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Effects of intensive induction and consolidation chemotherapy with idarubicin and high dose cytarabine on minimal residual disease levels in newly diagnosed adult precursor-B acute lymphoblastic leukemia☆

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ABSTRACT

An intensive induction regimen, consisting of idarubicin and high dose cytarabine, was assessed in 19 adult patients, median age 44 years, with newly diagnosed precursor-B acute lymphoblastic leukemia (ALL). Patients achieving a complete response (CR) were given an attenuated consolidation course. The primary endpoints were induction death rate and incidence of serious non-hematological toxicity. Grades 3–4 diarrhoea occurred in 47% of patients during induction. Two patients (11%) died during induction therapy, and 2 were withdrawn due to resistant disease or prolonged marrow hypoplasia. Fifteen patients achieved CR (79%), but levels of minimal residual disease (MRD) after induction were comparable with those previously observed using a modified pediatric protocol. Overall survival at 5 years was 36.8% while leukemia-free survival was 44.1%. An intensive AML protocol used in adults with ALL resulted in substantial toxicity and provided similar levels of cytoreduction to conventional ALL protocols, without improving long-term outcomes.

1. Introduction

The treatment of acute lymphoblastic leukemia (ALL) in adults remains unsatisfactory [1]. Combination chemotherapy protocols developed for treating children with ALL, and modified for use in adults yield less favourable outcomes than in children [2,3]. Although more intensive pediatric protocols have improved outcomes in adolescents and young adults with ALL, the results are still inferior to those obtained in children [4–7]. While complex issues relating to patient treatment compliance, as well as physician and institutional experience, likely contribute to these outcomes, differences in disease biology with increasing age are also a major factor in determining the higher risk of relapse. This is reflected in higher levels of minimal residual disease (MRD) observed in adults compared with children after induction therapy, indicating relatively greater inherent disease resistance to initial chemotherapy [8–11]. One potential way of achieving more rapid early cytoreduction would be to escalate the intensity of induction therapy. We therefore explored whether the use of an intensive combination chemotherapy protocol designed for the treatment of acute myeloid leukemia (AML) in adults might result in greater leukemia cytoreduction, and therefore produce higher response and lower MRD levels, than traditional modified pediatric ALL protocols

☆ This trial is registered with the Australian and New Zealand Clinical Trials Registry: registration number ACTRN12615000631505.

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previously used in adults with ALL. Herein, we report on long-term results of a Phase-2 trial using an intensive AML protocol, consisting of induction and consolidation with high dose cytarabine and idarubicin, in newly diagnosed adults with Philadelphia chromosome negative precursor B ALL.

2. Patients and methods

2.1. Trial conduct and eligibility

This phase II clinical trial was conducted and sponsored by the Australasian Leukemia & Lymphoma Group (ALLG) in seven Australian centres. The trial was registered at ACTRN12615000631505 and approved by the Human Ethics Committees of participating centres. All patients gave written informed consent to participate. Eligibility criteria included a diagnosis of untreated ALL by WHO criteria, with FAB morphological subtypes L1 and L2, precursor B phenotype, age 20–55 years inclusive, ECOG performance status 0–3 and adequate renal and hepatic function. Patients with T-cell and mature B-cell phenotypes, and patients with Philadelphia chromosome and/or positivity for *BCR-ABL* transcripts, were ineligible. The study opened in June 2002 with a proposed accrual target of 25 eligible patients, but was closed in November 2005 due to slower than expected accrual, after 20 patients had been enrolled.

2.2. Treatment protocol

Induction therapy consisted of cytarabine given as a 2 h intravenous infusion of 3 g/m^{2}on day 1, followed by a continuous intravenous infusion starting 12 h later for 96 h at a dose of 1.5 g/m^2 per 24 h, together with idarubicin 12 mg/m [2] IVI daily for the first 3 days. Intrathecal methotrexate 12 mg was also given at the start of induction therapy. Supportive treatment consisted of allopurinol, fluconazole 200 mg daily, and filgrastim 5 μg/kg subcutaneously daily from day 6 until neutrophil recovery to >2.0 × 10^9/L. Patients achieving a complete remission (CR) were given a second attenuated course as consolidation therapy, with cytarabine 3 g/m [2] over 2 h followed by a 72 h infusion at 1.5 g/m^2 per 24 h, and idarubicin 12 mg/m [2] IV on days 1 and 2.

Further therapy was not protocol specified, but it was recommended that patients in ongoing CR should receive high-dose methotrexate with leucovorin rescue as central nervous system prophylaxis, and then treatment according to the CALGB 8811 protocol for adult ALL [12].

2.3. Minimal residual disease detection

This was carried out as previously reported [8]. Briefly, DNA was extracted from diagnostic bone marrow biopsy samples, and the complementarity determining regions (CDR) 2 and 3 of the immunoglobulin heavy chain gene were amplified using consensus PCR primers and sequenced using Sanger sequencing. Patient specific primers were then designed, and used in a nested PCR to test for MRD in bone marrow aspirate samples taken at the end of induction treatment and again after the consolidation course.

2.4. Study endpoints

This study was designed to assess the toxicity and tolerability of intensive induction chemotherapy for newly diagnosed adult ALL. The primary endpoints were the induction death rate, defined as deaths occurring within 28 days of starting induction chemotherapy, and the incidence of grade-3 and -4 non-hematological toxicities, graded according to NCI Common Toxicity Criteria version 2.0. Secondary endpoints were the rates of CR after induction and consolidation therapy, overall survival and leukemia-free survival, and correlation of levels of MRD with clinical outcomes. CR was defined as: (i) absence of symptoms and signs of leukemia; (ii) neutrophil count >1.0 × 10^9/L at least 5 days after ceasing filgrastim; (iii) platelet count >100 × 10^9/L; (iv) absence of leukemic cells in the peripheral blood; and (v) normocellular bone marrow with active hemopoiesis and <5% blasts. Overall survival was measured from the date of commencing induction therapy until the date of death from any cause. For patients who achieved CR, leukemia-free survival was measured from the date of achievement of CR until the earlier of the dates of relapse and death. Patients who underwent allogeneic hemopoietic cell transplantation in first remission were censored at the date of transplant.

2.5. Statistical methods

The induction death rate was calculated as the percentage of eligible patients who died within 28 days of commencing induction therapy. Similarly the incidences of grade-3 and -4 non-hematological toxicities and CR rates were reported for the same group of patients. Ninety-five percent confidence intervals (95% CI) were reported using the Blyth-Still-Casella method.

Overall and leukemia-free survival curves were estimated using the Kaplan-Meier product limit method, with a close-out date of 28 July 2011. Survival times were censored at the close-out date for patients alive and leukemia-free at this date or at the date of last contact for patients lost to follow-up prior to the close-out date. Median follow-up was estimated by the Reverse Kaplan-Meier method. Statistical analyses were carried out using SAS, R version 2.15.2 and StatXact statistical software.

The statistical software SPSS version 21 was used to analyse the post-induction MRD data. Two-tailed tests with a significance level of 5% were used throughout. MRD levels were log transformed to approximate normality prior to analysis. Cox proportional hazards regression was used to test for association between post-induction MRD levels and leukemia-free survival. The independent two-sample *t*-test was used to test for differences in MRD levels between this patient group and a historical cohort of 29 adult patients treated with a standard modified pediatric ALL protocol [8].

3. Results

3.1. Patient characteristics (Table 1)

A total of 20 patients were registered between June 2002 and March 2005, with one excluded because of Philadelphia chromosome positivity. Therefore 19 eligible patients started protocol therapy. A second patient (case 16) was subsequently found to be Philadelphia chromosome-positive and was withdrawn after completing induction, but was included in the analysis of the primary endpoint.

Patients were aged 21 to 55 (median 44) years. There were 12 (63%) males. None had evidence of CNS leukemia. The median peripheral blood white cell count was 9.8 × 10^9/L (range 0.2–251), and median percentage blasts in the marrow was 91 (range 10–100). Cytogenetic analysis showed an abnormal karyotype in 10 patients, one each of; t(4;11), t(1;19), t(9;22), hypodiploid, high hyperdiploidy, and complex karyotype, and four others had other abnormalities (including three with hyperdipoidy 47–50).

3.2. Outcome of induction therapy (Fig. 1)

Of the 19 patients, 17 received ≥90% of the protocol dose of

Table 1
Patients baseline characteristics.

Characteristic		Evaluable patients	
		n	%
Total		19	100
Sex	Male	12	63
	Female	7	37
Age (years) at registration	Median	44	
	Mean (SD)	39 (12)	
	Range	21–55	
	<30	5	26
	30–39	4	21
	40–49	5	26
	50–55	5	26
ECOG performance status	0	6	32
	1	11	58
	2	2	11
Febrile (≥38 °C)	No	14	74
	Yes	5	26
Clinically evident infection	No	17	89
	Yes	2	11
FAB classification	L1	6	32
	L2	13	68
Presentation WCC ($\times 10^9$/L)	Median 9.8	Range 0.2–251	

idarubicin (2 patients received 83% and 88%). Eighteen patients received the full amount of cytarabine, with 1 patient receiving 75% of the planned infusional dose.

Two patients (11%; 95% CI: 2%–32%) died of treatment-related complications and infection within one month. During induction therapy, fourteen patients (74%; 95% CI: 50%–89%) had NCI-CTC grades 3–4 neutropenic fevers, while 8 (42%; 95% CI: 22%–66%) had grades 3–4 bleeding. Other grades 3–4 toxicities included 9 (47%; 95% CI: 24%–69%) patients with diarrhoea, 3 (16%; 95% CI: 4%–38%) with stomatitis, and 3 (16%; 95% CI: 4%–38%) with skin rash. One additional patient developed neutropenic enterocolitis.

Of the 19 patients starting induction therapy, 15 achieved CR (79%; 95% CI: 57%–92%). Two patients died before day 28 of treatment complications, 1 patient had residual leukemia, and 1 patient had marrow hypoplasia without evidence of leukemia. Both of the latter were withdrawn from the study.

3.3. Subsequent outcome

All 14 eligible patients achieving CR received the scheduled course of consolidation therapy (case 16 was withdrawn), with no treatment-related deaths. Four patients subsequently underwent allogeneic hemopoietic cell transplant in first remission; 1 of these patients relapsed and died post-transplant, while the remaining 3 remained alive and leukemia-free. Of the 10 patients not transplanted, 6 had bone marrow relapse; 1 of these had an allogeneic transplant in second remission and subsequently died of graft-versus-host disease, while the other 5 died of progressive leukemia. Four patients remained in continuous CR without allogeneic transplant at the study close-out date.

The median follow-up was 7.8 (range 6.1–8.6) years for survivors. The median overall survival was 3.0 years, with observed survival rates of 68.4% (95% CI: 45.2%–85.1%) at 1 year, 52.6% (95% CI: 31.1%–73.2%) at 2 years, and 36.8% (95% CI: 18.7%–59.7%) at 5 years (Fig. 2). Corresponding leukemia-free survival rates were 66.1% (95% CI: 35.8%–87.2%) at 1 year; 55.1% (95% CI: 26.3%–80.9%) at 2 years; and 44.1% (95% CI: 18.2%–73.6%) at 5 years (Fig. 3).

3.4. Association between MRD levels and clinical outcomes

Data on post-induction treatment residual disease levels were available on 9 of 16 assessable patients. Of these, MRD levels ranged from $<1.2 \times 10^{-6}$ to 1.2×10^{-2}. Two patients had a transplant in first remission, while of the 7 non-transplanted patients 5 relapsed and 2 remain in CR. The MRD levels in post-induction samples in these 9 patients were compared to the levels previously reported in 27 adult patients treated with a protocol based on a modified pediatric regimen [8]. Using a 2 tailed *t*-test for equality of means, there was no significant difference in MRD levels between the 2 groups (mean log (MRD day 28) ± SD for current study −3.76 ± 1.33, for historical control group −3.17 ± 1.30) ($p = 0.243$) (Fig. 4).

4. Discussion

The purpose of the study was to administer an intensive AML remission induction regimen based on high-dose cytarabine to adult patients with newly diagnosed precursor B ALL, with the

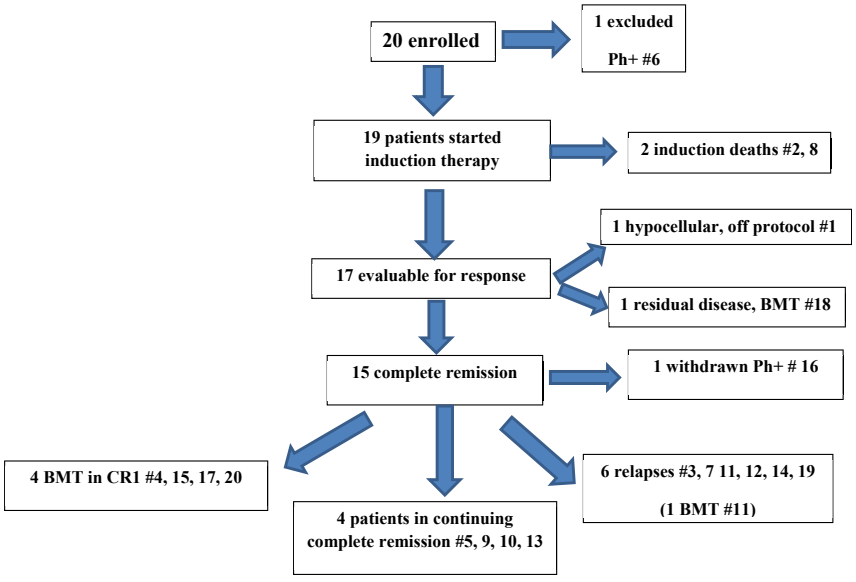

Fig. 1. Patient flow diagram for trial.

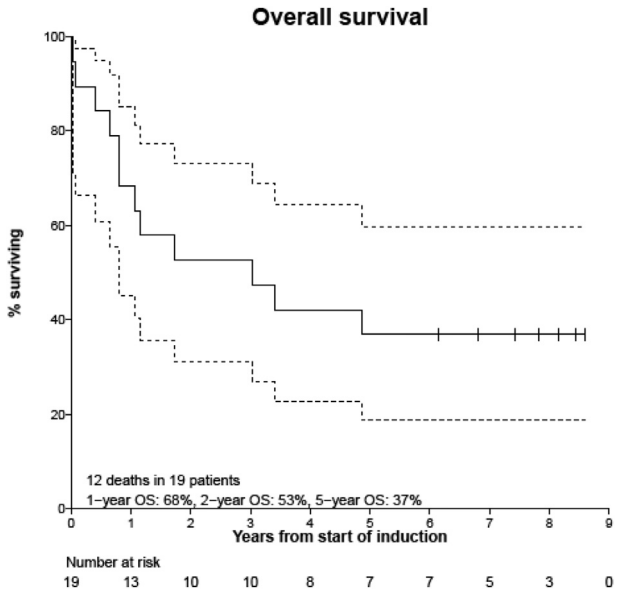

Fig. 2. Overall survival for eligible study patients.

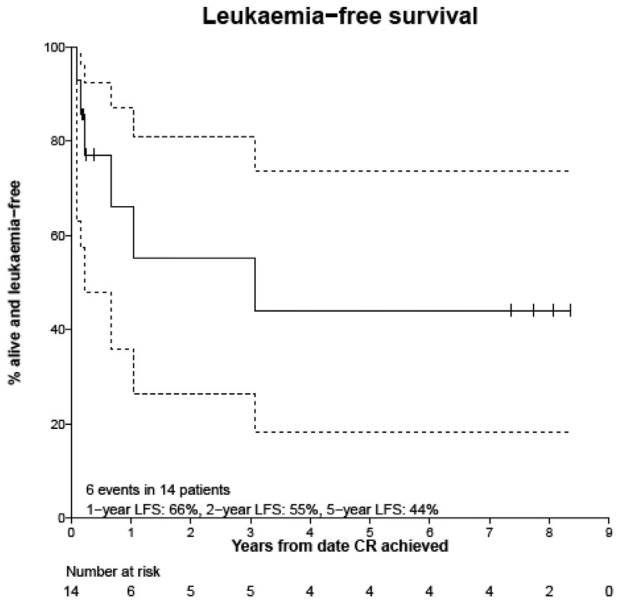

Fig. 3. Leukemia-free survival for eligible study patients achieving CR.

objective of achieving rapid cytoreduction and low MRD levels, thereby reducing the subsequent relapse risk. This was based on the known association between the achievement of low or negative MRD levels after induction therapy in both ALL and AML, and subsequent superior long-term leukemia-free survival [8–11,13]. We used a regimen consisting of infusional high-dose cytarabine and idarubicin in a schedule similar to that described for treatment of adult AML [14]. Although there was only 1 case of resistant disease, the CR rate, based on intention to treat, was only 79% and was broadly comparable with current ALL protocols used in adults. The regimen was toxic, with 11% death rate during induction therapy and substantial levels of grades 3–4 non-hematologic toxicity, particularly gastrointestinal.

We measured MRD levels in post-induction marrow samples using sensitive PCR technology to directly assess cytoreduction.

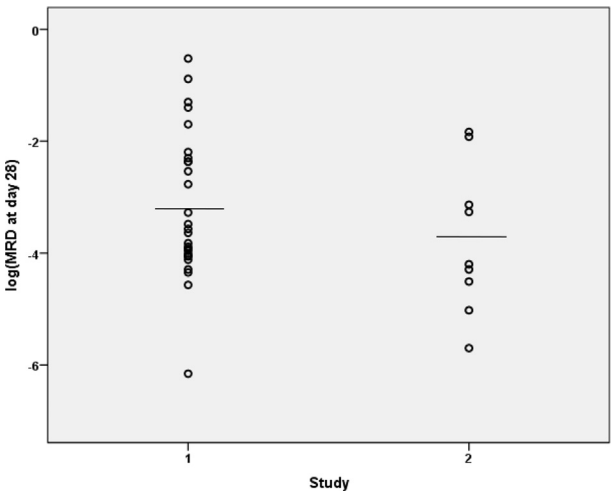

Fig. 4. Comparison of post-induction MRD levels between historical cohort of patients using modified pediatric ALL protocol [8] (group 1) and 9 assessable cases enrolled on current study (group 2).

Although 7 of 9 patients evaluated had MRD levels below 10^{-4}, 2 had high levels and relapsed 2 and 8 months after start of treatment. When we compared these MRD levels with those in a historical cohort of adult patients treated on a modified pediatric protocol, there was no significant difference between the 2 groups, suggesting that the more intensive AML regimen in fact did not produce materially greater cytoreduction compared with the more traditional adult ALL protocol.

High-dose cytarabine has efficacy in relapsed ALL and is widely used in this setting. However, there are only a limited number of reports of its use in initial therapy of newly diagnosed adult ALL [15–18]. Willemze and colleagues used intermediate-dose cytarabine (1 g/m^2 × 12 doses), together with etoposide, amsacrine, and prednisone in 32 patients with ALL [15]. There were 23 CR (72%), and overall survival at 5 years was 38%. Ifrah et al. treated 67 adults with cytarabine 1 g/m^2 for 6 doses, together with idarubicin and methylprednisolone [16]. Of 64 eligible cases, 50 achieved CR (78%), with 4 year overall survival 24%. Hallbook and colleagues treated 153 adults with ALL with cytarabine 3 g/m^2 for 6 doses, together with daunorubicin, cyclophosphamide, vincristine and betamethasone [17]. The CR rate was 90%, but overall survival at 3 years was only 29%, although 62% in a subgroup aged less than 40 years with precursor B disease. Finally, Lamanna and colleagues reported a multicentre US trial in adult ALL, comparing the L-20 protocol with the ALL2 protocol, consisting of cytarabine 3 g/m^2 daily for 5 days combined with a single high dose of mitoxantrone [18]. The CR rate was significantly higher with ALL2 compared with L-20 (83% versus 71%), with 9% induction deaths and 8% resistant disease, but only 34% 5 year survival. This latter study most closely approximated our own trial design, with no lympholytic drugs such as prednisone or vincristine used in induction. Results of our study approximate those of the US trial, with CR rate of 79%, and 5 year overall survival 37%, and leukemia-free survival 44%.

In conclusion, high-dose cytarabine and idarubicin for treatment of newly diagnosed precursor B ALL in adults demonstrated an acceptable CR rate, but with significant non-hematologic toxicity. The levels of MRD following the induction cycle were not significantly different from those using a more traditional modified pediatric protocol, and long-term outcomes were also comparable. More intensive pediatric protocols have been reported to improve outcomes for younger adults with ALL [7,8], and may be preferable.

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