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SWOG S0910: A Phase 2 Trial of Clofarabine/Cytarabine/ Epratuzumab for Relapsed/Refractory Acute Lymphocytic Leukaemia

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Summary

Precursor B-acute lymphoblastic leukaemias (pre-B ALLs) comprise the majority of ALLs and virtually all blasts express CD22 in the cytoplasm and on the cell surface. In the present study (Southwestern Oncology Group S0910), we evaluated the addition of epratuzumab, a humanized monoclonal antibody against CD22, to the combination of clofarabine and cytarabine in adults with relapsed/refractory pre-B ALL. The response rate [complete remission and complete remission with incomplete count recovery] was 52%, significantly higher than our previous trial with clofarabine/cytarabine alone, where the response rate was 17%. This result is encouraging and suggests a potential benefit to adding epratuzumab to chemotherapy for ALL; however, a randomized trial will be needed to answer this question.

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Author Contributions:

AA: performed the research, designed the research study, contributed patients, analysed the data, wrote the paper.
SM, MO: designed the research study, analysed the data, helped revise the final paper.
SC, MO, SE, MB, MM: performed the research, contributed patients, helped revise the final paper.
BW: performed the laboratory analyses (minimal residual disease analysis) and helped revise the final paper.
JR: helped review the laboratory analyses and helped revise the final paper.
FA: helped design the research study, analyse the data, and revise the final paper.

Conflict of Interest:

AS Advani has received some funding and honoraria from Genzyme

Keywords

acute lymphocytic leukaemia; relapse; Epratuzumab; CD22; treatment

Introduction

The prognosis of childhood acute lymphoblastic leukaemia (ALL) has improved significantly over the last decade, with 80–90% of children being cured. Unfortunately, the prognosis for adults with ALL remains poor. More than half of adults will relapse after their initial treatment, and only 10% of these patients are alive at five years (Fielding *et al.,* 2007). At the time of relapse, the only curative treatment is allogeneic haematopoietic cell transplant (HCT). However, most patients will require re-induction therapy prior to proceeding to HCT. Currently, no standard regimen for re-induction exists. Most salvage regimens incorporate drugs that are used in the initial treatment and complete remission (CR) rates have generally been disappointing: 37% with single agent high dose cytarabine, 10–15% with etoposide and 30–60% with various combination regimens (with a wide variation in response rate dependent on patient selection and degree of pre-treatment) (Hoelzer 1991; Hoelzer & Gokbuget, 2002). Therefore, novel treatments are needed.

Epratuzumab is a humanized monoclonal antibody against CD22. Precursor B-cell ALLs comprise the majority of adult ALLs. Investigators have demonstrated that CD22 is expressed not only in the cytoplasm but also on the cell surface of virtually all (15/16) precursor B-cell ALLs examined (Boue & LeBien, 1988). Antibodies to CD22 have been used to purge the bone marrow of patients with ALL prior to transplant (Herrera *et al.,* 2000). Immunotoxins against CD22 are effective in killing precursor B-cell ALL cells *in vitro* and *in vivo* (Herrera *et al.,* 2000); and encouraging results have been noted in a clinical trial of inotuzumab, an anti-CD22 antibody attached to calicheamicin, in patients with heavily pre-treated ALL (Kantarjian *et al.,* 2012). A clinical trial with epratuzumab has been conducted in children with relapsed CD22-positive ALL (Raetz *et al.,* 2008). Patients received epratuzumab 360 mg/m^2/dose twice weekly for 4 doses followed by four weekly doses of epratuzumab in combination with standard re-induction chemotherapy (vincristine, prednisone, PEG-asparaginase, doxorubicin) (Raetz *et al.,* 2008). Surface CD22 was not detected by flow cytometry of peripheral blood leukaemic blasts within 24 h of drug administration in all but one patient, indicating that CD22 sites were saturated after infusion. The treatment was well tolerated with the most frequent toxicities being Grade 1–2 infusion reactions (Raetz *et al.,* 2008). Nine of 15 patients achieved a CR after chemo-immunotherapy, 7 of whom were minimal residual disease (MRD) negative. The favourable rate of MRD negativity after administration of chemotherapy with epratuzumab suggests that the antibody may enhance the response to cytotoxic chemotherapy (Raetz *et al.,* 2008).

In the Southwestern Oncology Group (SWOG) S0910 trial, we evaluated the addition of epratuzumab to re-induction therapy in adults with relapsed/ refractory ALL, using the backbone chemotherapy regimen from our previous trial, S0530 (clofarabine/cytarabine), which demonstrated a CR/CR with incomplete count recovery (CRi) rate of 17% (Advani *et al.,* 2010). The goals of the current study were to evaluate the CR/ CRi rate of the previous

combination, but with the addition of Epratuzumab, to assess the toxicity of this new combination, and to assess MRD in patients achieving a CR/CRi.

Materials and Methods

Patients were treated at SWOG institutions between August 2010 and July 2012. Clofarabine was supplied by Genzyme (Cambridge, MA, USA), and epratuzumab by Immunomedics (Morris Plains, NJ, USA). All patients provided signed informed consent in accord with institutional and federal regulations. The study (ClinicalTrial.gov Identifier: NCT00945815) was conducted after securing an Investigational New Drug (IND) permission from the FDA, approval by local institutional review boards, and in accordance with an assurance filed with and approved by the Cancer Therapy and Evaluation Program Central Institutional Review Board, National Cancer Institute (NCI).

Eligibility Criteria—Eligibility required age ≥ 16 years, relapsed or refractory ALL (excluding Burkitt, Philadelphia chromosome positive, or mixed lineage leukaemia), ≥ 20% marrow and/or peripheral blood lymphoblasts expressing CD22 by flow cytometry, Eastern Cooperative Group (ECOG) performance status 0–2, no evidence of central nervous system involvement, no prior therapy with clofarabine or epratuzumab, no evidence of uncontrolled infection, creatinine ≤ 88.4 μmol/l or estimated glomerular filtration rate > 60 ml/min, aspartate aminotransferase (AST)/ alanine aminotransferase (ALT), alkaline phosphatase ≤ 2.5 times institutional upper limits of normal (IULN), bilirubin ≤ 1.5 times IULN, no pregnancy or active lactation, < Grade 2 neuropathy, and no chemotherapy within 2 weeks of registration (except for hydroxycarbamide or maintenance therapy). For this study, refractory ALL was defined as failure to achieve CR with the last chemotherapy received, whereas relapsed patients achieved a CR of any duration before developing recurrence. Patients with only extramedullary disease were not eligible. Patients may have received prior allogeneic or autologous HCT. However, the transplant must have been performed more than 90 days prior to registration, and patients could not have evidence of ≥ Grade 2 acute graft-versus-host disease (GVHD), moderate or severe limited chronic GVHD, or extensive chronic GVHD of any severity. For patients with a QTc interval > 500 ms on the screening electrocardiogram, the study coordinator had to be contacted prior to enrollment.

Statistical Considerations

The study was performed in 2 stages. If at least 2 of the first 20 patients achieved a CR or CRi, 15 additional patients would be accrued. This design had a critical level (probability of falsely concluding that an agent with a 10% true CR rate warrants further study) of 2% and power (probability of correctly concluding that an agent with a 30% CR rate warrants further study) of 87%. Logistic regression analysis and Fisher's exact tests (for CR and resistant disease) and proportional hazards regression (for overall survival) were used to test the association between patient outcomes and disease characteristics. Overall survival was estimated by the method of Kaplan and Meier (Kaplan and Meier, 1958). Confidence intervals (CI) were calculated at the 95% level; p-values are two-tailed and considered significant when <0.05.

Treatment regimen

Induction therapy consisted of one cycle of treatment with clofarabine 40 mg/m^2/day on days 2–6, cytarabine 1 g/m^2/day on days 1–5, and epratuzumab 360 mg/m^2/day on days 7, 14, 21 and 28. Clofarabine was administered 4 h after the completion of cytarabine on days when both drugs were given. Acetaminophen 650 mg by mouth and diphenhydramine 50 mg intravenously were administered 30–60 min prior to treatment with epratuzumab. Prior to administration of epratuzumab on Day 14 and 1 h after completion of epratuzumab on Day 28, triplicate electrocardiograms were performed. For QTc > 500 ms, the study coordinator was contacted prior to proceeding with treatment. Response was assessed between days 33–40 by bone marrow examination. It was recommended that all patients receive intrathecal methotrexate (12 mg) twice, at least 1 week apart, during induction. However, this was a requirement for patients < 22 years of age.

Treatment Interruptions/ Dose Modifications

Clofarabine—For patients developing tachypnea or unexplained tachycardia or hypotension during infusion, clofarabine was held until symptoms resolved and was reinitiated with the addition of pre-treatment steroids. Twenty-five percent or 50% dose reductions in clofarabine were made for Grade 2 or ≥ Grade 3 non-haematological toxicities, excluding alopecia and infection (unless the infection was life-threatening).

Cytarabine—Cytarabine was dose-reduced by 50% for creatinine ≥ 176.8 μmol/l.

Epratuzumab—Dose modifications for infusion reactions were made according to severity (NCI grading). Grade 1: infusion was slowed. Grade 2 (excluding urticaria and/ or asymptomatic bronchospasm): infusion was stopped temporarily then resumed at a slower infusion rate (50% of initial rate) if the patient was stable. Grade 2 urticaria and/ or asymptomatic bronchospasm: infusion was stopped permanently. ≥ Grade 3 infusion reaction: the infusion was stopped permanently.

Definition of Outcomes—CR was defined as < 5% marrow blasts, neutrophil count ≥ 1 × 10^9/l, platelet count ≥ 100 × 10^9/l and no evidence of extramedullary disease. CRi was defined as CR but without neutrophil or platelet count recovery. Partial remission (PR) required at least a 50% decrease in the marrow blast percentage compared to the pre-treatment value and marrow blast percentage ≥ 5% and < 25%, no circulating blasts, no increase in extramedullary disease, neutrophil count ≥ 1 × 10^9/l and platelet count ≥ 100 × 10^9/l. Overall survival was measured from the date of registration until death from any cause with observations censored at the date of last contact for patients last known to be alive. Toxicities were defined and graded according to the NCI Common Toxicity Criteria for Adverse Events version 4.0. (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

Cytogenetics—Pre-treatment cytogenetics were performed at each institution's preferred laboratory site and were grouped into 4 risk groups (standard, intermediate, high, very high) as previously described (Pullarkat *et al.,* 2008).

Minimal residual disease

Flow cytometry detection of MRD was performed in the College of American Pathologists/ Clinical Laboratory Improvement Amendments referral laboratory of Dr. Brent Wood at the University of Washington (sensitivity level 0.01%). The laboratory used the pre-treatment specimen to identify the immunophenotypic characteristics of the patient's leukaemia. MRD was performed using 6-colour flow cytometry and the following antibody combinations: CD20 fluorescein isothiocyanate (FITC)/ CD10 phycoerythrin (PE)/ CD38 peridinin chlorophyll-cyanin 5.5 (PerCP-Cy5.5)/ CD19 PE-Cy7/ CD58 allophycocyanin (APC)/ CD45 APC-H7 and CD9 FITC/ CD13+ CD33 PE/ CD34 PerCP-Cy5.5/ CD19 PE-Cy7/ CD10 APC/ CD45 APC-H7. In cases in which these antibody combinations were not informative, additional markers were employed.

Results

More than 2 of the first 20 patients responded, therefore, the study proceeded to the second stage. Thirty-five patients were enrolled, and the study was closed to accrual on 1 July 2012 after meeting the protocol-defined criterion for a positive study. Two patients were ineligible, one patient was determined to be Philadelphia chromosome positive after registration, and one patient never started protocol therapy. All four were excluded from the following analysis.

Patient Characteristics—Patient characteristics are listed in Table I. Of the 31 evaluable patients, the median age was 41 years (range 21–69) and median white blood cell count at registration was 5.0×10^9/l (range 0.2–108.7). Twenty-three patients (74%) were male. The median time from initial diagnosis to registration was 16 months (range 3–211). Nineteen patients (61%) were in first relapse, 7 (23%) in second relapse and 5 (16%) were refractory. Three patients had undergone prior allogeneic HCT. Two patients had pre-study QTc intervals > 500 ms.

Cytogenetics—Pre-treatment cytogenetic risk, classified according to SWOG criteria, showed the following (Pullarkat *et al.,* 2008): no growth (n=6), intermediate risk (n=13), high risk (n=5), very high risk (n=7).

Response to Treatment and Outcomes

Ten patients achieved CR and 6 achieved CRi for a CR/CRi rate of 52% (95% CI: 33–70%). The median overall survival was 5 months (95% CI: 3–9 months), with a median follow-up time of 4 months.

Minimal Residual Disease

Only 6 patients who achieved CR/CRi had MRD assessed at both time points. Of these, only 1 became MRD-negative (< 0.01%) and this patient survived for 11 months.

Toxicities

Twenty-four patients have died with 3 deaths occurring during treatment and attributed to sepsis (n=1) and cardiac arrest (n=2). Neither of the patients who died of cardiac arrest had

pre-existing cardiac abnormalities (i.e. prolonged QTc intervals). Causes of death in the remaining 21 patients included: leukaemia (n=13), refractory GVHD (n=1), infection/ sepsis (n=5), unknown (n=1), and acute respiratory distress syndrome (n=1). Six additional patients had Grade 4 non-haematological toxicities including hypercalcaemia, elevated transaminases, febrile neutropenia, acute kidney injury, hepatic failure, pneumonia, hypoxia and respiratory failure. A complete list of non-haematological Grade 3–5 adverse events is provided in Table II. The most common Grade 3–5 non-haematological toxicities possibly related to treatment were: transaminase elevation (n=11), febrile neutropenia (n=17), lung infection (n=4), and sepsis (n=3). No allergic reactions to epratuzumab were reported. No significant changes in the mean QTc interval occurred. The incidence of the majority of toxicities observed in this trial (n=36) were similar to those observed in S0530 (clofarabine/ cytarabine), where the incidence of Grade 3–5 non-haematological toxicities possibly related to treatment were: transaminase elevation (n=12), febrile neutropenia (n=16), and lung infection (n=4). However, there was a higher incidence of bacteraemia (n=10) and creatinine elevation (n=4) in S0530.

Discussion

Relapsed/ refractory ALL remains a difficult disease to treat. No current standard regimen exists although a few drugs have been approved over the last decade for this disease: nelarabine (for T-ALL), clofarabine (for paediatric ALL) and, most recently, liposomal vincristine (Marqibo, Spectrum Pharmaceuticals, Irvine, CA). The low single-agent response rates of these drugs (nelarabine: 21%; clofarabine (paediatric ALL): 30%; Marqibo: 15%) emphasizes the poor prognosis of this disease. Currently, the only curative option for this disease is allogeneic HCT and patients typically need to achieve a CR or CRi to have a reasonable chance of benefiting from transplant, thus emphasizing the need for better salvage therapies.

The response rate to clofarabine/cytarabine/epratuzumab in this study (52% CR/ CRi) was encouraging, particularly given the response rate with this same backbone chemotherapy regimen without epratuzumab (S0530) (17%) where the patient eligibility was identical except for the requirement of CD22+ lymphoblasts and the inclusion of Philadelphia-chromosome positive ALL patients. Although there was a higher percentage of patients with first relapse in the current study and patients with Philadelphia chromosome positive ALL were not included, a significant percentage of patients were still primary refractory/ subsequent relapses or had undergone prior allogeneic HCT. These results therefore strongly suggest that epratuzumab used in this setting is an active agent in recurrent adult ALL. A paediatric study evaluated epratuzumab and chemotherapy in relapsed ALL (Raetz *et al.,* 2011). The addition of epratuzumab in that study did not appear to improve second CR rates as compared to historical controls treated with chemotherapy alone. However, among those patients who attained a CR, those treated with epratuzumab were significantly more likely to become MRD negative as compared to those treated with chemotherapy alone (Raetz *et al,* 2011). Further follow-up of this paediatric trial is needed to determine whether this translates into improved disease-free or overall survival.

We did not analyse nucleoside transporter expression in our study. The status of such transporter expression may be relevant to response in these patients because transport of nucleoside analogues, such as clofarabine, across the plasma cell membrane of the tumour cell may determine its cytotoxicity and the backbone regimen in this trial was clofarabine-based.

Ultimately, a randomized trial in relapsed ALL with chemotherapy versus chemotherapy and epratuzumab is needed to answer the question of the benefit of adding epratuzumab. The European-based IntReALL consortium is sponsoring a randomized phase 3 trial in children with relapsed ALL. Currently, new therapeutic agents, inotuzumab, an anti-CD22 antibody attached to calicheamicin and blinatumomab, a bi-specific anti-CD19 antibody, have demonstrated encouraging results as single agents (Kantarjian *et al* 2012; Topp *et al* 2012) and are in the phase 3 setting for adults with relapsed ALL. Although the anti-CD22 immunoconjugate inotuzumab is very active, it also has toxicities with respect to veno-occlusive disease and cytopenias (Kantarjian *et al* 2012). Thus, the relative advantages and disadvantages of the conjugate versus the naked antibody in various settings will be of interest. For example, the conjugate may turn out to have advantages in the setting of re-induction, while the naked antibody may be more tolerable as maintenance post-allogeneic transplant. Like inotuzumab, the toxicity profile of blinatumomab is not completely defined, nor do we know the likelihood of the emergence of CD19 variants following therapy with a highly active anti-CD19 drug (or for that matter, the likelihood of emergence of CD22-negative variants after treatment with CD22 targeted therapy). However, the potential availability of epratuzumab, inotuzumab and blinatumomab, not to mention chimeric antigen receptor T cells targeting CD19, gives us many active agents that we need to learn how to combine and sequence in the treatment of adult ALL.

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Table I

Patient Characteristics

Median Age (years)	41 (range 21–69)
Median WBC at registration (× 10^9/l)	5.0 (range 0.2–108.7)
Gender (Male)	23 patients (74%)
Median time from initial diagnosis to registration (months)	16 (range 3–211)
Disease status	
1st relapse	19 patients (61%)
2nd relapse	7 patients (23%)
Refractory	5 patients (16%)
Prior Allogeneic Haematopoietic stem cell transplantation	3 patients (10%)

Table II

Non-Haematological Adverse Events (Grade 3–5) Possibly Related to Treatment

Adverse Event	Grade		
	3	4	5
ALT increased	4	1	0
AST increased	3	3	0
Abdominal pain	1	0	0
Acute kidney injury	0	1	0
Alkaline phosphatase	1	0	0
Anorexia	1	0	0
Cardiac arrest	0	0	2
Catheter-related infection	2	0	0
Diarrhoea	2	0	0
ECG QTc	1	0	0
Encephalopathy	2	0	0
Enterocolitis	2	0	0
Febrile neutropenia	16	1	0
Gum infection	1	0	0
Hepatic failure	0	1	0
Hypercalcaemia	0	1	0
Hyperglycaemia	1	0	0
Hyperkalaemia	1	0	0
Hypertension	1	0	0
Hypocalcaemia	1	0	0
Hypokalaemia	1	0	0
Hyponatraemia	1	0	0
Hypophosphataemia	1	0	0
Hypotension	2	0	0
Hypoxia	1	1	0
Infections (other)	1	0	0
Lung infection	3	1	0
Nervous system disorders	1	0	0
Oral pain	1	0	0
Respiratory failure	0	1	0
Sepsis	0	3	1
Tooth infection	1	0	0
Tumour lysis syndrome	1	0	0
Typhilitis	2	0	0

ALT, analine transaminase; AST, aspartate transaminase; ECG, electrocardiogram.