Incorporating Antibodies into Treatment Strategies for Acute Lymphoblastic Leukemia

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Abstract

Monoclonal antibodies hold significant promise in improving the outcomes of patients with acute lymphoblastic leukemia (ALL). Rituximab has been shown to improve overall survival in younger patients with CD20-positive ALL, and next-generation anti-CD20 antibodies may be able to further improve these outcomes. Antibody-drug conjugates such as inotuzumab ozogamicin, and the bi-specific T-cell engager, blinatumomab, represent novel antibody constructs that have shown significant clinical activity in ALL. Although most studies have focused on the use of these agents in the salvage setting, incorporation of these antibodies into front-line regimens, with the goal of achieving minimal residual disease negativity, is also imperative to achieve long-term survival for patients with this disease.

Key words: acute lymphoblastic leukemia, rituximab, ofatumumab, inotuzumab ozogamicin, blinatumomab, Burkitt leukemia, monoclonal antibodies

Introduction

Multiagent cytotoxic chemotherapy is the cornerstone of treatment for pediatric and adult patients with acute lymphoblastic leukemia (ALL). For children with ALL, optimized drug combinations and schedules result in a cure rate of almost 90%.[1] Adults with ALL have also seen significant improvements in outcomes with combination chemotherapy, although their cure rate of 40% to 50% is substantially lower than their pediatric counterparts.[2,3] Incorporation of novel agents into these highly effective chemotherapy regimens is needed to continue to improve survival in these patients. Monoclonal antibodies targeting CD19, CD20, or CD22 on the cell surface of leukemic blasts have shown significant promise in the treatment of ALL, both in the front-line and relapsed settings.[4] This review will discuss the clinical activity of these agents in ALL.

Anti-CD20 Antibodies: Rituximab and Ofatumumab

CD20 expression ≥20% is found on approximately 30% to 40% of precursor B-cell ALL (B-ALL) leukemia blasts and in nearly 100% of mature B-ALL.[5,6] Historically, CD20 positivity was associated with worse survival in precursor B-ALL,[7,8] although this appears to be attenuated by the addition of anti-CD20 antibodies to chemotherapy regimens for younger patients with CD20-positive disease. Retrospective studies have reported that the addition of rituximab, a chimeric anti-CD20 antibody improves survival in patients with CD20-positive B-ALL who are younger than 60 years compared with historical cohorts.[6,9]

In one study, the rituximab-containing hyper-CVAD regimen improved the 3-year complete remission (CR) duration from 38% to 70% and 3-year overall survival (OS) from 47% to 75% compared with hyper-CVAD alone.[9] These findings have recently been confirmed in a large prospective randomized trial in younger patients with Philadelphia chromosome (Ph)-negative ALL.[10] The addition of rituximab to the pediatric-inspired Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) regimen resulted in an improved 2-year event-free survival (EFS) rate (65% vs 52%; $P = 0.04$) and OS rate (74% vs 63%, $P = 0.02$) without a significant increase in toxicity. However, the role of rituximab in patients with ALL who are 60 years and older is less clear, as there are limited data and there have been no randomized studies evaluating anti-CD20 therapy in this population.

In patients with B-ALL, rituximab also has been shown to improve outcomes when combined with cytotoxic chemotherapy in several studies.[11-14] The addition of rituximab to the hyper-CVAD regimen resulted in a 3-year survival rate of 89% compared with 53% with chemotherapy alone.[11] Furthermore, these findings were confirmed by the LMBA02 randomized study where the addition of 4 infusions of rituximab to chemotherapy improved EFS from 60% to 80% ($P = .046$) and OS from 68% to 84% ($P = .024$).[14]

Given the success of incorporating rituximab into standard chemotherapeutic regimens for ALL, there is interest in investigating the role of other anti-CD20 antibodies in the treatment of this disease. Ofatumumab is a second-generation anti-CD20 monoclonal antibody that binds to a different epitope than rituximab and has increased ability to induce complement-mediated lysis, which may allow it to overcome rituximab-resistant disease.[15] In the recent interim analysis of 41 patients with

CD20-positive ALL who received front-line hyper-CVAD chemotherapy plus ofatumumab, this combination was associated with a minimal residual disease (MRD) negativity rate of 93% and 3-year progression-free survival (PFS) and OS rates of 75% and 67%, respectively.[16] These results compare favorably with those historically seen with rituximab and suggest that more potent anti-CD20 antibodies may be able to further improve the outcomes of patients with CD20-positive ALL.

Anti-CD22 Antibody-Drug Conjugate: Inotuzumab

CD22 is expressed in 93% to 98% of precursor B-ALL and universally in Burkitt leukemia.[4] Inotuzumab ozogamicin is an immunoconjugate made up of an anti-CD22 antibody linked to calicheamicin, a potent cytotoxic compound.[17] Upon binding to CD22 on leukemic cells, the antibody-drug conjugate is internalized and the calicheamicin is released inside the cell, inducing double-stranded DNA breaks. In a phase II trial of inotuzumab monotherapy in patients with relapsed or refractory ALL, a weekly schedule of inotuzumab was associated with an overall response rate (ORR) of 59% and a median OS of 9.5 months.[18] In a separate multi-center phase II trial in a heavily pretreated cohort of patients with relapsed/refractory ALL, inotuzumab resulted in an remission rate of 66%, with 78% of patients who achieved CR also becoming MRD-negative.[19] The median OS was 7.4 months. A randomized trial comparing inotuzumab with physician's choice of chemotherapy in patients with relapsed ALL in salvage 1 and 2 has completed accrual. Primary endpoints included response rates and OS. The objective response rates were 81% and 33%, respectively. Among responders, the MRD-negativity rates were 78% and 28%, respectively. The median response duration was 4.6 versus 3.1 months (P = .02), respectively.[20] We are awaiting the survival data.

Inotuzumab was also evaluated in both the front-line and salvage settings in combination with a dose-reduced mini–hyper-CVD regimen.[21,22] In recently reported interim results of a phase II study using this combination in 52 patients with relapsed/refractory ALL, this regimen resulted in a 77% ORR, with 82% of responders achieving MRD negativity.[21] The 2-year PFS and OS rates were 60% and 32%, respectively; in patients treated in salvage 1, the 2-year OS rate was 50%. The survival of patients treated with mini–hyper-CVD plus inotuzumab were superior to a historical cohort of patients treated with inotuzumab monotherapy in the salvage setting (median OS: 11 months vs 6 months, respectively; P = .03).

Given the promising results of de-intensified chemotherapy plus inotuzumab in the relapsed setting, this combination was also evaluated in the front-line setting for elderly patients with ALL. Full-intensity chemotherapy is associated with unacceptably high rates of toxicity in elderly patients. In one large retrospective study of older patients receiving hyper-CVAD chemotherapy, the induction mortality rate was 10% and the death in CR rate was 34%.[23] Therefore, less toxic, effective regimens are especially needed in this patient population. In the most recent update of a study of mini–hyper-CVD plus inotuzumab in older patients with newly diagnosed ALL, 97% of patients achieved CR or CR with inadequate platelet recovery.[22] Only one patient (3%) died in the first month of therapy. The 2-year OS was 70%, which compared favorably to the historical 2-year OS rate of 38% in elderly patients treated with full-intensity hyper-CVAD, in part due to lower toxicity with the inotuzumab plus mini–hyper-CVD regimen.

The most serious toxicity associated with inotuzumab is the development of veno-occlusive disease (VOD), the incidence of which is increased in patients with prior allogeneic stem cell transplant (ASCT). In initial studies of inotuzumab monotherapy using a monthly dose of inotuzumab at 1.8 mg/m2, VOD developed in 5 out of 22 patients (23%) with prior history of ASCT, 4 of whom died from VOD.[24] However, in subsequent studies using lower doses of inotuzumab (0.5-0.8 mg/m2) weekly, lower post-ASCT rates of 7% have been observed.[18] Nevertheless, even at these modified dosing schedules, clinicians should be aware of the VOD risk with inotuzumab, especially in patients with prior ASCT.

Anti-CD19 Bi-Specific T-Cell Engager: Blinatumomab

Blinatumomab is a bi-specific T-cell engager antibody against CD3 and CD19 that is designed to direct cytotoxic T cells to CD19-expressing leukemic cells.[25] CD19 is nearly universally expressed on the cell surface of both precursor and mature B-ALL leukemic blasts and therefore is a rational target for antibody-directed therapy for these diseases.[4] In a phase II study of 189 heavily pre-treated patients with relapsed/refractory Ph-negative ALL, blinatumomab given as a continuous intravenous infusion for 4 consecutive weeks, on a 6-week cycle, was associated with a CR plus CR with partial hematologic recovery (CRh) rate of 43% and a median response duration and OS of 9 months and 6 months, respectively.[26]

These promising results have provided the rationale for a phase III randomized trial (TOWER study) of blinatumomab versus investigator's choice chemotherapy for patients with ALL in first or second relapse. OS was the primary endpoint, and duration of CR, CR, and MRD negativity were secondary endpoints. So far, interim analysis shows promising results, as the primary endpoint has been met and final results are pending. A phase II trial combining blinatumomab with hyper-CVAD chemotherapy in the front-line setting is also planned.

Interim results of blinatumomab in patients with Ph-positive ALL suggest that it also has significant clinical activity in this subgroup of patients.[27] Forty-five patients with Ph-positive ALL who have relapsed or were refractory to tyrosine kinase inhibitor–based therapy were treated with single-agent blinatumomab, which resulted in a CR/CRh rate of 36%. Similar response rates of 35% and 40% were observed in patients with prior ponatinib treatment and known T315I resistance mutation, respectively.

Of 16 total responders, the MRD-negativity rate was 88%, and 44% of patients were able to receive ASCT.

In patients who remain MRD-positive after initial therapy or who develop MRD relapse after initial deep remission, blinatumomab results in a molecular CR rate of approximately 80% and is associated with promising long-term outcomes.[28,29] In one study of 116 patients with Ph-negative ALL who remained MRD-positive after initial chemotherapy and subsequently received blinatumomab, median OS was significantly longer in patients who subsequently achieved MRD negativity compared with those who remained MRD-positive (40 months vs 12 months, respectively; $P = .001$).[29] Notably, ASCT did not confer a survival benefit for patients who achieved MRD negativity in first remission. These results provide evidence that a strategy of MRD-directed therapy that uses monoclonal antibodies is useful in improving outcomes in ALL.

Conclusion

Monoclonal antibodies against CD20, CD22, and CD19 have shown encouraging clinical activity in patients with ALL, both in the front-line and relapsed settings. The addition of rituximab to cytotoxic chemotherapy has been shown to improve OS in younger patients, and next-generation anti-CD20 antibodies also show promise in the management of ALL. Both inotuzumab ozogamicin and blinatumomab are effective monotherapies in the salvage setting. Inotuzumab has also shown significant clinical activity when combined with dose-reduced chemotherapy, and the use of blinatumomab in MRD-positive disease suggests that MRD-directed strategies are a viable therapeutic approach in ALL. Future studies will need to address how best to combine these monoclonal antibodies with chemotherapy and possibly with each other, with the goal of decreasing our reliance on intensive cytotoxic chemotherapy and ASCT, and ultimately increasing the cure rates of adult ALL to those achieved in the pediatric population.

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