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# BURKITT'S LIKE LYMPHOMA IN PATIENTS WITH AND WITHOUT HIV INFECTION

## A report of 33 patients from north-east Italy

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**With the aim of comparing the clinical features of Burkitt's like lymphoma (BL) in HIV-infected patients and in the general population, we retrospectively analyzed 35 patients with HIV-positive non-Hodgkin's lymphoma (NHL) and 535 patients with HIV-negative NHL, from 1985 to 1990. A total of 33 patients with BL were diagnosed at our institute: 18 without and 15 with HIV infection; 3.3% and 43% of all HIV-seronegative and HIV-seropositive NHL respectively. No significant differences were found between these two series concerning clinical features, with the exception of peripheral adenopathy that was more common in the HIV infected patients ($p = 0.05$). In both groups BL was characterized by advanced stage and high incidence of bone marrow and gastrointestinal involvement. Response rate was lower in the HIV-positive patients, but the difference was not significant. No relevant differences in the toxicity after chemotherapy were observed. The median survival in the HIV-infected patients was lower (7 months) than in the other group (14 months), with borderline statistical significance ($p = 0.06$).**

Burkitt's lymphoma is a malignant B-cell high-grade non-Hodgkin's lymphoma (NHL) and a rapidly growing tumor most common among children. In the International Working Formulation it is recognized as small, non-cleaved diffuse high-grade lymphoma, a group which is subclassified as 'Burkitt's' when the case satisfies the morphologic criteria for Burkitt's lymphoma published by the WHO (1969), and as 'non-Burkitt's' when the pattern shows a greater cell and nuclear pleomorphism. The latter is probably identical with the so-called Burkitt's like lymphoma with plasmoblastic differentiation, identified by Lennert et al. (1988). Both these subsets are, however, classified as Burkitt's lymphoma according to the updated Kiel classification of NHL (1).

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Some investigators have defined clinico-pathologic features that distinguish Burkitt's lymphoma from non-Burkitt's lymphoma, but the importance of this distinction remains controversial. The clinical features may overlap considerably, the histologic distinctions can be subtle and unreliable and the two tumors may be ultrastructurally, cytochemically and immunologically indistinguishable. Therefore, it has been suggested to include these two entities into a common Burkitt's-like (BL) category (1–4).

BL occurs in Africa in the majority of cases in an endemic form and outside Africa in a sporadic form. The morphological cytological expressions of endemic and sporadic cases are very similar, in spite of clinical, immunological and virological differences (5).

Prior to the acquired immunodeficiency syndrome (AIDS) epidemic, BL was rare in the Western countries with only 30–40 new cases diagnosed in the United States per year, with a median age of 12 years (6). With the AIDS epidemic the incidence of BL in adults has greatly increased. In the USA BL now accounts for approximately one-third of the lymphomas seen in the AIDS population (7–8). In Europe, and particularly in Italy, there are some areas with

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relatively high incidence of sporadic BL (9–10). In these countries HIV-related BL accounts for c. 35% of the AIDS lymphomas (11–12).

Since both African and American BL occur most frequently in children, no large series composed of adult patients have been reported (3–4, 13). The present report summarizes the clinical features of 33 adult patients with BL, observed during the last five years in our institute.

## Material and Methods

From March 1985 through July 1990, 33 patients with Burkitt's like lymphomas, 18 without and 15 with HIV infection, were examined by the Division of Medical Oncology—AIDS Unit of the Centro Regionale di Riferimento Oncologico (CRO) of Aviano, Italy. During the same period, 535 patients with HIV-seronegative NHL and 35 patients with HIV-seropositive NHL were seen in the same division.

All pathologic specimens were classified by the Pathology Division at the CRO according to the histologic lymphoma classification of the Working Formulation for clinical use (13). The classification used was also related to the updated Kiel categories (1).

Routine staging procedures included hematologic and blood biochemistry studies, HIV serology, chest roentgenograms, computerized tomography of the abdomen and pelvis, and upper gastrointestinal radiography when indicated. Bone marrow biopsy and lumbar puncture were obtained before the initiation of therapy. Pleural effusions or ascites, if present, were aspirated for cytology. Subset and absolute numbers of CD4 and CD8 cells in the peripheral blood were determined in HIV infected patients. Stage for lymphoma was assigned according to Ann Arbor criteria (15). The criteria used to diagnose persistent generalized lymphadenopathy (PGL), AIDS-related complex (ARC) and AIDS were those defined by the CDC (16–17). HIV serology was performed by enzyme-linked immunoabsorbent assay and reconfirmed by Western blot (immunoblot). Complete remission (CR) was defined as complete disappearance of all evaluable lesions for at least one month; partial remission (PR) as more than 50% reduction of all evaluable lesions; and no response (NR) as stable disease or progression of the disease under treatment.

Survival was estimated according to the product-limit method of Kaplan-Meier (and distributional comparisons were made by the method of Mantel) (18–19). Significance tests for proportions were computed by means of $\chi^2$-tests (20), while for continuous variables the Mann-Whitney test were used (22).

## Results

Out of the 33 patients with Burkitt's like lymphoma 18 were HIV-negative and 15 HIV-positive, corresponding to 3.3% and 43% of all HIV-seronegative and HIV-seropositive NHL respectively. In the HIV-seropositive group the mean age was lower but the difference was not significant (29 yrs ± 5 vs 46 yrs ± 22, $p = 0.12$). The majority of patients in both groups were males. In the HIV-positive group, 9 were intravenous drug users (IVDU), 4 homosexual men, and 2 patients belonged to other risk groups (1 heterosexual, 1 homosexual male IVDU). At the diagnosis of BL, HIV infection was asymptomatic in 5/12 (42%) evaluable patients, whereas 4 (33%) has AIDS-related complex (ARC) and 3 (25%) CDC defined AIDS. In HIV-seropositive patients the median number of CD4 positive lymphocytes was 265/mm$^3$ (range 6–900), with 5/6 (56%) patients with CD4 count less than 200/mm$^3$. In HIV-seronegative patients the data were not available.

Comparisons between clinical features in the two groups are presented in Tables 1 and 2. Stage distributions in the 2 groups were pratically superimposable. Peripheral lymph node involvement was observed more frequently in the HIV-seropositive than in the HIV-seronegative patients ($p < 0.005$). No relevant differences in the distribution of extranodal localizations could be detected.

**Table 1**

*Stage distribution of Burkitt's like lymphoma in patients with and without HIV infection*

| Stage | HIV-negative (n = 18) | HIV-positive (n = 15) |
|---|---|---|
| I | 2*/18 (11%) | 2**/15 (13%) |
| II | 4/18 (22%) | 1/15 (7%) |
| III | 1/18 (22%) | – |
| IV | 11/18 (61%) | 12/15 (80%) |

* $I_E$ 2/2 (E = GI tract, testis).
** $I_E$ 1/2 (E = spleen).

**Table 2**

*Sites of involvement in Burkitt's like lymphoma with and without HIV infection*

| | HIV-negative (n = 18) | HIV-positive (n = 15) |
|---|---|---|
| Lymph nodes only | 0/18 | 2/15 (13%) |
| Peripheral lymph nodes with and without other sites | 6/18 (33%) | 11/15 (73%)* |
| GI tract | 10/18 (56%) | 4/15 (27%) |
| Bone marrow | 6/18 (33%) | 5/15 (33%) |
| Spleen | 3/18 (17%) | 4/15 (27%) |
| Liver | 1/18 (6%) | 4/15 (27%) |
| CNS | 3/18 (17%) | 1/15 (7%) |
| Omentum | 3/18 (17%) | 1/15 (7%) |
| Kidney | 1/18 (6%) | 3/15 (20%) |
| Other | 7**/18 (39%) | 8***/15 (53%) |

* $p < 0.05$.
** Waldeyer's ring 2, bladder 1, testis 1, bone 1, soft tissue 1, vagina 1.
*** breast 2, soft tissue 2, uterus-ovary 1, pancreas 1, skin 1, adrenal gland 1.

All 18 patients with HIV-seronegative BL were submitted to therapy: 8 patients received chemotherapy (CT) plus radiation therapy (RT), 5 patients CT alone, 3 patients combined surgery, CT and RT, 1 patient surgery alone and 1 patient surgery plus CT. Various combination chemotherapy regimens were used: Stanford's regimen (cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate high-dose and methotrexate intrathecally) in 7 patients, other intensive NHL's protocols including cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin, nitrogen mustard (CHOP, BEPP/CHOP, pro-MACE/MOPP) in 6 patients and a new combination of etoposide, mitoxantrone and prednimustine (VMP) in 2 elderly patients.

In the HIV-seropositive group, 14 patients were submitted to therapy, one patient could not receive any treatment because of rapid disease progression. Thirteen patients were treated with CT, one patient with surgery followed by CT. Five patients were treated with an Italian-French cooperation protocol (doxorobucin, cyclophosphamide, vindesine, bleomycin, prednisone, methotrexate, ifosfamide, etoposide, L-asparaginase and cytarabine), 4 patients with CHOP or CHOP-like regimens and further 4 patients with various multiagent chemotherapy regimens including doxorubicin or mitoxantrone. In 4 patients zidovudine was added to chemotherapy. Table 3 shows response to treatment and haematologic toxicity in the two groups. More complete remissions were observed in the HIV-serpositive patients, but no statistically significant differences between the two groups were seen. The incidence of WHO grade III and IV haematologic toxicity was similar in the two groups. Four (40%) out of 10 evaluable HIV-seropositive patients developed opportunistic infections during treatment or follow-up. The median survival for the patients with HIV-seronegative BL was 14 months and for the HIV-seropositive patients only 7 months (Figure), a difference with borderline statistical significance ($p = 0.06$). Mortality and causes of death in the two groups were comparable: the main cause was BL progression in all patients (Table 4).

**Table 3**

*Response to therapy and toxicity of patients with Burkitt's like lymphoma, with and without HIV infection*

| | HIV-negative | HIV-positive |
|---|---|---|
| Response | | |
| CR | 7/12 (58%) | 2/10 (20%) |
| PR | 3/12 (25%) | 5/10 (50%) |
| NR | 2/12 (17%) | 3/10 (30%) |
| Hematologic toxicity | | |
| G3* | 1/15 (7%) | 3/10 (30%) |
| G4* | 6/15 (40%) | 5/10 (50%) |

* according to WHO.

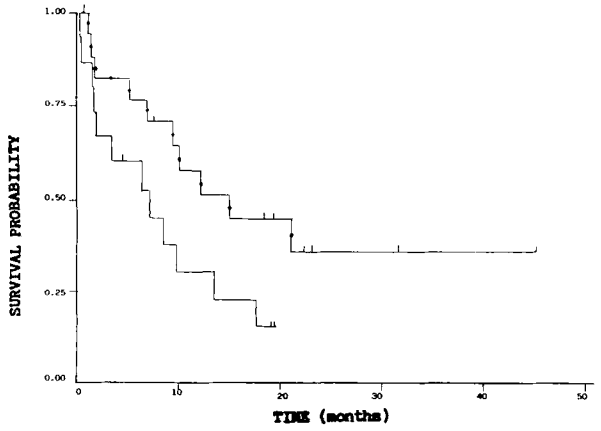


*Figure.* Actuarial survival of patients with Burkitt's like lymphoma with and without HIV infection. HIV-positive: ——; HIV-negative: —●—.

**Table 4**

*Mortality and cause of death of patients with Burkitt's like lymphoma, with and without HIV infection*

| | HIV-negative | HIV-positive |
|---|---|---|
| Mortality | 10/18 (56%) | 9/15 (60%) |
| Cause of death | | |
| NHL | 6/10 | 5/9 |
| Opportunistic infection | – | 3/9 |
| Toxicity | 1/10 | 1/9 |
| Unknown | 3/10 | – |

## Discussion

BL, a rapidily growing lymphoma, has been a rare tumor in the Western countries, but has largely increased in incidence with AIDS (6–8). The annual incidence of BL in endemic areas in Africa has been reported to be 2.2 to 3.8 cases/100.000 inhibitants, with a peak incidence at 4–8 years of age and a male/female ratio of 2/1. Initial clinical findings include jaw lesions (c. 60%), frequently associated with abdominal disease (c. 60%), involving the retroperitoneum, mesentary and omentum more often than the bowel itself (4–5). Kidneys, ovaries, pancreas, liver and adrenals are also frequently involved. Peripheral lymph node involvement is uncommon (< 1%). Bone marrow disease is initially present in 12% of the cases, and central nervous system (CNS) in 30% (4–5, 21). The annual incidence of sporadic BL in children below 16 years in Western countries is 20–40-fold lower than that in endemic regions (3, 10). General population-based data from 1970 revealed an overall annual incidence of 0.13 cases/100 000 in males and 0.03/100 000 in females (10). The most common presentation is abdominal disease (70%–90%), often gastrointestinal, followed by peripheral lymph node and bone marrow involvement (20% each). CNS infiltration occurs as meningeal infiltration or epidural

mass in 20%–30% of cases. Two-thirds of CNS cases are associated with bone marrow involvement. Jaw tumor is rare (7%–18%) (3–5, 10).

Data from literature show similar survival rates for endemic and sporadic BL; cure was obtained in 90% of localized and 35–60% of extensive BL (3–5). In our series, HIV-seronegative BL, which represented 3.3% of NHL seen at our center, included patients who were born and lived in a region of north-east Italy with a radius of 150 km. The median age was high, with 10 patients older than 40 years. The presenting sites of this HIV-seronegative series were typical of non-endemic areas, according to a previous study carried out between 1975 and 1982 (9).

HIV-positive BL represented 43% of HIV-related NHL seen at our institution. The higher prevalence of BL in this series than in national data (34%) reported by the Italian Cooperative Group on AIDS and Tumors (GICAT) is related to the difficulty in obtaining a correct initial diagnosis of BL (23). The frequency of a retrospective diagnosis of BL was high both in our series and in other series reported (9, 24). On the whole there were no striking differences between BL in HIV-positive and HIV-negative patients, concerning the clinical features. In both groups BL was characterized by advanced stage and high incidence of bone marrow and gastrointestinal tract involvement, a typical pattern of non-endemic BL.

Survival analysis showed a longer survival for the HIV-negative patients when compared with the other group (14 months vs 7 months), with a borderline statistical significance ($p<0.06$). Probably HIV-related immunodeficiency contributed to the poorer outcome of the HIV-positive patients. For these patients classical prognostic criteria as histology, tumor stage and response to therapy have to be supplemented by 'host' criteria, related to the immunological dysfunction and stage of HIV infection (25). In our series, age, HIV disease, and clinical characteristics of HIV-positive BL were similar to those of other HIV-related NHL (personal communication). These findings are in some disagreement with those of other retrospective cohort studies, where patients with small non-cleaved cell lymphoma showed a lower degree of immunodeficiency and better outcome and survival than patients with large cell immunoblastic lymphoma (26–27).

In conclusion, HIV-negative and HIV-positive BL show a clinical similarity with the 'sporadic' rather than the 'endemic' form of the disease. The main differences between BL in the two groups were a very common peripheral lymph node involvement and a poorer prognosis in HIV-infected patients.

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