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Biologic features and treatment outcome of secondary acute lymphoblastic leukemia—a review of 101 cases

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Background: Secondary acute lymphoblastic leukemia (sALL) is a rare disease and its biologic features are not well characterized.
Patients and methods: We describe a cohort of seven patients and discuss 94 additional cases from the literature for whom biological parameters were described. Cases with incomplete data were excluded.
Results: Hodgkin's disease (HD) was more common in the 18–59 age group while breast and prostate cancers were prevalent only in the ≥18-year-old patients. The time interval to develop sALL was similar among all age groups but was significantly longer for HD and neuroblastoma primary diagnoses and sALL with complex karyotype. T-cell immunophenotype was more common in the <18 age group. Complete remission was infrequent in the ≥60 age group. The overall survival was poor for all sALL regardless of age, primary diagnoses, cytogenetic subgroups, or immunophenotype. Allogeneic transplantation most probably represents the only chance of cure.
Conclusion: Better identification of prognostic factors to prevent the occurrence of sALL is indicated.
Key words: acute lymphoblastic leukemia, 11q23 aberrations, secondary neoplasms

introduction

Secondary acute lymphoblastic leukemia (sALL), defined as ALL following another malignancy, irrespective of whether patients received prior therapy, is a rare disease. While therapy-related acute myeloid leukemia (AML), or secondary AML, is a well-recognized entity accepted by the World and Health Organization [1], therapy related or sALL is not, most probably due to the rarity of this disorder. The Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Archive of Adult Acute Leukemia from 62 Hematologic Divisions reported the occurrence of sALL in 21 of 901 (2.3%) cases of ALL [2] aged 15–94 years in association with older age and a high prevalence of pre-B-cell immunophenotype. Similarly, Burkitt-type sALL occurred at an older age when compared with *de novo* Burkitt disease [3]. We encountered seven cases of adult sALL at Roswell Park Cancer Institute, Buffalo, NY, from 1992 to 2007 out of 213 (3.3%) cases diagnosed from 1983 to 2007. Since most of the literature on sALL consists of single case reports or small series with no comprehensive large-scale review, we examined the English literature on all sALL cases between the years 1982–2005 with reported biologic features. Based on the GIMEMA report [2] claiming an association of sALL with older age, we hypothesized that the biologic features of patients with sALL would differ according to age at the time of primary malignancy.

patients and methods

We present data on seven sALL patients diagnosed at Roswell Park Cancer Institute, Buffalo, NY, in addition to 94 sALL cases described previously (please see supplemental material, available online, for the references) on whom biologic features were reported. Cases with incomplete data were excluded. Patients were grouped according to age at the time of primary malignancy: <18, 18–59, and ≥60 years old. We recorded patient gender, primary malignancy diagnosis and treatment, time interval from primary malignancy to sALL, sALL karyotype (by specific abnormalities since most reports lacked full karyotype presentations) and immunophenotype, treatment of sALL (including allogeneic transplantation if applicable), achievement of complete remission for sALL, and overall survival. For Burkitt diagnoses, we used either the morphological classification or the presence of *myc* rearrangement, as reported. No censoring for allogeneic transplant was carried out.

Statistical analysis

Binary variables were summarized through the calculation of simple proportions. Fisher's exact test was used to study the association between categorical variables and age groups. Analysis of variance was utilized to test for difference in continuous variables. Estimation of the overall survival distributions was done using the Kaplan–Meier method. Using this distributed estimate, summary descriptive statistics such as the median survival was obtained. Statistical assessment of observed differences in the survival distributions of age groups was done using the log-rank test. A 0.05

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nominal significance level was used in all testing. All statistical analyses were carried out using SAS (version 9.1).

results and discussion

patient characteristics

As shown in Table 1, there was no significant difference in gender among the different age groups. As expected [4], there was male preponderance in the sALL cases presenting with Burkitt disease. The distribution of the primary diagnoses among the three age groups was as expected: neuroblastoma was seen only in patients <18 years old, Hodgkin's disease (HD) was more common in the 18–59 year old cohort, and breast and prostate cancers were detected only in the ≥18 age groups. There was no significant difference in the frequency of breast and prostate cancers between patients aged 18–59 and ≥60 years old. AML was detected only in patients <60 years old. Twelve patients underwent only surgical treatment for their primary malignancies.

The time interval to the development of sALL was not different among the three age groups. However, the time interval to develop sALL was longer for HD than AML, breast, or prostate cancers ($P < 0.01$; Figure 1A). Moreover, the time interval to develop sALL following neuroblastoma was significantly longer than the time interval to develop sALL following AML ($P < 0.04$). Of special interest are the patients who developed sALL after prior AML. The median time interval to develop sALL in this patient population was 1 year (range 0.8–9 years). The presentation differed by immunophenotype alone in four cases and by immunophenotype and karyotype in two cases. This suggests the presence of two clones at diagnosis with eradication of one clone by chemotherapy, allowing the expansion of the other clone [5]. Another possibility is the development of the leukemia at a more undifferentiated stem-cell level. Similar questions were recently raised in cases of sALL following ALL treatment [6]. Finally, the time interval to develop sALL was significantly longer for patients with sALL characterized by complex karyotype than sALL with all other aberrations (Figure 1B).

The disease characteristics of the 101 patients were as follows: T-cell ALL was more prevalent among patients <18 than among patients ≥18 years old. Burkitt disease subtype, sALL with cytogenetic aberrations involving 11q23, t(9;22), complex, or normal karyotype were not significantly different among the different age groups. However, aberrations involving 11q23 were more commonly detected when compared with other abnormalities. Eleven of the 37 (30%) patients with 11q23 aberrations had breast cancer as their primary diagnosis; four (11%) had HD, four (11%) had testicular cancer, three (8%) had neuroblastoma, and three (8%) had osteosarcoma. Only one or two cases were reported for the other diagnoses. Interestingly, two patients who presented with sALL with 11q23 aberrations received radiation therapy but not chemotherapy for their primary malignancies (one had breast cancer and the other had uterine cancer). A total of 15 (41%) patients received anthracycline-containing regimens, 11 (30%) received etoposide-containing regimens, and eight (22%) received combination of both (data were not reported on the type of chemotherapy administered to one patient) for their primary malignancies. In summary, most of the patients (94%) with sALL and 11q23 aberrations were treated with topoisomerase II

Table 1. Patient characteristics by age groups

Variable	Sample size	<18	18–59	≥60	*P*
Gender	101	29	54	18	
Female	46	10 (34%)	28 (52%)	8 (44%)	0.311
Male	55	19 (66%)	26 (48%)	10 (56%)	
Primary diagnosis[a]	101	29	54	18	
Hodgkin's disease	20	4 (14%)	15 (28%)	1 (6%)	0.084
Breast cancer	17	0	14 (26%)	3 (17%)	0.003
Acute myeloid leukemia	6	3 (10%)	3 (6%)	0	0.392
Prostate cancer	5	0	1 (2%)	4 (22%)	0.005
Neuroblastoma	5	5 (17%)	0	0	0.003
Time to development of sALL (in years; median)	97	3	2.2	1.8	0.561
Range		0.25–20	0.5–16	0.3–14	
Immunophenotype	76	21	41	14	
B cell	64	14 (67%)	37 (70%)	13 (87%)	0.386
T cell	12	7 (33%)	4 (8%)	1 (7%)	0.016
Burkitt disease	12	1 (7%)	7 (19%)	4 (27%)	0.394
Karyotype[a]	87	25	48	14	
11q23	37	11 (44%)	23 (49%)	3 (21%)	0.200
Normal	19	6 (24%)	8 (17%)	5 (36%)	0.271
Complex[b]	12	2 (8%)	8 (17%)	2 (14%)	0.635
t(9;22)	11	6 (24%)	3 (6%)	2 (14%)	0.073

[a]Displayed in this table are those karyotypes for whom at least five cases were reported among the 101 patients.
[b]Complex karyotype was defined as three or more aberrations, excluding those with an established translocation.

inhibitors [7]. These data are similar to the data on secondary acute myeloid leukemia (sAML) with 11q23 aberrations [8].

Only 72 of 101 (71%) sALL patients were offered therapy (Table 2). The complete remission rate was dismal among the ≥60 cohort and only 25% of those <60 underwent allogeneic stem-cell transplantation. However, these differences did not result in a better overall survival among the three age groups. There was no significant correlation between the different primary diagnoses and patient outcome following sALL treatment. Analyses carried out including or excluding the 12 patients who received only surgical treatment for their primary malignancies did not affect overall outcomes. Most patients succumb to their sALL (Table 2). Examination of the clinical characteristics of the five patients surviving >2 years after sALL diagnosis demonstrated no significant common factors predictive of improved response (Table 3). Two of four surviving patients (one not reported) underwent allogeneic transplantation to suggest that allogeneic transplantation most probably represents the only chance of cure.

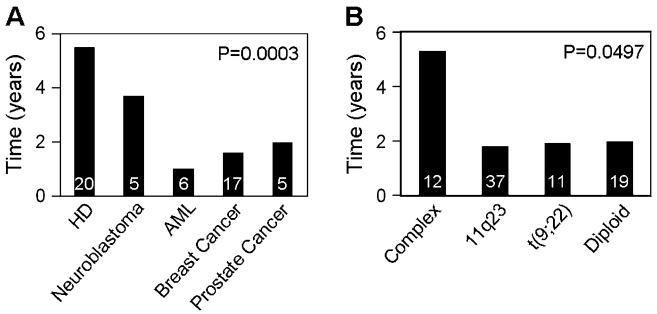

Figure 1. The relationship between median time interval and (A) primary diagnosis and (B) karyotype in secondary acute lymphoblastic leukemia. The numbers on the columns represent number of patients per cohort. The *P* value in panel A represents an overall *P* value; for individual *P* values please refer to the text. AML, acute myeloid leukemia; HD, Hodgkin's disease.

Our finding that 12 sALL patients received only surgical management for their primary malignancies without exposure to chemotherapy or radiation may suggest that the occurrence of the two malignancies was either unrelated or that common genetic mechanisms underlie the development of both primary cancers and sALL in some patients [for example, Li-Fraumeni syndrome [9]]. Recent studies showing that loss of tumor suppressor genes at the 11q23 chromosomal regions can contribute to ovarian [10] and breast [11–13] cancer development suggest that alteration of tumor suppressor genes at this specific breakpoint region in different cells may predispose the cells to both solid and hematological cancers.

Our comprehensive review of the literature and our own institute experience with sALL describes the unique biologic features of sALL as compared with *de novo* ALL. Of note are the increased frequency of 11q23 aberrations in all age groups (42.5% in sALL versus 6% in children [14] and 17% in adults with *de novo* ALL [15]), the increased frequency of t(9;22) in the <18 age group (24% in sALL versus 2.3% in *de novo* ALL [16]), and its decreased frequency in the ≥60 age group (14% in sALL versus 35% to 50% in *de novo* ALL [17]).

Table 2. Treatment outcome among the three age groups

Variable	Sample size	<18	18–59	≥60	*P*
Treatment for sALL	72	24 (83%)	32 (59%)	16 (89%)	**0.015**
CR (%)[a]	40	17 (74%)	21 (68%)	2 (22%)	**0.025**
SCT (%)[a]	14	8 (33%)	6 (19%)	0	0.102
OS (in months, median)	61	7.5	6	6.5	0.794
Cause of death[a]		17	20	7	
sALL	34	12 (70%)	15 (75%)	7 (100%)	0.3595
Primary diagnosis	1	1 (6%)	0	0	0.5455
Treatment related	8	3 (18%)	5 (25%)	0	0.4444
MVA	1	1 (6%)	0	0	0.5455

[a]Of the patients on whom data were available.
sALL, secondary acute lymphoblastic leukemia; CR, complete remission; SCT, allogeneic stem-cell transplant; OS, overall survival; MVA, motor vehicle accident.

Table 3. Characteristics of patients surviving beyond 2 years

Age at primary diagnosis (in years)	Primary diagnosis	Time to development of sALL (in years)	Prior chemo/ radiotherapy	Immunophenotype	Karyotype	SCT	OS (in months)
0.25	Neuroblastoma	1.9	Yes	B	11q23	No	36
9	AML	9	Yes	B	46,XX	Yes	144
22	Ewing's sarcoma	16	Yes	B	Complex	Yes	26
59	Breast cancer	2	Yes	B	11q23	NR	54
60	Prostate cancer	0.33	No	Burkitt	46,XX	No	45

sALL, secondary acute lymphoblastic leukemia; SCT, allogeneic stem-cell transplant; OS, overall survival; AML, acute myeloid leukemia; NR, not reported.

The overall dismal outcome of patients with this disease regardless of treatment modality highlights the need for better understanding of the molecular and genetic variables underlying this disease. Possible variables include genetic polymorphism of detoxification enzymes, such as NAD(P)H:quinone oxidoreductase, glutathione *S*-transferases, and cytochrome P450 CYP3A; polymorphism in these genes was shown to be related to secondary leukemia [18]. Another variable may be the occurrence of germ line mutations in the *ATM* (ataxia-telangiectasia mutated) gene that were associated specifically with T-lineage ALL [19]. Analyzing these genes and others may help discover pathogenetic events in sALL.

Our data on the difference in time interval to develop sALL should be cautiously considered. Previous literature [20] reported a longer mean latent period (8.3 years) for development of any secondary malignancy (not exclusively leukemia) after HD than time to development of secondary malignancy after breast cancer (2.75 years) [21]. In contrast, Smith et al. [22] reported similar latent period to develop sAML after HD (5.2 years) and after breast cancer (5.4 years). These differences may be related to the number of patients studied; there were 75 patients with prior HD and 30 patients with prior breast cancer in the report by Smith et al. Because of the rarity of sALL, our results presented here on 101 sALL patients are unlikely to change in the near future pending accumulation of a larger study cohort.

A short latent period associated with 11q23 aberrations has been previously described for sAML [8] but not for sALL. Similarly, a long latent period for disease associated with complex karyotype, especially involving the whole or parts of chromosomes 5 and/or 7, has been described for sAML [8]. Therefore, the longer latent period associated with sALL with complex karyotype reported here mimics the data on sAML, though chromosomes 5 and 7 aberrations were rarely detected in the sALL patients. The shorter time interval associated with normal karyotype sALL should be considered with caution since attaining good-quality metaphase cells in ALL is often suboptimal and cryptic aberrations may have not been identified in all patient samples.

Comparing the outcome of sALL patients by cytogenetic groups with the recent Medical Research Council/Eastern Cooperative Oncology Group ALL trial [23] shows that no sALL patients with 11q23 survived 5 years as compared with 24% and 33% 5-year survival for *de novo* ALL patients with t(4;11) and for those with other 11q23 aberrations. Similarly, only one of 11 (9%) treated sALL patients with diploid karyotype survived beyond 5 years as compared with 48% of *de novo* ALL patients. This poor outcome for sALL is similar to that reported for sAML patients [24]. Therefore, identification of prognostic factors, especially genetic biomarkers, predictive of sALL in patients with primary malignancies should be pursued in order to prevent the occurrence of this disease.

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