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Inotuzumab Ozogamicin in Combination with Low-Intensity Chemotherapy (mini-hyper-CVD) As Frontline Therapy for Older Patients with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Single-Arm, Phase II Study

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Abstract

Background: Inotuzumab ozogamicin, a CD22 monoclonal antibody bound to a toxin, calicheamicin, has shown single-agent activity in relapsed/refractory acute lymphoblastic leukemia (ALL). We aimed to assess the efficacy and safety of inotuzumab added to low-intensity chemotherapy in elder patients with ALL.

Methods: Patients ≥ 60 years with newly diagnosed Philadelphia chromosome-negative B-cell ALL were eligible. The chemotherapy (mini-hyper-CVD) was lower intensity than conventional hyper-CVAD. Odd-numbered cycles included cyclophosphamide (150 mg/m^2 every 12 hours on Days 1 to 3) and dexamethasone (20 mg per day on Days 1 to 4 and 11 to 14); no anthracycline was administered. Vincristine (2 mg flat dose) was given on day 1 and 8. Even-numbered cycles

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Authorship

H.K. and E.J. designed the study, treated patients and wrote the manuscript; N.J.S., X. H., K.S., J.J., and R.G. collected and analyzed the data; F.R., N.J., N.D.,, N.P., J.K., J.J., Y.A., M.K., G.G.M., T.K., M.Y., G.B.,, J.B., S.K., W.W., C.D., A.F., and S.O. treated patients. All authors reviewed and approved the manuscript.

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included methotrexate (250 mg/m^2 on Day 1) and cytarabine given 0.5 g/m^2 given every 12 hours on Days 2 and 3. Inotuzumab was given on Day 3 of the first 4 courses at the dose of 1.8–1.3 mg/m^2 for Cycle 1, followed by 1.3–1.0 mg/m^2 for subsequent cycles. Maintenance was given for 3 years. The primary endpoint of this study was event-free survival at 2 years. The primary and safety analyses were by intention-to-treat. The study is ongoing, but the treatment plan has been significantly modified by protocol amendment. The trial is registered at ClinicalTrials.gov (NCT01371630).

Findings: Between November 11, 2011 and April 22, 2017, 52 patients were enrolled. The median age was 68 years (range, 60 to 81). With a median follow-up of 29 months (IQR 13–48 months), the 2-year event-free survival rate was 59% (95% CI, 43–72%). The most grade 3–4 adverse events included prolonged thrombocytopenia (42 [81%]), infections during induction (27 [52%]) and consolidation (36 [69%]), hyperglycemia (28 [54%], hypokalemia (16 [31%]), increased transaminases (10, [19%]), hyperbilirubinemia (9, [17%]), and hemorrhage (7, [13%]). Veno-occlusive disease occurred in 4 patients (8%). Six patients (12%) died from adverse events deemed treatment-related (sepsis, 5 [10%] and veno-occlusive disease, 1 [2%]).

Interpretation: Inotuzumab plus mini-hyper-CVD is safe and effective in elderly patients with newly diagnosed ALL and represents a new therapy for this population. A phase 3, randomized trial comparing this regimen to standard of care is warranted.

Keywords

inotuzumab ozogamicin; elderly; ALL

Introduction

Remarkable advances have been made in the recent decade toward gaining a better understanding of the biological mechanisms of acute lymphoblastic leukemia (ALL) and in developing novel therapies. This culminated in a significant improvement of outcome in specific subsets of ALL.[1–10] Similar strategies have not yielded comparable results in elderly patients with ALL, who have estimated cure rates of only 10–20%.[1,11–15]

The incidence of ALL increases after the age of 50 years. In elderly patients with ALL (defined as older than 55–60 years), intensive chemotherapy results in lower response rates than those observed in younger patients with ALL, and a high rate of toxicities. One-third of patients achieving CR may die of myelosuppression-associated complications during consolidation-maintenance.[12] The GMALL reported a complete response (CR) rate of 76%, an early death rate of 14%, a death in CR rate of 6%, and a 5-year survival rate of 23% in 268 elderly patients treated with less intensive induction and consolidation regimen.[11,13] Li and colleagues recently reported a median survival of 10 months among 727 elderly patients (>65 years) diagnosed between 2007 and 2012 and treated under Medicare.[14]

Inotuzumab ozogamicin is a humanized monoclonal antibody that binds CD22 with subnanomolar affinity. Upon binding, it is rapidly internalized, delivering the conjugated calicheamicin inside the cell after the linker is hydrolyzed.[16] Calicheamicin is a potent cytotoxic antibiotic that binds in the minor groove of DNA and causes double strand DNA

breaks leading to an apoptotic response in cells. Inotuzumab ozogamicin was previously evaluated in 89 patients with heavily pretreated refractory/relapsed ALL and was found to be safe and highly active.[17,18] This was confirmed in a randomized phase III trial where inotuzumab ozogamicin resulted in an overall response rate of 80% and a median survival of 7.7 months, which was significantly better than standard cytotoxic chemotherapy.[19]

The goal of treating elderly patients with ALL is to maintain or improve efficacy and reduce toxicity. The addition of targeted therapy to low-intensity chemotherapy in older patients with ALL might improve their outcome. Herein we report the results of a phase II study that evaluated the efficacy and safety of the combination of inotuzumab ozogamicin with low-intensity chemotherapy (mini-hyper-CVD).

Methods

Study design and participants

Patients 60 years and older with newly diagnosed Philadelphia chromosome-negative ALL were eligible. Patients who received minimal prior therapy (defined as less than 1 week of steroids, vincristine, and/or 1 dose of anthracycline or alkylating agents) were also eligible. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, normal cardiac function (defined by ejection fraction above 50%), and adequate organ function (serum bilirubin ≤ 1.95 mg/dL and serum creatinine ≤ 2.0 mg/dL). Patients were excluded if they had an active infection not controlled by antibiotics, clinical evidence of grade 3 to 4 heart failure as defined by the New York Heart Association criteria, or second malignancy. Patients with a Philadelphia chromosome (i.e. t(9;22)(q34.1;q11.2) or variant) by conventional karyotype or evidence of a BCR-ABL fusion by either fluorescent *in situ* hybridization or polymerase chain reaction were also excluded. All patients signed a consent form in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center. The approved protocol is provided in the appendix. This trial was registered on clinicaltrials.gov with the identifier NCT01371630.

Procedures

The chemotherapy was lower intensity than conventional hyper-CVAD and referred to as mini-hyper-CVD. Odd-numbered cycles included cyclophosphamide intravenously (IV, 150 mg/m^2 every 12 hours on Days 1 to 3) and dexamethasone orally (PO) or IV (20 mg per day on Days 1 to 4 and 11 to 14); no anthracycline was administered. Vincristine 2 mg flat dose IV was given on day 1 and 8. Even-numbered cycles included methotrexate IV (250 mg/m^2 on Day 1) and cytarabine IV given 0.5 g/m^2 given every 12 hours on Days 2 and 3. Cycles were administered every 4 weeks, as permitted by peripheral count recovery, for a total of 8 cycles.

Inotuzumab was administered on Day 3 of each of the first 4 cycles. We initially performed a short “run-in” phase with the aim to determine the dose-limiting toxicities and maximally tolerated dose of inotuzumab in combination with low-intensity chemotherapy. The first 6 patients received 1.3 mg/m^2 IV for Cycle 1 followed by 0.8 mg/m^2 IV for subsequent

cycles. Patient 7 and onwards received the recommended phase II dose of 1.8 mg/m^2 IV for Cycle 1 followed by 1.3 mg/m^2 IV for subsequent cycles. After the observation of veno-occlusive disease (VOD), the protocol was amended in September 2015 to use lower doses of inotuzumab. After this amendment (Patient 35 and onwards), inotuzumab was given at 1.3 mg/m^2 IV for Cycle 1 followed by 1 mg/m^2 IV for subsequent cycles and ursodiol prophylaxis was used in all patients.

Rituximab was administered IV during the first 4 cycles in patients with CD20 expression ≥ 20%.[5,9] Central nervous system (CNS) prophylaxis consisted of intrathecal therapy with methotrexate and cytarabine given alternately on Days 2 and 7 of cycles 1–4 for a total of 8 doses. For patients presenting with active CNS disease, confirmed by cytologic examination of the cerebrospinal fluid (CSF), the intrathecal regimen was repeated twice weekly until the CSF became clear of leukemic cells and the CSF cell count normalized. Patients then received intrathecal therapy once a week for 4 weeks or until initiation of the next cycle of chemotherapy, when the regimen was resumed.

Maintenance therapy was given with monthly vincristine at 2 mg IV for 1 year, prednisone 50 mg PO daily for 5 days every month for 1 year, 6-mercaptopurine 50 mg PO twice daily for 3 years, and methotrexate 10 mg/m^2 PO orally weekly for 3 years (dose-reduced POMP regimen[20]). Early initiation of maintenance due to treatment-related toxicity prior to completion of 8 cycles was allowed. Dose reductions of the cytotoxic agents according to the type and degree of side effects or toxicity were permitted and followed previously published guidelines.[5,9,21] The decision to proceed with allogeneic stem cell transplantation (ASCT) in first remission was based at the discretion of the treating physician after discussion with the patient.

Supportive care measures were implemented according to standard guidelines. Tumor lysis prophylaxis with allopurinol, or alternatives such as rasburicase, and appropriate intravenous hydration were administered in the first course to all patients. Prophylactic antimicrobial therapy was administered to all patients during periods of neutropenia beginning in induction. Pegfilgrastim 6 mg subcutaneously was administered on Day 4 (+ 2 days) of each of the induction/consolidation cycles. Although the protocol was written that patients could receive pegfilgrastim at the discretion of the treating physician, in practice all patients received pegfilgrastim with each cycle. Ursodiol 300 mg orally three times daily as VOD prophylaxis was systematically administered since the protocol was amended in September 2015.

Response to therapy was monitored by analysis of blood and bone marrow aspirates. Response assessment was performed at the end of cycle 1 and then every 2–4 cycles of consolidation and every 3 months during maintenance to confirm ongoing response. Adverse events and laboratory values, graded according to the Common Terminology Criteria for Adverse Events version 4.0, were evaluated at least once every cycle during induction and consolidation and then at least every 3 months during the maintenance phase.

Outcomes

The primary endpoint was event-free survival (EFS) at 2 years. The secondary endpoint was safety of the regimen, and exploratory endpoints included response rates, minimal residual disease (MRD) negativity rates, and overall survival. CR was defined as the presence of ≤5% blasts in the bone marrow, with more than 1×10^9/L neutrophils, more than 100×10^9/L platelets in the peripheral blood, and no extramedullary disease. CR without platelet recovery (CRp) was defined as CR except for platelets less than 100×10^9/L. CR without complete hematologic recovery (CRi) was defined as CR but with an absolute neutrophil count of less than 1×10^9/L neutrophils and platelets less than 100×10^9/L.

MRD assessment by 6-color flow cytometry was performed on whole bone marrow specimens as previously described.[22,23] A distinct cluster of at least 20 cells that showed altered antigen expression was regarded as an aberrant population, which yielded a sensitivity of 1 in 10,000 cells (for adequate specimens in which 2×10^5 cells could be collected). EFS was calculated from the time of treatment initiation until date of no response (after 2 cycles), relapse, or death. Overall survival (OS) was calculated from the time of treatment initiation until death.

Adverse events were defined as any event that occurred between the first dose and 2 months after the last dose, all treatment-related events that occurred after the last dose, and all cases of VOD (of any cause) that occurred within 2 years after inotuzumab therapy. VOD was assessed and diagnosed by the investigators and evaluated according to previously defined clinical criteria.

Statistical analysis

This is a phase II study in newly diagnosed elderly patients with Philadelphia chromosome-negative ALL; 52 consecutive patients were treated. The primary efficacy and safety analyses were performed on the intention-to-treat population. Response rate was only assessed in patients who had active disease at the time of enrollment. The initial study design was based on our previous experience in elderly patients with ALL, for which the reported 2-year EFS rate was 30%.[12] With more than 6 years of follow-up, the current study with 52 patients enrolled has 90% power to prove if the combination of mini-hyper-CVD and inotuzumab can achieve at least 50% relative improvement in the 2-year EFS rate (from 30% to 45%). The trial was continuously monitored, with an early stopping rule in place if the likelihood of this improvement was less than 3%. No stopping rules were met, but the sample size in this report was less than the originally planned 60 due to significant change of treatment plan to incorporate blinatumomab into the treatment regimen. This report therefore describes the safety and efficacy of hyper-CVD plus inotuzumab in the 52 patients enrolled prior to this amendment.

All patients who received at least one dose of any drug of the study regimen were included in the primary efficacy analysis (i.e. EFS), the secondary safety analyses, and the exploratory overall survival analysis. For the exploratory analysis of response rate, only patients who had received no prior treatment were assessed. For the exploratory analysis of MRD negativity rate, only patients in morphological remission who had MRD testing

performed were assessed. Survival curves were plotted by the Kaplan-Meier method on GraphPad Prism 6. The analyses of the primary, secondary and exploratory endpoints are all descriptive. The trial is registered at ClinicalTrials.gov (NCT01371630).

Role of the funding source

This trial was funded by an MD Anderson Cancer Center Support Grant. Inotuzumab ozogamicin was provided free of charge by Pfizer, but Pfizer had no role in the study design, collection, analysis or interpretation of data, or writing of the manuscript. All authors had full access to all of the data. The corresponding author had final responsibility for the decision to submit for publication.

Results

From November 12, 2011 to April 22, 2017, 52 patients were consecutively treated (Figure 1). The median follow-up of patients for all analyses was 29 months (IQR 13–48 months). Baseline characteristics are summarized in Table 1. The median expression of CD22 was 97% (range, 27 to 100%). Thirty-one patients (60%) were CD20-positive and received rituximab during the first 4 cycles. Of the 52 patients enrolled, 48 were untreated and 4 patients were enrolled in CR after 1 cycle of prior therapy. Among the patients without prior treatment, median bone marrow blasts were 80% (range, 25% to 96%).

Of the 48 untreated patients, all were evaluable for morphologic response. Responses were observed in all but one patient, for an overall response rate of 98%. Forty-one patients (85%) achieved CR, 5 patients (11%) had CRp, and 1 patient (2%) had CRi. CR was achieved after 1 cycle in 38 patients; the 3 other patients improved their response from CRp to CR after 2 cycles (n=2) or after 3 cycles (n=1). The median time to best response was 23 days (range, 13 to 90 days).

All 26 patients with abnormal karyotype at enrollment achieved a complete cytogenetic response for an overall cytogenetic response rate of 100%. Among patients who responded, 46 patients were assessed for MRD status at the time of morphologic response and 47 had an MRD assessment within 3 cycles of therapy. The MRD negativity rates at the time of morphologic response and at any time within 3 cycles were 78% (36 of 46 patients) and 96% (45 of 47 patients), respectively.

Among the 52 enrolled patients, 21 patients did not respond to therapy, relapsed or died. The estimated 2- and 3-year EFS rates were 59% (95% CI 43%−72%) and 49% (95% CI 32%−64%) (Figure 2). The estimated 2- and 3-year OS rates were 66% (95% CI 50%−78%) and 56% (95% CI 39%−70%). The median EFS was 35 months. The median OS has not been reached. Thirty-four patients (65%) are alive, 30 of whom (58%) are in CR and MRD-negative status: 1 after ASCT, 6 receiving consolidation, 11 receiving POMP maintenance therapy, and 12 who have completed all treatment. Overall, 18 patients have died. One patient had primary refractory ALL and died of disease progression. Six patients relapsed, four of whom died of progressive disease. Twelve patients died in CR: 5 died from sepsis (two in Cycle 2, one in Cycle 4, one after 28 cycles of maintenance therapy, and one after being taken off study due to VOD and then receiving one cycle of

hyper-CVAD plus rituximab); one from VOD; one from gunshot wound; one from dementia and deconditioning after Cycle 2; one from end-stage renal disease; and three from unknown causes. Three patients (two of them with *TP53* mutation) underwent ASCT: one of them died of extensive graft-versus-host disease, sepsis, and multiple organ failure; two are alive (one in continued remission and one with active disease).

Safety

All 52 patients were evaluable for safety analyses. The treatment was well-tolerated with most side effects being Grade 1 to 2. Early mortality defined as death within 4 weeks was not observed. Overall, patients received a median of 4 cycles of induction-consolidation therapy (range, 1 to 8 cycles). Of 202 induction/consolidation cycles received by all the patients, 105 (52%) cycles were delivered within 4 weeks, 82 (41%) were delivered within 4 to 8 weeks, and 15 (7%) were delivered over 8 weeks interval. Twenty-two patients (42%) switched to maintenance before completing their full induction-consolidation therapy [median number of cycles was 5 (range, 2 to 7 cycles)] for myelosuppression (n=17), deconditioning (n=1), and infections (n=4). Thirty-four patients (65%) received all four planned doses of inotuzumab. Ten patients (19%) had inotuzumab dose reduction after a median of 3 cycles (range, 1 to 3 cycles).

Median time to platelet and neutrophil recovery for cycle 1 was 23 and 16 days, respectively, and for subsequent cycles was 22 and 17 days, respectively. Overall, 42 patients (81%) had prolonged thrombocytopenia beyond 6 weeks either during induction in 11/48 patients (23%) or subsequent courses in 42/50 (84%). Six patients (12%) had prolonged neutropenia beyond 6 weeks either during induction in 2/48 patients (4%) or subsequent courses in 4/50 (8%). Infections occurred in 27 patients (52%) during induction and in 36 patients during (69%) during consolidation; 28 patients (54%) had grade 3–4 hyperglycemia; 16 (31%) had grade 3–4 hypokalemia; 10 (19%) had grade 3–4 increased transaminases; 9 (17%) had grade 3–4 hyperbilirubinemia; and 7 (13%) had grade 3 hemorrhage (Table 2). Six patients (12%) died from adverse events deemed treatment-related (sepsis, 5 [10%] and veno-occlusive disease, 1 [2%]).

Fifty-two patients (100%) had hepatic adverse events of any grade, including grade ≥3 in 17 patients (33%). VOD occurred in 4 patients (8%) after a median of 3 cycles (range, 1 to 4); in one of them VOD occurred after ASCT (appendix p 1). This last patient developed VOD 43 days post-ASCT after conditioning with fludarabine and busulfan; he subsequently died from multiple organ failure. Two patients developed VOD after 2 cycles and were taken off study: one of them developed anasarca and multiple organ failure and expired thereafter; the second patient had mild VOD with multiple comorbidities and ultimately died from deconditioning. One patient developed VOD after 3 cycles, subsequently recovered, and completed chemotherapy with mini-hyper-CVD in combination with ofatumumab. After the emergence of VOD, the study was amended on September 2015 to reduce the dose of inotuzumab and add ursodiol prophylaxis. No further VOD events have been observed in the 18 patients treated since the study amendment.

Discussion

In this phase II study, the immunochemotherapy combination of inotuzumab with mini-hyper-CVD was safe and effective in elderly patients with newly diagnosed ALL. The overall response rate was 98%. The 3-year EFS and OS rates were 49% and 56%, respectively. No patients died within 4 weeks of treatment, and 4 patients (8%) experienced VOD, one of them after ASCT.

Therapies targeting either specific molecular targets (e.g. BCR-ABL1 tyrosine kinase inhibitors) or specific leukemic cell surface antigens (e.g. CD20, CD22, and CD19 monoclonal antibodies) are major breakthroughs in the treatment of ALL.[24] Current treatment approaches yield long-term survival in approximately 50% of patients with precursor B-cell ALL[5,6], 50–60% with Philadelphia chromosome-positive ALL,[7–9] and nearly 80% with mature B-cell ALL.[2–4] Despite these advances, the 5-year survival remains dismal (~20%) among adults age ≥60 years treated at academic centers and in multi-institutional clinical trials using established first-line regimens.[11–15]

Park and colleagues used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to assess survival among 1675 older US adults (age ≥60 years) with ALL between 1980 and 2011. The median survival was 4 months, and the 3-year survival rate was 12.8%.[15] These data include patients who did not receive any chemotherapeutic agent. Therefore while they reflect real-life practice, the outcomes are significantly influenced by patients who did not receive any anti-leukemic treatment, in contrast with the results of selected patients enrolled in this and other clinical trials. In an analysis of older patients with ALL treated under Medicare, the majority of elderly patients did not receive cytotoxic chemotherapy, likely due to physician opinion that these patients were unsuitable for standard therapies.[14] In this study, 32% of patients received treatment with only chemotherapy, 7% with chemotherapy plus a tyrosine kinase inhibitor and 2% with a tyrosine kinase inhibitor alone. Among the 235 patients who received chemotherapy, the median survival was 10 months. The results obtained with hyper-CVD plus inotuzumab in an elderly population also compare favorably with our previous experience using the more intensive hyper-CVAD regimen in which a 5-year overall survival rate of 20% was observed.[12]

In a GMALL multicenter trial of 268 older patients with Ph-negative ALL, a moderate intensity chemotherapy regimen was associated with a CR rate of 76%, an early death rate of 14%, a death in CR rate of 6% and 5-year survival of 23%.[13] The median age of these patients was 67 years and notably this study included patients with T-ALL who were excluded from the present study. The results of hyper-CVD plus inotuzumab appear superior to those obtained in this GMALL study. However, it is important to note that in a subset of patients in the GMALL study who received a modified regimen with optimized CNS prophylaxis and consolidation (n=43), CR and 5-year survival rates were improved (86% and 52%, respectively), which more closely approximate to the outcomes observed in the present study.

Mini-hyper-CVD plus inotuzumab was safe and well-tolerated. The combination of low-intensity chemotherapy with inotuzumab with 52% of cycles being delivered within 4 weeks as designed. No early death (within 4 weeks) was reported, contrasting with an induction mortality rate of 10% with more intensive treatment.[12] Fewer deaths in CR were observed as well compared to our historical published data with hyper-CVAD in this older population (23% versus 34%).[12] Although improved from historical data, this rate of death CR is still relatively high, driven in part by the advanced age of the study population and deaths from non-treatment-related causes. However, death from sepsis was still observed in 5 patients. Modifications of the regimen, including further dose reductions of chemotherapy possibly with the addition of less myelosuppressive novel agents (e.g. blinatumomab) may help to reduce the death in CR rate. Nevertheless, mini-hyper-CVD plus inotuzumab appears to be better tolerated than intensive chemotherapy, which likely contributed to the improvement in survival compared to the published data with hyper-CVAD (i.e. 5-year overall survival rate of 20%).[12] Efficacy did not appear to be compromised by using lower-intensity chemotherapy in this population, in combination with a novel monoclonal antibody. Given the excellent 2-year OS rate of 66% observed in the present study, a randomized trial in elderly adults with ALL comparing this regimen with standard intensive therapy and using OS as the primary endpoint is warranted.

Liver toxicities and VOD are known to occur with inotuzumab treatment. In this study, the grade 3–4 rates were 33% and 8%, respectively. The rate of VOD was lower than what was reported in the ALL relapse setting (approximately 15%).[17–19,25] In patients with relapsed disease, VOD has been more commonly encountered in older patients heavily treated and in those who received ASCT, especially with dual-alkylator conditioning. The association with ASCT is less relevant in the elderly frontline population, as only 3 patients received an ASCT in the present study. Furthermore, all 4 cases of VOD were encountered in patients who received higher dose of inotuzumab (1.8 mg/m^2 during cycle 1 followed by 1.3 mg/m^2 during cycles 2–4) (4/28; 14%), while none of the patients who received lower doses (1.3 mg/m^2 during cycle 1 followed by 1.0 mg/m^2 during cycles 2–4) and were given ursodiol prophylaxis have developed VOD.

This study is limited by its single-arm design, which prevents definitive conclusions about its relative safety and efficacy compared to standard of care. Furthermore, the dosing structure of the inotuzumab may not be optimal, and several modifications to the present regimen may further improve outcomes. First, the rate of VOD may be lowered by using a weekly schedule of inotuzumab, which has been associated with less liver toxicity.[17,26] Second, the use of lower dose of inotuzumab may also decrease the rate of prolonged thrombocytopenia, which is considered a dose-limiting toxicity in early inotuzumab trials.[18] Third, the sequential addition of blinatumomab, a bi-specific T-cell engaging CD3-CD19 antibody construct that has shown significant activity in patients with relapsed/refractory B-cell ALL[24,27] and which seems to be acceptably tolerated in older adults[28], may further improve the efficacy and safety of this regimen. The sequential addition of blinatumomab may allow the use of less chemotherapy, lower doses of inotuzumab and a longer duration between inotuzumab and ASCT, which could theoretically decrease VOD rates. It is important to note that ASCT with reduced intensity conditioning continues to remain a reasonable consolidative option for elderly fit, patients. However, as only 3 patients in the

present study underwent ASCT in first remission (a decision generally driven by lack of patient fitness for the procedure or absence of a high-risk disease-related factor), the survival data reported here are largely driven by a population of patients who did not undergo ASCT.

In summary, we have demonstrated the safety and efficacy of combining low-intensity chemotherapy with inotuzumab ozogamicin in older patients with newly diagnosed Philadelphia chromosome-negative ALL. The regimen is highly effective with an overall response rate of 98% and a 2-year EFS and OS rates of 59% and 66%, respectively. A prospective confirmation of these findings in a randomized phase III trial compared to standard intensive induction regimens for this older population is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Pfizer provided free drug from the Pfizer Investigator Sponsored Trial program. Dr. Elias Jabbour had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Research in Context

Evidence before this study

A systemic review was not performed before starting this trial. However, we searched Pubmed for studies on the outcomes of older adults with acute lymphoblastic leukemia (ALL) and clinical trials in this population. Multiple studies suggested that the outcome of elderly patients with newly diagnosed ALL is poor with a median survival of 5 to 10 months. This is driven in part by high rates of induction mortality and death in remission when older patients are treated with intensive chemotherapy. The anti-CD22 antibody-toxin conjugate inotuzumab ozogamicin has been shown to be effective in relapsed/refractory ALL with minimal myelosuppression. No published study had evaluated this agent in the frontline setting, either alone or in combination with chemotherapy.

Added value of this study

In this phase 2 study, we show that the combination of inotuzumab with low-intensity chemotherapy was highly effective in elderly adults with Philadelphia chromosome-negative ALL, with high rates of minimal residual disease negativity and promising survival. The safety profile was tolerable, with no patients experiencing death during induction therapy.

Implications of all the available evidence

The combination of inotuzumab with low-intensity chemotherapy is effective and shows encouraging results in elderly patients with newly diagnosed ALL. Further confirmation of these findings is warranted in elderly patients with ALL.

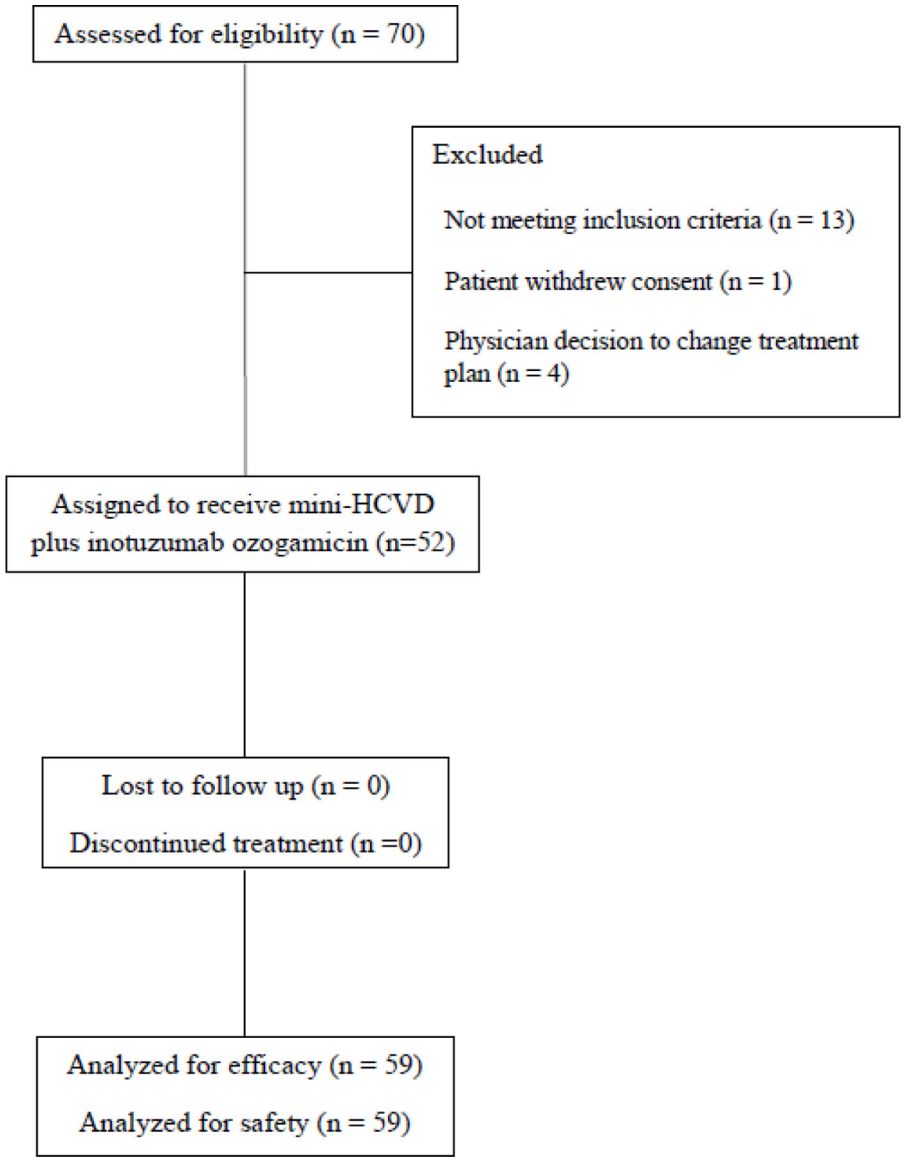

Figure 1:
Trial profile

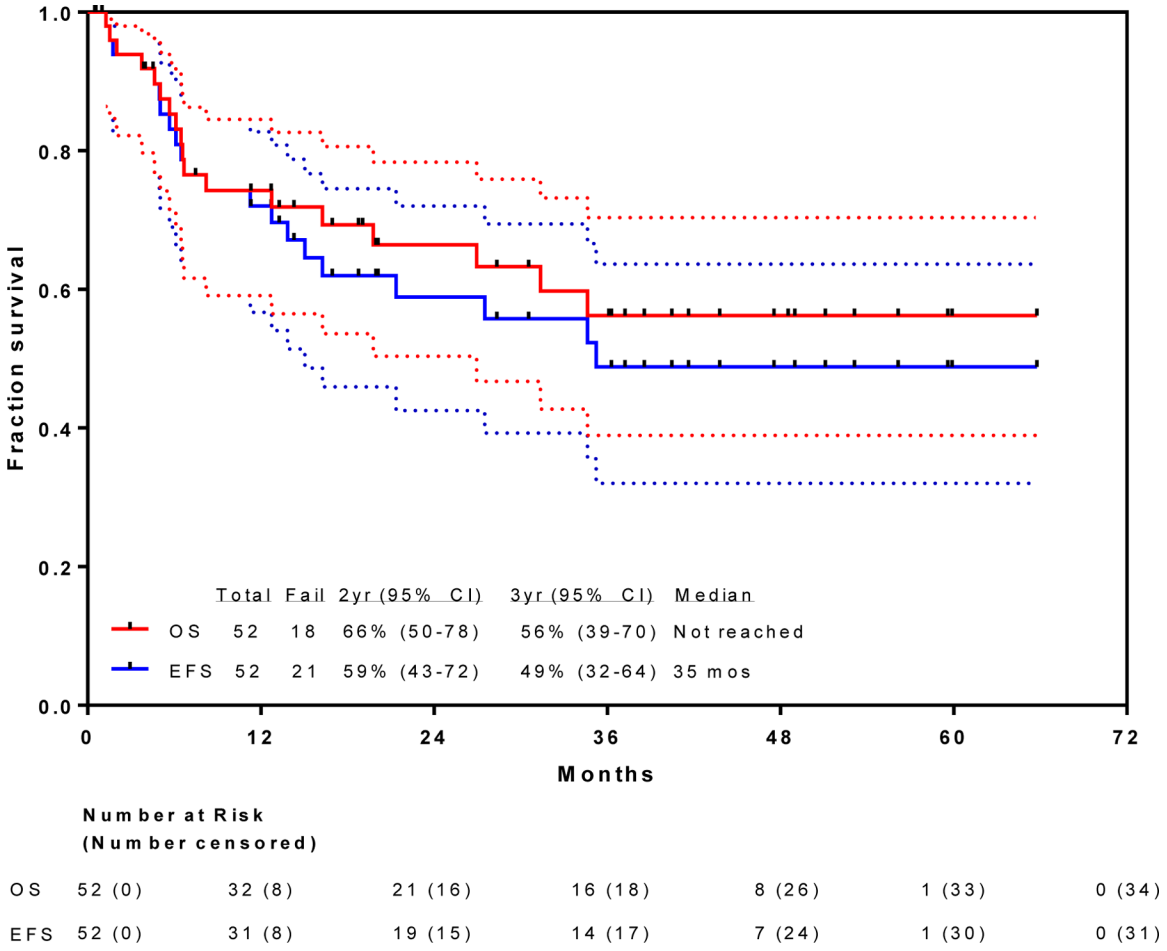

Figure 2:
Event-free and overall survival for the entire cohort

Table 1.

Patient characteristics (N=52)

Characteristic	Category	N (%)/ Median [IQR]
Age (years)		68 [63.5–71.5]
Gender	Male	32 (62)
ECOG performance status	≥2	7 (13)
WBC (x 10^9/L)	Median	3.0 [1.5–5.6]
	≥50	4 (8)
PB blasts (%)		11 [0–45]
BM blasts ≥50%		43 (83)
Karyotype	Diploid	16 (31)
	Ho-Tr	11 (21)
	t(4;11)	0 (0)
	HeH	5 (10)
	Tt	3 (6)
	Complex	1 (2)
	Miscellaneous	6 (12)
	ND/IM	10 (19)
CD22 expression (%)	Median	97 [88.4–99.5]
CD20 expression	≥20%	31 (60)
CNS disease at diagnosis		3 (6)

IQR=interquartile range; ECOG= Eastern Cooperative Oncology Group; BM=bone marrow; WBC=White blood cell; PB=peripheral blast; Ho-Tr=low hypodiploidy/triploidy; HeH=high hyperdiploidy; Tt=tetraploidy; ND=not done; IM=insufficient metaphases; CNS=central nervous system

Table 2.

Adverse events

	N (%)			
Parameter	**Grades 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Infections	0 (0)	41 (79)	2 (4)	3 (6)
Increased bilirubin	38 (73)	9 (17)	0 (0)	0 (0)
Increased transaminases	37 (71)	9 (17)	1 (2)	0 (0)
Nausea	32 (62)	1 (2)	0 (0)	0 (0)
Fatigue	30 (58)	2 (4)	0 (0)	0 (0)
Constipation	29 (56)	4 (8)	0 (0)	0 (0)
Hypomagnesemia	23 (44)	1 (2)	0 (0)	0 (0)
Hyperglycemia	22 (44)	27 (52)	1 (2)	0 (0)
Neuropathy	22 (42)	2 (4)	0 (0)	0 (0)
Pain	21 (40)	4 (8)	0 (0)	0 (0)
Headache	19 (37)	2 (4)	0 (0)	0 (0)
Hemorrhage	18 (33)	6 (13)	1 (2)	0 (0)
Diarrhea	18 (35)	4 (8)	0 (0)	0 (0)
Edema	17 (33)	3 (6)	0 (0)	0 (0)
Mucositis	17 (33)	0 (0)	0 (0)	0 (0)
Hypokalemia	13 (25)	14 (27)	2 (4)	0 (0)
Vomiting	12 (23)	1 (2)	0 (0)	0 (0)
Cardiac arrhythmia	10 (19)	2 (4)	0 (0)	0 (0)
Insomnia	9 (17)	1 (2)	0 (0)	0 (0)
Mood alteration	8 (15)	0 (0)	0 (0)	0 (0)
Increased alkaline phosphatase	8 (15)	0 (0)	0 (0)	0 (0)
Rash	8 (15)	0 (0)	0 (0)	0 (0)
Acute kidney injury	7 (13)	1 (2)	0 (0)	0 (0)
Anorexia	7 (13)	0 (0)	0 (0)	0 (0)
Weakness	7 (13)	0 (0)	0 (0)	0 (0)
Allergic reaction	7 (13)	0 (0)	0 (0)	0 (0)
Dyspnea	6 (12)	1 (2)	0 (0)	0 (0)
Hypocalcemia	5 (10)	1 (2)	0 (0)	0 (0)
Dysgeusia	5 (10)	0 (0)	0 (0)	0 (0)
Hyponatremia	4 (8)	3 (6)	1 (2)	0 (0)
Hypophosphatemia	4 (8)	2 (4)	0 (0)	0 (0)
Increased amylases	3 (6)	1 (2)	0 (0)	0 (0)
Deep vein thrombosis	3 (6)	1 (2)	0 (0)	0 (0)
Altered mental status	2 (4)	3 (6)	0 (0)	0 (0)
Hypertension	2 (4)	1 (2)	0 (0)	0 (0)
Hypotension	2 (4)	1 (2)	0 (0)	0 (0)

	N (%)			
Parameter	**Grades 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Increased lipase	0 (0)	2 (4)	2 (4)	0 (0)
Ascites	0 (0)	2 (4)	0 (0)	0 (0)
Myocardial infarction	0 (0)	2 (4)	0 (0)	0 (0)
Hypofibrinogenemia	0 (0)	1 (2)	0 (0)	0 (0)