PATHOLOGY ONCOLOGY RESEARCH
Vol 2, No 4, 1996

Science Press Publishing Ltd. TUDOMÁNY KIADÓ

SPECIAL REPORT

Current Management of AIDS Related Non Hodgkin's Lymphoma

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Non Hodgkin's lymphoma is the AIDS defining illness in 3-3.5% of patients and is increasing in incidence as the survival of HIV infected people improves. The incidence of these intermediate/high grade B cell malignancies is sixty times higher than in the general population. The most important prognostic factors are a CD4 positive lymphocyte count of <100 cells/mm^3, a prior AIDS defining diagnosis, an ECOG performance status >2 and primary cerebral origin. Patients with any of these factors are most likely to benefit from palliative rather than radical treatment. Good prognosis patients have a 30-40% chance of cure from their lymphoma with carefully administered intensive chemotherapy. (Pathology Oncology Research Vol 2, No 4, 272–275, 1996)

Key words: AIDS, Non-Hodgkin's lymphoma

Epidemiology

The Center for Disease Control (CDC) included high grade B-cell Non-Hodgkin's lymphoma (NHL) as an AIDS defining illness in 1985 following the description of NHL in 90 men from a population at risk for AIDS.[29] It is now recognized that NHL in HIV positive patients is 60 times commoner than in the general population.[1] NHL is the AIDS defining diagnosis in 3.0-3.5% patients in Europe.[17,22] The annual rate of developing NHL after a diagnosis of AIDS is 2.4% per year, remaining constant over a 5 year period.[17] An estimated 5-10% of patients will therefore develop HIV NHL at some time during their illness.[20] HIV-associated NHL accounts for 12-16% of all deaths attributable to AIDS.[19] It appears to be slightly commoner in hemophiliacs and less common in intravenous drug users than in other HIV transmission groups.[1] The age incidence is bimodal with peaks in the 10-19 year and 50-59 year age groups reflecting peaks in Burkitt's and diffuse large cell/immunoblastic lymphomas respectively.

The incidence of HIV NHL rises with progressive immunosuppression and hence is becoming more common as HIV infected people live longer owing to better prophylaxis and management of opportunistic infections. The cumulative risk of NHL 3 years after commencing antiretroviral therapy was 19% in one cohort.[20] Primary CNS lymphoma has a constant incidence of 0.6% across all age groups. It is associated with a CD4 positive lymphocyte count of less than 50 and a greater probability of a prior AIDS diagnosis and therefore has a particularly poor prognosis.[16,20]

Biology

HIV-associated NHL are B-cell aggressive lymphomas of high or intermediate grade. Other lymphomas also occur with increased frequency, particularly Hodgkin's disease, but are not AIDS defining diagnoses. The commonest histological types and their frequencies from three large series are shown in *Table 1*.[3,11,21]

HIV-associated diffuse large cell and immunoblastic lymphomas are frequently polyclonal and may be associated with Epstein Barr Virus. The EBV genome in these lymphomas expresses latent antigens including EBNA-2 and LMP-1 & 2 which have transforming activity in vitro. However, the EBV genome can be detected in only half of these HIV-associated large cell lymphomas compared to almost all cases of post-transplantation NHL. This implicates other factors in the etiology of these malignancies associated with HIV infection including polyclonal B-cell expansion and impaired T-cell immunosurveillance. In contrast, the presence of EBV is a universal feature of HIV-associated primary cerebral lymphomas, which are

Received: Oct 2, 1996, accepted: Oct 20, 1996

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monoclonal immunoblastic tumours, but is not found in other primary cerebral NHL.

Burkitt's lymphoma is not associated with other forms of immunosuppression. The HIV-associated Burkitt's lymphoma resembles sporadic Burkitt's lymphoma in that only 40% are EBV positive and c-*myc*/immunoglobulin gene translocations are found in most cases. These translocations usually involve the immunoglobulin heavy chain switch regions which are rearranged late in B-cell ontogeny during isotype class changes.

Table 1. **Frequency of HIV NHL subtypes according to Working Formulation (WF) and Revised European American Lymphoma (REAL) Classifications[10]**

WF	*REAL*	*Frequency*
Small noncleaved cell: J		24–38%
Burkitt's	Burkitt's	
non-Burkitt's	High-grade B-cell lymphoma Burkitt-like	
Large cell Immunoblastic: H	Diffuse Large B cell lymphoma	18–31%
Diffuse Large Cell: G	Diffuse Large B cell lymphoma	17–40%

In addition, two rare HIV-associated lymphoproliferative disorders have been recognized in which Kaposi's sarcoma herpes virus (KSHV), also known as human herpes virus 8 (HHV8), has been demonstrated. KSHV is a novel gamma herpes virus with sequence homology to the oncogenic viruses EBV and herpes saimiri and is etiologically linked to Kaposi's sarcoma.[5] Primary effusion lymphoma is a rare high grade B-cell malignancy characterized by malignant effusions in the absence of nodal disease. Castleman's disease is a multicentric angiofollicular hyperplasia that may co-exist with Kaposi's sarcoma. KSHV has been detected at high frequency in both diseases.[4,24]

Prognostic factors

The staging of HIV-associated lymphomas follows the Ann Arbor system and is identical to that employed for the staging of non-HIV related NHL. The majority of patients present with advanced stage, B symptoms and/or extranodal disease and these factors are therefore less discriminatory regarding prognosis. The most influential prognostic factors in patients with HIV-associated NHL relate to the severity of immunosuppression rather than lymphoma related factors. *Table 2* shows major prognostic factors, which have shown to be significant indicators of a poor prognosis in most series, and other variables which have been of prognostic significance in individual series.[9,13,16] An International Prognostic Index for lymphoma has recently been introduced for aggressive lymphomas[23] and this scoring system has been evaluated in HIV-associated lymphomas. Elevated serum LDH, age over 40 years and CD4 lymphocyte count <100/mm^3 were confirmed as adverse prognostic variables.[27]

Table 2. **Prognostic factors in HIV NHL**

Major poor prognostic factors	*Minor poor prognostic factors*
Prior AIDS diagnosis	Bone marrow involvement
CD4 cells < 100/mm^3	Extranodal disease
ECOG performance status > 2	Raised serum LDH
Primary cerebral origin	Age > 35

In one series of 73 patients with HIV-associated lymphoma from Italy a subgroup of 13 patients who achieved a durable complete remission of at least 2 years was identified. This group had a higher CD4 lymphocyte count and better prognostic score at presentation than the remaining patients. However there were no differences in the histological subtypes between the long term survivors and the other patients.[26] This group have subsequently found that the 2 year survival for good prognosis patients treated with chemotherapy was 50% compared with 24% for poor prognosis patients.[27] Good prognosis patients in complete remission following chemotherapy had a median survival of 34.5 months. In an earlier series, a similar group of patients was found to have a median survival of 18 months.[16]

Management

A biopsy is essential for the diagnosis of systemic lymphomas as they can be mimicked by many AIDS related illnesses. Many centers do not routinely biopsy patients with suspected cerebral lymphoma but make a presumptive diagnosis if the CT scan lesions fail to resolve on anti-toxoplasmosis therapy. Patients with systemic NHL should be staged with CT scan of chest/abdomen/pelvis, a bone marrow biopsy and lumbar puncture with instillation of intrathecal methotrexate or cytosine arabinoside. The most frequent extranodal sites of lymphoma are the gastrointestinal tract, liver and bone marrow. Meningeal disease is common and not necessarily associated with bone marrow involvement or a poor prognosis. CNS directed treatment should therefore be given to patients with meningeal involvement or at high risk of cerebral disease by virtue of Burkitt's histology or extensive sinus and base of skull disease.

Treatment should be stratified according to prognostic factors. Generally, patients with any of the major poor prognostic factors listed in *Table 2* should undergo palliative treatment with low toxicity chemotherapy with the aim of improving or maintaining their quality of life. A suitable chemotherapy regimen would be vincristine,

bleomycin and prednisolone. Radiotherapy may be of value for relief of specific symptoms. The median survival in this group of patients is 3-6 months depending on their response to treatment. Primary cerebral lymphoma may be successfully palliated with a short course of radiotherapy (for example, 20 Gy in 5 daily fractions) although median survival is only 2.5 months.[16]

Patients in the good prognostic category (the minority) may be treated with conventional NHL chemotherapy regimens with the aim of cure. However, because of the underlying immunodeficiency, poor bone marrow reserve owing to HIV myelodysplasia and concomitant use of myelosuppressive agents such as zidovudine, many patients develop opportunistic infections, neutropenic sepsis or persisting neutropenia causing chemotherapy delays and hence suboptimal treatment. Because of these factors the complete response rate to chemotherapy (approximately 50%) is lower than in a non-HIV infected population and the median survival is in the region of only 7-9 months. The relapse rate is also higher. However, 30-40% of good prognosis patients may be cured and survive long term until other AIDS related illnesses ensue. The use of bone marrow stimulatory factors may facilitate giving chemotherapy but improved survival has not been demonstrated.[7,14] There is also concern that GM-CSF may enhance HIV replication in monocytes, although this does not appear to occur with G-CSF.[18]

There appears to be no advantage in using high intensity chemotherapy regimens in these patients. Indeed, patients treated with a novel intensive regimen had a significantly higher risk of early death compared to those treated with m-BACOD.[8] A randomized study of standard vs. low dose m-BACOD resulted in equivalent survival.[12] Treatment with conventional regimens such as CHOP[14] gives equivalent outcomes in terms of complete response (67%) and median survival (9 months) to 2nd and 3rd generation regimens, as is the case with non-HIV lymphomas.[6] We have treated 14 patients with BEMOP-CA,[2] a weekly regimen with a 3 month overall duration, with similar results and toxicity. Short duration regimens such as BEMOP-CA have the advantage of being able to adjust doses of particular drugs weekly in accordance with specific toxicities. Frequent patient observation and short overall duration allow optimal compliance and administration of the schedule.

Two new approaches to the management of HIV NHL have shown promising early results. A longer median survival of 18 months has been found for the infusional CDE regimen comprising monthly cycles of a 4 day continuous infusion of cyclophosphamide, doxorubicin and etoposide.[25] MGBG (methyl-glyoxal-bis guanylhydrazone) is a relatively non-myelotoxic spermidine analogue which inhibits cellular polyamine synthesis has been used with some success in both relapsed systemic NHL[28] and in primary cerebral NHL

Conclusion

HIV related NHL is an increasingly common disease. Carefully selected patients with good prognostic features have a reasonable chance of cure of their lymphoma with moderately intensive chemotherapy regimens. Treatment must be closely monitored owing to the high risk of toxicity in these patients, particularly myelotoxicity. Patients with poor prognostic features may gain worthwhile palliation from the use of low toxicity chemotherapy, oral corticosteroids and radiotherapy when appropriate.

Acknowledgment

The authors are supported by grants from the Crusaid/Star Foundation.

References

1. *Beral V, Peterman T, Berkelman R and Jaffe H:* AIDS-associated non-Hodgkin lymphoma. Lancet 337:805-809, 1991.
2. *Bower M, Brock C, Gulliford T, et al:* A weekly alternating chemotherapy regimen with low toxicity for the treatment of aggressive lymphoma. Cancer Chemother Pharmacol 38:106-109, 1996.
3. *Carbone A, Dolcetti R, Gloghini A, et al:* Immunophenotypic and molecular analyses of acquired immune deficiency syndrome-related and Epstein-Barr virus-associated lymphomas: a comparative study. Hum Pathol 27:133-146, 1996.
4. *Cesarman E, Chang Y, Moore P, et al:* Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related Body-cavity-based lymphomas. N Engl J Med 332:1186-1191, 1995.
5. *Chang Y, Cesarman E, Pessin M, et al:* Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 266:1865-1869, 1994.
6. *Fisher R, Gaynor E, Dahlberg S, et al:* Comparison of a standard regimen (CHOP) with intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993.
7. *Gabarre J, Lepage E, Thyss A, et al:* Chemotherapy combined with zidovudine and GM-CSF in human immunodeficiency virus-related non-Hodgkin's lymphoma. Annal Oncol 6:1025-1032, 1995.
8. *Gill PS, Levine AM, Krailo M, et al:* AIDS-related malignant lymphoma: results of prospective treatment trials. J Clin Oncol 5:1322-1328, 1987.
9. *Gisselbrecht C, Oksenhendler E, Tirelli U, et al:* Human immunodeficiency virus-related lymphoma treatment with intensive combination chemotherapy. French-Italian Cooperative Group. Am J Med 95:188-196, 1993.
10. *Harris N, Jaffe E, Stein H et al:* A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 84:1361-1392, 1994.
11. *Ioachim HL, Dorsett B, Cronin W, et al:* Acquired immunodeficiency syndrome-associated lymphomas: clinical, pathologic, immunologic, and viral characteristics of 111 cases. Hum Pathol 22:659-673, 1991.
12. *Kaplan L, Straus D, Testa M and Levine A:* Randomized trial of standard dose mBACOD with GM-CSF vs. reduced dose

mBACOD for systemic HIV-associated lymphoma: ACTG 142. Proc. ASCO 14:288, 1995.

13. *Kaplan LD, Abrams DI, Feigal E, et al:* AIDS-associated non-Hodgkin's lymphoma in San Francisco. JAMA 261:719-724, 1989.
14. *Kaplan LD, Kahn JO, Crowe S, et al:* Clinical and virologic effects of recombinant human granulocyte-macrophage colony-stimulating factor in patients receiving chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma: results of a randomized trial. J Clin Oncol 9:929-940, 1991.
15. *Levine A, Tulpule A, Espina B, et al:* Mitoguazone (MGBG) with radiation therapy in AIDS-related primary CNS-lymphoma. Proc XI Internat Conference AIDS 2:222, 1996.
16. *Levine AM, Sullivan Halley J, Pike MC, et al:* Human immunodeficiency virus-related lymphoma. Prognostic factors predictive of survival. Cancer 68:2466-72, 1991.
17. *Pedersen C, Barton S, Chiesi A, et al:* HIV-related non-Hodgkin's lymphoma among European AIDS patients. Eur. J. Haematol. 55:245-250, 1995.
18. *Perno CF, Cooney DA, Gao WY, et al:* Effects of bone marrow stimulatory cytokines on human immunodeficiency virus replication and the antiviral activity of dideoxynucleosides in cultures of monocyte/macrophages. Blood 80:995-1003, 1992.
19. *Peters BS, Beck EJ, Coleman DG, et al:* Changing disease patterns in patients with AIDS in a referral centre in the United Kingdom: the changing face of AIDS. BMJ 302:203-7, 1991.
20. *Pluda JM, Venzon DJ, Tosato G, et al:* Parameters affecting the development of non-Hodgkin's lymphoma in patients with severe human immunodeficiency virus infection receiving antiretroviral therapy. J Clin Oncol 11:1099-1107, 1993.
21. *Raphael M, Audouin J, Tulliez M, et al:* Anatomic and histologic distribution of 448 cases of AIDS-related Non Hodgkin's lymphoma. Proc Annual Meeting American Soc Haematology. Blood 82:386a (suppl.1), 1993.
22. *Serraino D, Salamina G, Franceschi S, et al:* The epidemiology of AIDS-associated non-Hodgkin's lymphoma in the World Health Organization European Region. Br J Cancer 66:912-916, 1992.
23. *The International Non-Hodgkin's Lymphoma Prognostic Factors Project:* A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987-994, 1993.
24. *Soulier J, Grollet L, Oksenhendler E, et al:* Kaposi's sarcoma-associated Herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 86:1276-1280, 1995.
25. *Sparano J, Wiernik P, Strack M, et al:* Infusional cyclophosphamide, doxorubicin, and etoposide in Human Immunodeficiency Virus- and Human T-cell Leukaemia Virus Type I-related non-Hodgkin's lymphoma: a highly active regimen. Blood 81:2810-2815, 1993.
26. *Tirelli U, Errante D, Spina M, et al:* Long-term survival of patients with HIV-related systemic non-Hodgkin's lymphomas. Hematol Oncol 14:7-15, 1996.
27. *Vaccher E, Tirelli U, Spina M, et al:* Age and serum lactate dehydrogenase level are independent prognostic factors in Human Immunodeficiency Virus-related Non-Hodgkin's lymphomas: a single-institute study of 96 patients. J Clin Oncol 14:2217-2223, 1996.
28. *Von Hoff D:* MGBG: Teaching an old drug new tricks. Ann Oncol 5:487-493,1994.
29. *Ziegler JL, Beckstead JA, Volberding PA, et al:* Non-Hodgkin's lymphoma in 90 homosexual men. Relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. N Engl J Med 311:565-570, 1984.