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Lymphoblastic Lymphoma in Adults: a Clinicopathological Study of 34 Cases Treated at the Institut Gustave-Roussy

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Abstract—*We report a series of 34 adult patients with lymphoblastic lymphoma treated at our Institute between 1977 and 1986. At presentation, mediastinal involvement was seen in 76%, extranodal involvement (not including bone marrow) in 20%, stage IV in 53% and circulating blasts in 15%. In the 15 cases where immunological studies were performed, 12 proved to be of T type and the other three lacked both T and B markers. Chemotherapy with acute lymphocytic leukemia (ALL) protocols was given to 58% and lymphoma protocols to the other patients, with CNS prophylaxis given to a total of 28 patients. Although complete remission (CR) was observed overall in 74% of patients, 5 year survival was only 22% (42% in stages I–II and 8% stages III–IV) with improved results seen with recent aggressive anti-leukemic protocols. Five relapsed patients entered second CR and two were still in CR at this time. CNS relapse occurred in a total of eight patients (three without prophylaxis), and was isolated in two of six patients who achieved CR (despite CNS prophylaxis). In an analysis of prognostic factors, only the attainment of a CR was statistically significant ($P < 0.001$). Thus we are unable to confirm other studies which demonstrated prognostic variations in this disease and believe that all such patients should receive aggressive chemotherapy with substantial CNS prophylaxis similar to those currently used for ALL.*

INTRODUCTION

STERNBERG was the first to report a case of mediastinal lymphoma which terminated in acute leukemia [1]. Subsequently, the clinical features of these patients [2] and immunological characteristics of similar cases were described with the suggestion that this lymphoma originated from thymic lymphocytes [3]. The term 'convoluted lymphoblastic lymphoma' was first used by Barcos and Lukes [4]. However, as nuclear convolutions were not apparent in all cases, and hence helpful but not essential to the diagnosis, the term lymphoblastic lymphoma (LBL) was proposed by Nathwani *et al.* [5].

LBL is a distinct clinical entity [4–6] included in the high-grade category of the Working Formulation for non-Hodgkin's lymphoma (NHL) [7]. It accounts for as many as one-third of NHL in childhood, and 3–5% of NHL in adults [5, 8, 9]. It is an aggressive disease commonly occurring in adolescents and young adults with a marked male preponderance [5]. Many patients have a mediastinal mass, and respiratory distress from tracheal compression and superior vena cava syndrome (SVCS) are commonly associated complications that require prompt diagnosis and institution of therapy. Although LBL may be localized at diagnosis, there is usually rapid progression to a leukemic phase and/or central nervous system (CNS) involvement [5, 10–15]. In the characteristic dissemination of the disease to the bone marrow with evolution to an overt leukemic phase, the disease is indistinguishable morphologically from T-cell acute lymphoblastic leukemia (ALL) [5, 7, 9, 16, 17]. Therefore, LBL is considered to be the lymphomatous counterpart of an unfavorable form of ALL. Despite multimodality therapy [9, 17, 18], prognosis has been poor in adults treated for LBL, with the most promising approach appearing to be the application of intensive CT regimens designed for the treatment of cases of poor prognostic childhood ALL [9]. With this aggressive chemotherapeutic approach including prophylactic CNS therapy, a remarkable improvement has been noted in the overall prognosis of this disease [19–21]. We report

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here our experience with 34 adult patients with LBL treated at the Institut Gustave-Roussy (IGR) between 1977–1986.

PATIENTS AND METHODS

Records from January 1977 to December 1986 of IGR were reviewed for detection of all cases diagnosed as LBL over 16 years of age. This retrospective study initially detected 44 patients, but after histological re-evaluation, only 34 patients were still diagnosed as having had LBL. The remaining 10 patients on review were considered to have had other subtypes of aggressive NHL.

Age and sex distribution

There were 28 males (82%) and six females with an age range of 16–56 years (mean 24). The median age of males was 20 years and females 23.

Clinical features

a. *Symptoms and performance status.* B symptoms, including fever ≥38.5°C and/or weight loss or night sweats were present in 12/34 patients (35%). Pretreatment performance status evaluated according to the Karnofsky scale [22] was >50 in 18 patients (53%).

b. *Mediastinal involvement.* Twenty-six patients (76%) had initial mediastinal involvement, 20 males and six females. The median age of this group was 21 years. Symptoms and signs of SVCS were observed in 12 (35%) patients (10 male and two female). The delay between the appearance of the first sign and diagnosis was on average less than 3–4 weeks. One patient presenting with SVCS required mechanical ventilation for 3 days during induction chemotherapy (CT), the only patient requiring special assistance.

c. *Peripheral lymphadenopathy–hepatosplenomegaly.* Supradiaphragmatic peripheral lymphadenopathy was seen in 23/34 (68%) patients, and in 4/34 (12%) inguinal adenopathy was the presenting complaint. However, on evaluation, there were no cases of isolated inguinal lymphadenopathy found without supradiaphragmatic disease. Splenomegaly was found on palpation in eight cases (24%) and hepatomegaly in seven (21%).

d. *Extranodal and CNS involvement* (n = 7). Two patients presented with testicular involvement, two with breast localization, one with isolated skin, two with initial CNS involvement (in one the CNS was the only site of disease, originating in the meninges with local extension to the fronto-parietal bone).

e. *Clinical staging.* Chest X-ray, ultrasound or abdominal C.T. scans were performed in all patients, with chest C.T. scans performed in several. All patients underwent an iliac bone marrow biopsy, and in 14 (41%) there was initial bone marrow (BM) involvement, with five patients leukemic at presentation (WBC <50,000/mm^3). Exploratory lumbar puncture at the time of diagnosis was performed in all but three patients. Two of these were misdiagnosed originally, and the third was stage I. Clinical staging according to Ann Arbor criteria [23] was:

Stage I:	three patients	(9%)
Stage II:	12 patients	(35%)
Stage III:	one patient	(3%)
Stage IV:	18 patients	(53%)

Laboratory findings

There were no cases of severe anemia (<10 g/dl) or thrombocytopenia (<100,000/mm^3) at presentation. Initial circulating lymphoblasts were noted in five of 34 patients (15%).

Erythrocyte sedimentation rate (ESR) was above 30 mm (Westergren, 1 h) in eight cases (24%), normal in 25 cases and not performed in one patient. In 11 cases where the LDH level was determined, six had >450 IU (normal <450).

Histopathological findings

All biopsy specimens were reviewed by two of the authors (B.C. and C.B.). Of the 44 cases initially classified as LBL, only 34 were re-classified as such on review, according to the criteria of Nathwani *et al.* [5]. All 34 cases had a diffuse histological pattern. Neoplastic lymphoid cells were small to medium-sized with scanty cytoplasm. The cell borders were not well defined. Numerous mitotic figures were seen and the chromatin was finely stippled in most cells. Eighteen of 34 (53%) had convoluted and 16 non-convoluted nuclei. Convolutions were sometimes difficult to distinguish, particularly when histological sections were of poor quality.

Immunological studies

Immunological cell surface markers were studied by monoclonal antibodies (MoAb) in 15 cases. In 12 of these, the lymphoblasts were of T-cell type with the phenotypes generally reflecting an immature' or incompletely differentiated T-cell phenotype. In the other three patients, the cells lacked both B- and T-cell characteristics but were indistinguishable morphologically from the T-cell cases. No malignant cell reacted with any MoAb specific for B-cells or for surface immunoglobulin (SIg).

Therapy

While treatments varied over the period of study, three principal categories of initial therapy were administered:

1. CHOP or CHOP-like regimen [24]: 10 patients (30%)
2. Poor prognosis ALL-like regimen
   LAL 83 [25]: seven patients (21%)
   LAL 85: seven patients (21%)
3. Other ALL-like (six patients) or NHL-like treatment (two patients).

All but two patients received initial combination CT. One received mediastinal irradiation (false diagnosis of malignant thymoma), and the second was irradiated for an isolated cutaneous mass of the fronto-parietal area (with initial unclear diagnosis).

Therefore, 20 patients were treated with an ALL-like regimen and 14 patients with NHL-like treatment. Two patients initially treated with radiation due to incorrect diagnosis were considered as starting therapy only upon relapse.

CNS prophylaxis was given in all but six patients. Eleven received intrathecal CT plus cranial irradiation, 14 intrathecal CT without subsequent cranial RT, and one patient received RT alone. The two patients with initial CNS infiltration received cranial RT plus intrathecal CT.

Except for one patient (false diagosis of malignant thymoma), none of the other 33 patients received mediastinal irradiation for initial respiratory distress or SVCS. One patient with localized disease in the tonsil (staged IE) received complementary RT to the initial site of disease after CHOP.

Eleven patients underwent bone marrow transplantation (BMT) as consolidation therapy after intensive CT plus total body irradiation, eight allogeneic and three autologous. Seven patients underwent BMT in first complete remission (CR) and four patients in second CR.

Statistical analysis

Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. All tests given were two-tailed.

Initial characteristics, histological features, type of treatment and response to treatment were each separated into two or three groups that were assessed in relation to freedom from relapse and overall survival. Only one dividing threshold for each measure was tested for significance. The difference between actuarial curves was assessed with the log-rank test ($P < 0.05$ was considered significant).

Patients were analyzed as of October 1987.

RESULTS

The 5 year overall survival for the whole group was 22% (Fig. 1), 21% in males and 17% in females. Disease-free survival was 30%. Stage I–II patients had a better survival than stage III–IV patients, 42% vs. 8% respectively, but this was not statistically significant. While six of 10 patients treated with a CHOP-like regimen achieved a CR, this was

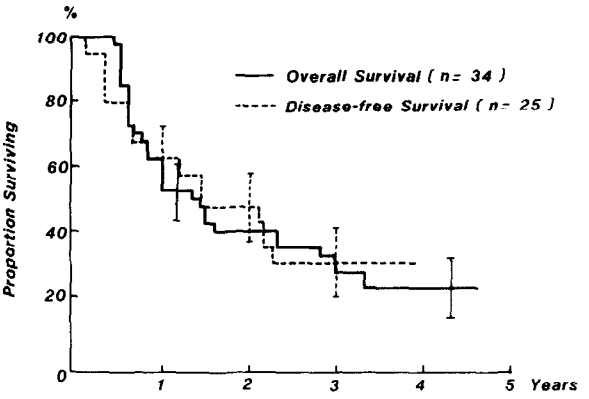

Fig. 1. Disease-free and overall survival.

of short duration, except for the two patients with stage I disease. However, for the 14 patients treated with recent protocols for adult ALL (LAL 83 and LAL 85), the CR rate was 72%. Although this is similar to the earlier protocols, none of the recent patients had stage I disease, and eight of 14 were stage IV with BM disease at the time of initial diagnosis. Twenty-five of 34 patients (74%) were in CR at the end of induction therapy. Six patients had a partial response (PR) of short duration and three patients had progressive disease (PD). Pathological CR was documented in all cases with BM involvement. Fifteen of the 25 patients who achieved CR have subsequently relapsed. Table 1 shows the sites of relapse. The median interval between initial therapy and relapse was 6 months (1–27). Patients who relapsed were treated with alternate CT of which 10 had only transient responses and five achieved a second CR.

Two of the above five patients were in a second CR 8 and 21 months respectively. One of the remaining surviving patients had isolated initial CNS disease and relapsed with disease in the BM. The other underwent an allogenic BMT and developed a melanoma (Clark level II) 14 months after initial diagnosis of LBL. The other three patients died due to therapy complications (Lyell syndrome secondary to Trimethoprim-sulfametoxazole, veno-occlusive disease of the liver, and septic shock). Table 2 shows the main characteristics of the 10 patients who were still alive and in CR. All but one, who presented with isolated CNS disease, were off therapy. Overall, 24 patients in this series have died, including the nine patients with initial PR or PD, and two patients who died in first CR secondary to therapy complications (acute graft vs. host disease).

Leukemic progression was seen in eight patients: two were already leukemic at presentation, two had had positive BM aspirations/biopsies at presentation, and four had had negative BM studies at initial evaluation.

Table 1. Principal characteristics of relapsed patients (15 patients)

Initial involved sites	Treatment	CNS prophylaxis	Site of relapse	Time to relapse (months)
BM, M	NHL-1	CI	CNS, RPL	27
BM, M, T	ALL-1	it CT + CI	CNS	26
Skin	RT	—	BM, B, CNS	25
SDL	ALL-1	it CT + CI	BM, B	17
CNS	NHL-1	Initial CNS disease	BM, B	17*
M, M, SDL	ALL-1	it CT	CNS	8
M, T, Skin	NHL-1	—	CNS, Skin	7
BM, B, M, SDL, liver, spleen	NHL-1	it CT	BM, B, M, SDL	7
BM, SDL	NHL-1	it CT	BM, B, SDL	4
BM, M, SDL	ALL-1	it CT	BM, B, CNS, M	4
M, liver	NHL-1	it CT	BM, SDL	4
BM, B, M, SDL	ALL-1	it CT	BM, B	4*
M	RT	— —	BM, SDL, B	3
BM, M, SDL	ALL-1	it CT + CI	BM, SDL	2

BM: Bone marrow; B: blood; M: mediastinum; T: testis; SDL: supra diaphragmatic lymphadenopathy; RPL: retroperitoneal lymphadenopathy; ALL-1: ALL-like protocol; NHL-1: NHL-like protocol; CI: cranial irradiation; it CT:intrathecal chemotherapy; RT: radiotherapy.
*Alive in second CR.

Table 2. Principal features of patients in CR (10 patients)

Stage	Treatment	CNS prophylaxis	BMT	Survival (months)
IV	ALL-1	it CT + CI	—	63+
II	ALL-1	it CT + CI	—	48+
I	NHL-1	—	—	45+
II	ALL-I	it CT + CI	—	40+
I	NHL-1	—	—	39+
IV	ALL-1	it CT	Allogeneic	27+*
I	ALL-1	it CT	—	25+
II	NHL-1	it CT + CI	Autologous	24+
IV	NHL-1	Initial CNS disease	—	23+*
IV	ALL-1	it CT	Allogeneic	11+

ALL-1: ALL-like protocol; NHL-1: NHL-like protocol; it CT: intrathecal CT; CI: cranial irradiation; BMT: bone marrow transplantation.
*In second CR.

Two of 34 patients presenting with initial CNS disease received cranial irradiation and intrathecal CT. One had isolated CNS disease and the other disseminated disease including bone marrow and breast involvement. CNS relapse was isolated without bone marrow relapse in four of six patients who achieved CR. One of these patients, who had initial testicular involvement, presented isolated CNS relapse in spite of adequate CNS prophylaxis with cranial irradiation and intrathecal CT. Both patients with initial testicular localization ultimately relapsed in the CNS. There were eight CNS relapses, three in patients who received no CNS prophylaxis, two intrathecal CT, one radiation and two CT and radiation.

None of the clinical and laboratory pretreatment parameters (Table 3) analyzed for prognostic significance with respect to survival and duration of CR were statistically significant at the 0.05 level. Response to therapy was the sole important survival determinant. Thus patients with a CR had a significantly improved survival ($P < 0.001$). There were no significant survival differences noted among the three major different protocols used (CHOP, LAL, 83 and 85). The 5 year survival rates for patients initially treated with an ALL-like protocol

Table 3. Univariate analysis of patient characteristics

	P value	
	Relapse	Survival
Age ≤20/>20 (years)	0.30	0.39
Sex	0.83	0.27
Karnofsky scale <50%/≥50%	0.26	0.10
B symptoms	0.62	0.63
Mediastinal mass	0.25	0.14
Sup. vena cava syndrome	0.99	0.91
Bone marrow disease	0.29	0.18
Initial leukemic disease	0.44	0.81
Stage I–II/III–IV	0.12	0.11
Convoluted nuclei	0.61	0.88
CR/PR and PD	<0.001	<0.001

CR: Complete remission; PR: partial remission; PD: progressive disease.

(n = 20) and those treated with an NHL-like protocol (n = 14) were 22% and 18% respectively.

DISCUSSION

LBL is a distinct clinicopathological entity histologically and cytologically similar to ALL [26] that typically presents in older children and adolescents with a high male to female ratio [4, 17, 19, 20, 27, 28]. Mediastinal mass is frequent at the time of diagnosis [4, 9, 17, 20, 21, 29, 30]. Although the disease may appear localized, there is usually rapid progression to a leukemic phase and/or CNS involvement.

Recent publications have emphasized that this disease also occurs in adults with similar characteristics as in childhood disease [19, 21]. Our study of adult LBL confirms the male preponderance and the high frequency of mediastinal mass. There was a 41% initial bone marrow involvement with five of 34 patients demonstrating circulating blasts. Seven patients presented with extra nodal localization at the time of initial diagnosis. The evolution of these patients was similar to nodal presentation, with a high propensity to disseminate.

Nathwani *et al.* [17] suggested that young patients (<30 years) appear to have both a higher frequency of mediastinal disease as well as a greater incidence of leukemic conversion than do older patients. While none of our seven patients older than 30 years presented with leukemia, five of seven had a mediastinal mass at diagnosis. There were no specific morphological or immunological differences between patients with or without mediastinal involvement either in our series or others [31].

As already described, ALL and LBL cannot be distingished morphologically, both appear histologically like lymphoblasts. The identification of convoluted nuclei is a helpful feature but is absent in about 50% of reported cases [5], identical to our series. No differences of clinical presentation, leukemic presentation, content of terminal deoxynucleotidyl transferase (TdT), acid phosphatase staining, immunological characteristics and prognosis have been seen between convoluted and non-convoluted nuclear groups of LBL [5, 30, 32].

Although immunological studies confirm the predominant T-cell origin of this disease [3, 8, 9, 33], it is clear that non-T LBL does occur [34, 35] and that these patients have several distinguishing clinical features. More recently, a case of LBL presenting monoclonal immunophenotypic characteristics of mature B-cells was reported [36], with morphology indistinguishable from the convoluted cell type. Thus, the occurrence of nuclear convolutions in the blasts of B, pre-B cell and non-T–non-B LBL shows the non-specificity of this morphological feature. Although morphologically homogeneous, LBL include immunologically diverse groups of neoplasms [35]. Bernard *et al.* [37] studied 25 cases of LBL and demonstrated that although all of them had some T-cell marker, phenotypically they were quite heterogeneous. A correlation has also been observed between differentiation of malignant T-cell and leukemic conversion [38]. Also, tumor cells from most LBL possess a surface antigen characteristic of the cytotoxic and suppressor cell subpopulation of normal peripheral blood T-cells, whereas only 20% of T-cell ALL display this antigen [39]. In our 15 cases where immunological studies were performed, the lymphoblasts were of T-cell origin in 12 cases and non-T–non-B in the three other cases.

It appears that the existence of LBL with common ALL phenotype is rare [40]. The enzyme TdT has been found in almost all the cases studied [35, 36, 41–43], similar in convoluted and non-convoluted type [30]. No specific chromosomal pattern in LBL has been discovered [44].

Given the unusual occurrence of adult LBL, few therapy series have been reported. Most reports deal exclusively with children or with all age groups.

Long-term survivors among adults were unusual [9, 17, 18, 45] before the use of intensive and prolonged CT [16, 19, 21, 46, 47]. With first and second generation CT used for unfavorable diffuse lymphoma, these patients achieve low CR rates with poor survival [9, 18, 48], and have only started to show prolonged responses since the utilization of intensive ALL-like protocols [10, 19, 20, 28, 49]. In particular, like ALL, it appears that CNS prophylaxis is an important addition to the therapy of these diseases [21]. Newer drug combinations may also open new avenues in therapy [50]. The use of bone marrow transplantation in this disease remains to be defined, particularly in patients with definable high risk of relapse.

The clinicopathological features of our reported population with adult LBL are comparable to other studies. However, the CR rate, the median survival, the overall survival and DFS are not as good as those reported in the more recent studies. This is likely due to our use of less intensive, short and inadequate CT in the earlier patients of this series.

The role of RT, except as an adjunct to CNS prophylaxis, is questionable, since isolated relapse in previously involved sites is unusual [16]. In addition, mediastinal RT administered with the intensive anthracycline-based regimens currently used is likely to produce significant morbidity. None of our patients relapsed either with isolated mediastinal mass or with previously involved lymph nodes, supporting this concept in adults, similar to results from pediatric trials [21]. Therefore, RT should be reserved for the emergency treatment of acute airway compromise, major SVCS or in cases of isolated incomplete response to induction CT.

While it is clear now that early CNS prophylaxis is required with regimens resembling those used for childhood ALL, the optimal method is difficult to determine, with few randomized studies available. High-dose i.v. methotrexate (MTX) does cross the blood–brain barrier to produce therapeutic levels. The experience of the IGR pediatric group in childhood LBL has been that CNS relapse is very low when prophylaxis is given with high dose i.v. (3 g/m^2) and combined intrathecal MTX without cranial irradiation [51].

Patients with high grade testicular lymphoma have a high rate of CNS relapse [52]. Although equal success has been reported in ALL with intrathecal CT or cranial RT plus intrathecal MTX [53], probably a combination of the two is advisable for adults with LBL, and in particular those especially at high risk such as testicular involvement.

Two recent studies with a relatively large number of adults treated for LBL have been reported. One study analyzed 51 patients treated with five successive intensive CT protocols for ALL [20]. Thirty-one patients (61%) presented with leukemia. Poor prognostic factors in this study were age older than 30, WBC >50,000/mm^3, failure to achieve CR and late CR during induction. The presence of leukemia at presentation, mediastinal mass or T-cell surface markers did not adversely affect survival.

The other study was composed of a relatively large, homogeneously treated series of adults with LBL [16]. Forty-four patients were treated with two protocols differing by the timing of CNS prophylaxis. CR was achieved in 95% of patients, with 56% DFS at 3 years. More intensive treatment was recommended for high-risk patients (in that study, stage IV BM or CNS disease, or initial elevated serum LDH level). DFS of low and high-risk groups at 5 years were 95% and 19% respectively.

In contrast, we were not able to identify any clinical or pathological factor that might predict response to therapy or eventual relapse. The initial response to therapy was the sole important determinant for survival, with patients achieving CR having a significantly improved survival. Since our initial therapy was possibly less effective than newer regimens and hence more likely to identify prognostic factors, we believe that the question of prognostic factors in this disease remains to be clarified.

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