calicheamicin, a potent cytotoxic compound.[22]

In a single-institution phase 2 study in 49 patients with relapsed/refractory ALL, inotuzumab ozogamicin was administered at a starting dose of 1.3 to 1.8 mg/m^2 intravenously every 3 to 4 weeks.[23]

Table 2. Clinical activity of blinatumomab and inotuzumab ozogamicin in relapsed/refractory ALL

	Blinatumomab				Inotuzumab ozogamicin				
		Ph^- ALL							
Parameter	Ph^+ ALL phase 2	Pivotal phase 2	Confirmatory phase 2	TOWER phase 3 trial	Single dose	Weekly dose	Weekly dose	INO-VATE phase 3 trial	Inotuzumab + mini-HCVD
No. of patients	45	36	189	271	49	41	35	109	52
ORR, %	36	69	43	45	57	59	66	81	77
Median OS, mo	7.1	9.8	6.1	7.7	5	7.3	7.4	7.7	11

mini-HCVD, mini-hyperfractionated cyclophosphamide, vincristine, and dexamethasone; ORR, objective response rate; OS, overall survival.

The objective response rate was 57%, and the median survival was 5.1 months. Nearly half the patients treated with inotuzumab ozogamicin were able to proceed to allogeneic SCT. Notable serious toxicities included sinusoidal obstruction syndrome (SOS) or veno-occlusive disease (VOD) after allogeneic SCT (23%), mainly observed in patients who received double alkylators as part of their pretransplant conditioning or double SCT; older age was also a risk factor. To minimize toxicities without compromising efficacy, inotuzumab ozogamicin was administered on a weekly basis at 0.8 mg/m^2 intravenously on day 1 and 0.5 mg/m^2 intravenously on days 8 and 15 every 3 to 4 weeks in 40 patients.[24] The objective response rate was 59%; the median survival was 9.5 months. The weekly administration of inotuzumab ozogamicin resulted in fewer adverse events, including lower rates of SOS and VOD. Minimizing the rate of SOS and VOD is the aim of an ongoing trial assessing a lower-dose schedule of inotuzumab ozogamicin (50% dose reduction; 0.9 mg/m^2 per cycle).

In a separate multicenter phase 2 trial in heavily pretreated patients with relapsed/refractory ALL, inotuzumab resulted in a remission rate of 66%, with 78% of patients who achieved CR also becoming MRD negative.[25] The median survival was 7.4 months. A randomized trial compared inotuzumab ozogamicin with physician's choice of chemotherapy in patients with relapsed ALL in the first and second salvage treatments.[26] Patients were randomly assigned (1:1) to receive either inotuzumab ozogamicin or the investigator's choice of standard therapy; no crossover between groups was allowed. Stratification factors at random assignment were the duration of first remission ($<$12 vs $\geq$12 months), the salvage treatment phase (first vs second), and age ($<$55 vs $\geq$55 years). Patients who achieved CR could undergo allogenic SCT at the investigator's discretion. The 2 primary end points of the trial were objective response rate and survival. The objective response rates were 81% and 33% ($P < .001$), respectively. Among responders, the MRD-negative status rates were 78% and 28% ($P < .001$), respectively. The median progression-free survival was 5.0 vs 1.8 months ($P < .001$). The median overall survival was 7.7 vs 6.7 months ($P = .02$). The 2-year survival rates were 23% and 10%, respectively. The most frequent grade 3 or higher nonhematologic adverse events with inotuzumab ozogamicin were liver-related. VOD of any grade occurred in 11% of patients who received inotuzumab ozogamicin. VOD occurred particularly in older patients who received allogenic SCT after conditioning with a dual alkylator.[26] Improvement in outcome of patients treated with inotuzumab ozogamicin followed by allogeneic SCT could be optimized by eliminating dual-alkylator regimens, using lower dose schedules, and using VOD preventive measures (eg, ursodiol or defibrotide).

Inotuzumab ozogamicin was also evaluated in both the first-line[27] and salvage[28] settings in combination with a dose-reduced mini-HCVD regimen (no anthracycline; 50% dose reduction of steroid and cyclophosphamide; 75% dose reduction of methotrexate; and 83% dose reduction of cytarabine). In 52 patients with relapsed/refractory ALL, this regimen resulted in an overall response rate of 77%; 82% of responders achieved MRD-negative status in CR.[27] The 2-year progression-free and overall survival rates were 60% and 32%, respectively.[28] In 38 elderly patients with de novo Ph$^-$ ALL, the objective response rate was 97% (CR rate of 80%); all patients in CR also achieved MRD-negative status. The 2-year CR duration and survival rates were 81% and 64%, respectively.

MoAbs or CAR T cells for ALL?

CD19-directed CAR T cells have similarly shown promise in the treatment of patients with ALL. In the relapsed/refractory setting, the use of CAR T cells results in high rates of MRD negativity, which has translated into long-term survival in some responders.[29,30] Given the impressive results seen with both MoAbs and CD19 CAR T cells, we believe that we have the tools necessary to cure the vast majority of adults with ALL. However, with all of these options available, the question arises: How should we best incorporate these therapies into ALL treatment? Improving outcomes in ALL will require appropriate sequencing and incorporation of these tools into rational treatment regimens.

We do not view these 2 treatment modalities as competitive but rather that MoAbs and CAR T cells should be administered sequentially to produce the deepest remission possible. Future studies should therefore incorporate the use of both MoAbs and CAR T cells given sequentially in the first-line setting. The rational combination of MoAbs and CAR T cells should reduce the need for intensive, toxic chemotherapy, and through the eradication of MRD, it may also obviate the need for allogeneic SCT in many patients. With less reliance on intensive chemotherapy and SCT and their associated treatment-related mortality, we anticipate that these novel MoAb and CAR T-cell-based regimens will translate into improved long-term outcomes, especially for older patients who are most susceptible to complications from intensive treatment approaches.[31] Through such novel combination therapies, we hope to achieve cure rates in adult ALL that approach those seen in the pediatric population.

Conclusion

The development of MoAbs in adult ALL is producing exciting results, and their role continues to be defined. Most of these MoAbs are currently being evaluated in the ALL salvage setting, although the most active agents will likely need to be incorporated into the first-line regimens to optimize efficacy. The incorporation of both active MoAbs and CAR T cells into first-line adult ALL therapy, in a concomitant or sequential fashion, may induce higher rates of MRD negativity, reduce the need for intensive and prolonged chemotherapy schedules, and significantly increase the cure rates in adult ALL.

Authorship

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References

1. Raponi S, De Propris MS, Intoppa S, et al. Flow cytometric study of potential target antigens (CD19, CD20, CD22, CD33) for antibody-based immunotherapy in acute lymphoblastic leukemia: analysis of 552 cases. *Leuk Lymphoma*. 2011;52(6):1098-1107.

2. Jabbour E, O'Brien S, Ravandi F, Kantarjian H. Monoclonal antibodies in acute lymphoblastic leukemia. *Blood*. 2015; 125(26):4010-4016.

3. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346(4): 235-242.

4. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23(18):4079-4088.

5. Hallek M, Fischer K, Fingerle-Rowson G, et al; International Group of Investigators; German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.

6. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer*. 2006;106(7):1569-1580.

7. Hoelzer D, Walewski J, Döhner H, et al; German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. *Blood*. 2014;124(26): 3870-3879.

8. Rizzieri DA, Johnson JL, Byrd JC, et al; Alliance for Clinical Trials In Oncology (ACTION). Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. *Br J Haematol*. 2014; 165(1):102-111.

9. Ribrag V, Koscielny S, Bosq J, et al. Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016;387(10036):2402-2411.

10. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol*. 2010;28(24):3880-3889.

11. Hoelzer D, Gökbuget N. Chemoimmunotherapy in acute lymphoblastic leukemia. *Blood Rev*. 2012;26(1):25-32.

12. Maury S, Chevret S, Thomas X, et al; for GRAALL. Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia. *N Engl J Med*. 2016;375(11):1044-1053.

13. Issa GC, Kantarjian HM, Ravandi F, et al. Updated results from the phase II study of hyper-CVAD in combination with ofatumumab as frontline therapy for adults with CD20 positive (CD20+) acute lymphoblastic leukemia (ALL) [abstract]. *J Clin Oncol*. 2016;34. Abstract 7042.

14. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.

15. Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science*. 2008;321(5891):974-977.

16. Goekbuget N, Dombret H, Bonifacio M, et al. BLAST: A confirmatory, single-arm, phase 2 study of blinatumomab, a bispecific T-cell engager (BiTE) antibody construct, in patients with minimal residual disease B-precursor acute lymphoblastic leukemia (ALL) [abstract]. *Blood*. 2014;124(21). Abstract 379.

17. Gökbuget N, Dombret H, Bonifacio M, et al. Long-term outcomes after blinatumomab treatment: follow-up of a phase 2 study in patients (Pts) with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukemia (ALL) [abstract]. *Blood*. 2015;126(23). Abstract 680.

18. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16(1):57-66.

19. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy in advanced acute leukemia. *N Engl J Med*. In press.

20. Martinelli G, Dombret H, Chevallier P, et al. Complete molecular and hematologic response in adult patients with relapsed/refractory (R/R) Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia (ALL) following treatment with blinatumomab: results from a phase 2 single-arm, multicenter study (ALCANTARA) [abstract]. *Blood*. 2015; 126(23). Abstract 679.

21. Thomas X. Inotuzumab ozogamicin in the treatment of B-cell acute lymphoblastic leukemia. *Expert Opin Investig Drugs*. 2012;21(6):871-878.

22. Yilmaz M, Richard S, Jabbour E. The clinical potential of inotuzumab ozogamicin in relapsed and refractory acute lymphocytic leukemia. *Ther Adv Hematol*. 2015;6(5):253-261.

23. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol*. 2012;13(4):403-411.

24. Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer*. 2013;119(15):2728-2736.

25. Advani AS, Stein AS, Kantarjian HM, et al. A phase II study of weekly inotuzumab ozogamicin (InO) in adult patients with CD22-positive acute lymphoblastic leukemia (ALL) in second or later salvage [abstract]. *Blood*. 2014;124(21). Abstract 2255.

26. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med*. 2016;375(8):740-753.

27. Sasaki K, Kantarjian HM, O'Brien S, et al. Salvage chemotherapy with inotuzumab ozogamicin (INO) combined with mini-hyper-CVD for adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) [abstract]. *Blood*. 2015; 126(23). Abstract 3721.

28. Jabbour E, O'Brien S, Sasaki K, et al. Frontline inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-hyper-CVD) for older patients with acute lymphoblastic leukemia (ALL) [abstract]. *Blood*. 2015;126(23). Abstract 83.

29. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014;371(16):1507-1517.

30. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet*. 2015;385(9967): 517-528.

31. O'Brien S, Thomas DA, Ravandi F, Faderl S, Pierce S, Kantarjian H. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. *Cancer*. 2008;113(8):2097-2101.

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