Defining the Course and Prognosis of Adults With Acute Lymphocytic Leukemia in First Salvage After Induction Failure or Short First Remission Duration

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Abstract

BACKGROUND—Results from salvage therapy in adult patients with acute lymphocytic leukemia (ALL) are wide-ranging and depend on several disease and patient characteristics. The objectives of this study were to define the prognosis for adult patients with ALL after first salvage through multivariate analyses of patient and disease characteristics.

METHODS—Adults with ALL who had primary resistance to frontline therapy or who had a disease recurrence after a first complete response (CR) duration <1 year were analyzed. Multivariate analyses for subsequent CR and survival were conducted.

RESULTS—Seventy-five of 245 patients (31%) achieved CR. The median CR duration was 5 months, the median survival was 4.7 months. In multivariate analysis, independent poor prognostic factors for not achieving CR were age >55 years, bone marrow blasts 20%, and platelet count $<75 \times 10^9$/L Variables that were associated independently with shorter survival were age >55 years, bone marrow blasts 20%, platelet count $<75 \times 10^9$/L, albumin level <3 g/L, and lactic dehydrogenase level 1000 IU/L. Patients who had 3 of the 5 adverse factors (45%) had a median survival of 2 to 3 months and CR rates of 8% to 15%. Achieving CR was associated independently with improved survival in a landmark multivariate analysis (*P*<.0001; hazard ratio, 0.40; 95% confidence interval, 0.03–0.72).

CONCLUSIONS—The current analyses identified a subset of adults patients ALL in first salvage for whom standard therapies were associated with an extremely poor outcome. The results also confirmed the importance of achieving CR to attain improved survival.

Keywords

acute lymphocytic leukemia; salvage therapy; prognosis; survival; complete response

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Modern multiagent, dose-intensive chemotherapy regimens have resulted in cure rates of 80% to 90% in childhood acute lymphocytic leukemia (ALL).[1,2] Regimens in adult ALL patterned after the pediatric programs have increased the complete response (CR) rates to 90% and have increased the long-term survival rates to 30% to 50%.[3–8] Still, most adults with ALL will die from disease progression. Therefore, there is a need to discover new agents with anti-ALL activity.

Approving new anti-ALL agents for front-line therapy is a daunting task, because it requires large randomized studies that compare standard regimens versus the same regimens with the addition of the new agent. Because ALL is an uncommon disease (annual US incidence, 1500–3000 cases), such endeavors are almost impossible. Therefore, the discovery and regulatory approval of new agents in ALL have relied on development in niche indications. Examples include clofarabine for pediatric ALL in second salvage,[9,10] nelarabine for T-cell ALL salvage,[11] and tyrosine kinase inhibitors in Philadelphia chromosome (Ph)-positive ALL.[12,13]

Patients with primary refractory disease or in first recurrence have CR rates of 30% to 50% with salvage therapy but have a cure rate of 5%.[14–17] Their outcome depends on several factors, the most important of which is the duration of first complete remission (CRD). It is anticipated that adults who have primary refractory disease or a short first CRD will have a poor outcome, probably as poor as the outcome of patients in second salvage[18]; however, to our knowledge, no studies have investigated their outcome. Defining the precise course and prognosis of adults with ALL and primary refractory disease or with a short first CRD will help speed the development of investigations aimed at this subgroup.

MATERIALS AND METHODS

Study Group

Patients aged 16 years with a diagnosis of ALL who were receiving first salvage therapy for either ALL with primary failure on front-line induction therapy or for ALL in first recurrence with a first CRD <12 months were analyzed. This review included patients in the Leukemia Department at The University of Texas M. D. Anderson Cancer Center who had failed on our front-line therapy regimens and patients who had been referred from outside institutions after failure on front-line therapy. Only patients who had received treatment since 1990 were included to account for potential improvements in chemotherapy regimens and in supportive care that may have resulted in differences in outcomes compared with patients who were treated before 1990. Patients were treated on protocols that were available during different time periods.

Statistical Considerations

The criteria for response were standard. A CR was defined as a bone marrow blast count 5% in a cellular bone marrow sample with normalization of peripheral counts, including a granulocyte count $>10^9$/L and a platelet count $>100 \times 10^9$/L. The criteria for a partial response (PR) were the same as those for a CR except for decrease in bone marrow blasts by 50% but remaining in the range of 6% to 25%. A CR with incomplete platelet recovery

(CRp) referred to the achievement of a CR but with platelets remaining $< 100 \times 10^9$/L. Early mortality referred to death within 15 days of the start of therapy, and induction death referred to death during the first course of therapy. All other patients were classified with resistant disease. Survival was measured from the start of first salvage therapy. Response duration was measured from the date of response to the date the patient had evidence of ALL recurrence. Survival was calculated from the start of salvage therapy to the date of death from any cause. Multivariate analyses to define prognostic factors for achieving CR and for survival were conducted by using established methods.[19,20] The prognostic value of continuous variables was assessed using a Cox proportional hazard model. Cutoff points for categorical values were based on previous historically tested cutoff points as well as optimized cutoff points based on Martingale residual analysis.

RESULTS

In total, 245 patients were analyzed. These included 124 patients who had refractory-recurrent ALL after receiving frontline therapy at our institution and 121 patients who were referred. Among them, 68 patients had primary refractory disease, and 177 patients had achieved a first CR that lasted <12 months. The patient characteristics are listed in Table 1. The median patient age was 40 years (range, 16–81 years), and *47* patients (19%) were aged 60 years.

Overall, 75 patients (31%) achieved a CR with first salvage therapy (Table 2). Response by treatment regimen is shown in Table 3. Nine patients received salvage therapy with single-agent clofarabine (n = 6) or with clofarabine combinations (n = 3), and 2 CRs were observed.

Response by pretreatment characteristics is shown in Table 4. Prognostic factors that were associated with CR rates were age, karyotype, hemoglobin level, white blood cell count, platelet count, percentage blasts, lactic dehydrogenase (LDH) and albumin levels, and year of salvage. In multivariate analysis, age >55 years, platelet count $<75 \times 10^9$/L, and bone marrow blasts 20% remained as independent poor prognostic factors for response (*P*< .05). Response according to the presence of zero, 1, 2, or 3 adverse factors is shown in Table 5.

The median remission duration was 5 months (95% confidence interval, 4–8 months) (Fig. 1). The median survival was *4.7* months (95% confidence interval, 3.8–6.0 months) (Fig. 1).

Prognostic factors (excluding first salvage treatment effect) that were associated significantly with survival were age, karyotype, hemoglobin level, percentage bone marrow blasts, platelet count, LDH, and albumin levels. Multivariate analysis selected the following independent poor prognostic factors for survival: age >55 years (*P*= .001), bone marrow blasts 20% (*P* = .002), platelet count $<75 \times 10^9$/L (*P*< .001), albumin level <3 g/L (*P*< .001), and LDH level 1000 IU/L (*P*< .001). Survival according to the presence of zero or 1, 2, 3, and 4 or 5 adverse factors is shown in Table 5 and Figure 2.

Table 5 also shows the prediction of survival based on the risk model for CR and prediction of the CR rate based on the risk model for survival. This suggests that, for simplicity, each group of predictive factors still can be used to predict both the CR rate and survival.

Twelve patients underwent allogeneic stem cell transplantation as first salvage for active disease with preparative regimens that included total body irradiation (TBI) in 2 patients and non-TBI regimens in 10 patients. The donor was a related matched sibling in 11 patients and a matched unrelated donor in 1 patient. Overall, 4 patients (33%; 3 CRs and 1 CRp) achieved a CR with allogeneic SCT (Table 3). Their 1-year survival rate was 17%, which was not different from the outcome of other patients (17%; $P = .7$). Of the 75 patients who achieved a CR, 20 underwent allogeneic SCT in second CR. Five of those patients remained alive without disease for a median of 52 months (range, from 7 months to 190 months). The median survival of patients after allogeneic SCT in second CR was 14 months (95% confidence interval, 10–26 months).

Effect of First Salvage Therapy on Prognosis

The previous model included pretreatment patient and disease characteristics. First salvage regimens may have different efficacies (Table 3) and significant interactions with pretreatment characteristics. To account for the treatment-related factors, we repeated the multivariate analyses and included first salvage therapy (vincristine, doxorubicin, and dexamethasone-hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; cytarabine combinations; and allogeneic SCT vs others). The multivariate analysis for CR still identified a higher percentage bone marrow blasts ($P = .0004$), older age ($P = .04$), and thrombocytopenia ($P < .0001$) as independently prognostic and also identified the "ineffective regimens" (defined as single-agent therapy regimens) as independently prognostic ($P = .001$). Similarly, the multivariate survival analysis selected some previously identified significant factors (percentage bone marrow blasts [$P = .02$], platelet count [$P = .002$], albumin level [$P = .001$], age [$P = .003$], and LDH [$P < .0001$]) and also identified type of salvage therapy as an independent prognostic factors.

Achievement of CR and Prognosis

To assess the benefit of achieving a CR, we repeated the multivariate survival analysis using a 6-week landmark that excluded patients who died within 6 weeks. The multivariate analysis included 213 patients and selected independent factors associated with survival similar to those described above (ie, age, percentage bone marrow blasts, LDH, and albumin) but did not select platelet count. Adding response (CR vs no CR) to the multivariate analysis indicated that a CR added significantly to the survival benefit ($P < .0001$; hazard ratio, 0.40; 95% confidence interval, 0.03–0.72).

DISCUSSION

In the current analysis, we attempted to identify a subgroup of adult patients with ALL who have an extremely poor prognosis when receiving salvage therapy. It is known from previous studies that patients with a long first CRD (>12 months) still may have a favorable early outcome and can achieve reasonable CR rates of 40% to 70% with combination salvage regimens. They also may have reasonable long-term expectations with estimated 3-year survival rates of 10% to 20%. The objective of this study was to identify patients in first salvage for whom the prognosis with standard salvage combination regimens is poor. Such patients may benefit from novel investigational therapies that potentially might be

approved for these niche orphan indications, as in the case with clofarabine, nelarabine, and the Bcr-Abl tyrosine kinase inhibitors.[9–13] Therefore, we focused on patients in first salvage who had failed primary front-line therapy or who had a first CRD <12 months. In this analysis of 245 patients, the CR rate was only 31%, the median response duration was 5 months, and the median survival for the entire study cohort was *4.7* months (Fig. 1). A multivariate analysis of prognostic factors independently associated with worse survival identified older age, increased bone marrow blasts, lower platelet count, lower albumin level, and higher LDH level as adverse features (Table 5). Patients who had   3 or of these 5 factors (45% of patients) had a median survival of 2 months to 3 months. Achieving a CR improved survival significantly (*P*< .0001; hazard ratio, 0.40).

In the current analysis, we identified a subgroup of patients with ALL in first salvage who have a very poor prognosis. In such patients, novel single-agent or combination strategies are justified. Such approaches that have demonstrated promise include monoclonal antibodies targeted against CD19 (which is expressed universally in all patients with ALL), against CD20 (which is expressed in 30%–50% of adults with ALL), against CD22 (which is expressed in   80% of adults with ALL), and against dual monoclonal antibodies (eg, against CD19 and CD22) either as native antibodies or attached to toxins (eg, diphtheria toxin, calicheamicin).

Although several studies have reported experience with ALL in first salvage,[9–13] to our knowledge, no studies have detailed the outcome of patients who had a poor prognosis after first salvage, ie, those with primary refractory disease or with short first CRD. Clofarabine has been approved for the treatment of pediatric ALL in second salvage,[9,10] nelarabine has been approved for the treatment of T-cell ALL salvage,[11] and the Bcr-Abl tyrosine kinase inhibitors imatinib and dasatinib have been approved for the treatment of Ph-positive ALL.[12,13] Most patients in the current study were either treated prior to availability of these agents or were not candidates for these approved therapeutic options and, thus, are in need of alternative new agents with anti-ALL activity. In summary, our experience in adults with ALL who had a poor prognosis after first salvage emphasizes the need to develop novel strategies in this setting and establishes baseline expectations against which new approaches can be compared.

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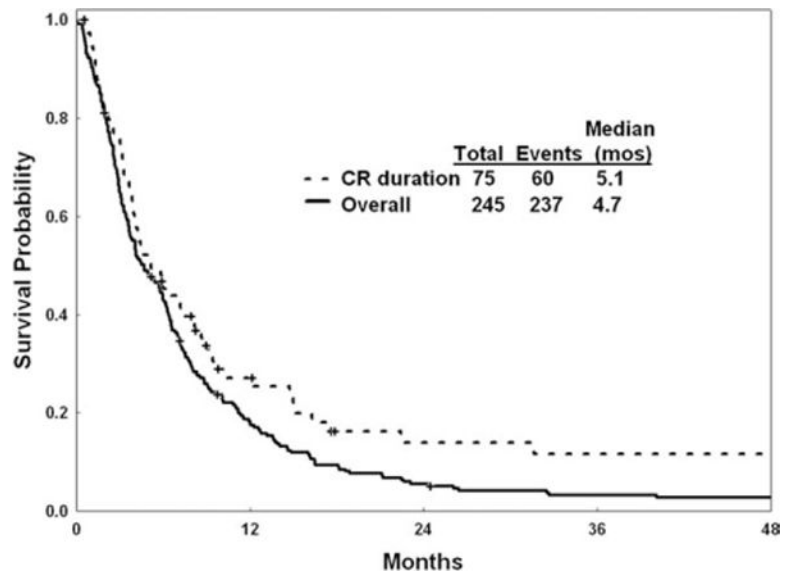20. Cox DR. Regression models and life tables. J Stat Soc (B). 1972; 34:187–220.

Figure 1.
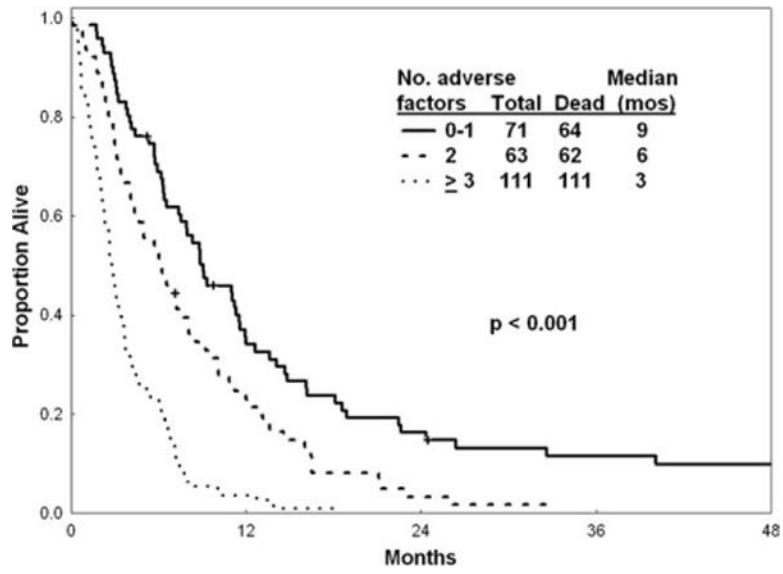Remission duration and survival are illustrated. CR indicates complete response.

Figure 2.
Survival is illustrated according to the number of adverse factors derived from multivariate analysis.

Table 1

Characteristics of the Study Group (N=245)

Characteristic	No. of Patients (%)
Age, y	
Median [range]	40 [16–81]
60	46 (19)
Response to frontline therapy: CR	177 (72)
Karyotype	
Diploid	75 (31)
Philadelphia chromosome-positive	43 (18)
Other	89 (36)
Insufficient metaphases/not done	31 (13)/7 (3)
Hemoglobin, g/dL	
Median [range]	10.4 [3.8–16.10]
<10	105 (43)
WBC:n = 243, $\times 10^9$/L	
Median [range]	8 [0.2–292.5]
5–20	73 (30)
>20	77 (32)
Bone marrow blasts, %	
Median [range]	68 [0–99]
20–50	43 (18)
>50	155 (64)
Peripheral blasts, %	
Median [range]	8 [0–98]
1–10	41 (17)
>10	115 (47)
Platelets, $\times 10^9$/L	
Median [range]	62 [4–418]
<25	56 (23)
25–50	47 (19)
>50	140 (58)
Albumin, g/dL	
Median [range]	3.6 [1.7–5.0]
<3.0	35 (15)
Year of study	
1990–1999	149 (61)
2000	96 (39)
LDH, IU/L	
Median [range]	970.5 [195–12,100]
970	119 (50)

CR indicates complete response; WBC, white blood cells; LDH, lactate dehydrogenase.

Table 2

Response (n=245)

Response	No. of Patients (%)
CR	75 (31)
PR	2 (1)
CRp	3 (1)
Early death <2 wk	9 (4)
Induction death	19 (8)
Resistant disease	132 (54)
Unknown response	5 (2)

CR indicates complete response; PR, partial response; CRp, complete response with incomplete platelet recovery.

Table 3

Response by Therapy

Therapy	No. of Patients	No. of CR+CRp (%)
VAD/Hyper-CVAD	103	48 (47)
Cytarabine combinations	32	8 (25)
Methotrexate-asparaginase combinations	15	5 (33)
Other combinations	29	6 (21)
Single agents	54	7 (13)
Allogeneic stem cell transplantation	12	4 (33)

CR indicates complete response; CRp, complete response with incomplete platelet recovery; VAD, vincristine, doxorubicin, and dexamethasone; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

Table 4

Prognostic Factors for Response and Survival

Characteristic	No.	No. of CRs (%)	P	1-Year Survival, %	P
Age, y			.003		<.001
<50	169	62 (37)		19	
50	76	13 (17)		13	
Response to frontline therapy			.25		.07
CR	177	50 (28)		26	
No CR	68	25 (37)		15	
Karyotype			.04		.02
Diploid	75	31 (41)		22	
Philadelphia chromosome-positive	43	12 (16)		21	
Other	89	19 (25)		10	
Insufficient metaphases/not done	31/7	9 (12)/4 (5)		26/0	
Hemoglobin, g/dL			.02		.004
<10	105	23 (22)		11	
10	138	51 (37)		22	
WBC, ×10⁹/L			.12		.03
<5	93	34 (37)		23	
5–20	73	23 (32)		18	
>20	77	17 (22)		9	
Bone marrow blasts, %			.0002		<.0001
<20	45	25 (56)		35	
20–50	43	12 (28)		14	
>50	155	37 (24)		13	
Peripheral blasts, %			.03		.001
0	86	35 (41)		30	
1–10	41	10 (24)		12	
>10	115	28 (24)		10	
Platelets, ×10⁹/L			<.0001		<.0001
<25	56	5 (9)		5	

Characteristic	No.	No. of CRs (%)	P	1-Year Survival, %	P
25–99	100	27 (27)		12	
100–140	22	8 (36)		32	
>140	65	34 (52)		29	
Albumin, g/dL			.01		<.0001
<3.6	108	24 (22)		13	
3.6	129	49 (38)		20	
LDH, IU/L			.005		<.0001
<970	119	47 (40)		25	
970	119	26 (22)		8	
Year of study			.04		.36
1990–1994	85	24 (28)		21	
1995–1999	64	13 (20)		11	
1999–2004	47	16 (34)		21	
2004–2009	49	22 (45)		15	
Salvage therapy			.001		.0002
VAD/Hyper-CVAD	103	47 (46)		22	
Cytarabine combinations	32	8 (25)		9	
Allogeneic transplantation	12	3 (25)		17	
Methotrexate-asparaginase combinations	15	4 (27)		40	
Other	29	6 (21)		14	
Single agent	54	7 (13)		9	

CR indicates complete response; WBC, white blood cells; LDH, lactate dehydrogenase; VAD, vincristine, doxorubicin, and dexamethasone; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

Table 5

Response and Survival According to the Number of Independent Adverse Factors Present

No. of Adverse Factors	No. of Patients	No. of CRs (%)	Median Survival, mo	1-Year Survival, %
Independent adverse factors for response[a]				
0	24	16 (67)	9	41
1	78	36 (46)	7	25
2	107	21 (20)	4	13
3	36	2 (6)	2	0
Independent adverse factors for survival[b]				
0–1	71	36 (51)	9	35
2	63	25 (40)	6	23
3	74	11 (15)		5
4–5	37	3 (8)	2	0