Bone Marrow Involvement and the Prognosis of Low Grade Non-Hodgkin’s Lymphoma

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Aim. To analyze the bone marrow (BM) infiltration in low-grade non-Hodgkin’s lymphomas (LGNHL) and assess its association with the histopathology type, clinical behavior, and disease prognosis.

Method. BM smears obtained by needle biopsy and stained by standard methods were analyzed in 60 patients with LGNHL using the Working Formulation.

Results. BM infiltration was observed in 57% of the lymphocytic lymphomas (A), in 48% of lymphoplasmocytic/plasmocytoid lymphomas (AI), and in 31% of follicular lymphomas (follicular small cleaved cell and follicular mixed B and C). The difference was not significant. The 5-year survival rates for patients with and without bone marrow infiltration were 53% and 56% respectively, and 10-year survival rates were 31% and 45% (p>0.05).

Conclusion. The presence of bone marrow infiltration at diagnosis did not significantly affect the prognosis of LGNHL.

Key words: bone marrow examination; chemotherapy; lactate dehydrogenase; lymphoma, low grade; lymphoma non-Hodgkin; non-Hodgkin lymphoma

Non-Hodgkin’s lymphomas (NHL) are a group of heterogeneous diseases with wide variations with respect to the prognosis and response to treatment (1). The histopathological classification and clinical staging provide the basis for the subdivision of NHL patients into prognostic subgroups (2-5). Over the past few decades, many of the prognostic factors have been tested to determine characteristics in individual tumors, which would predict clinical behavior and response to treatment. One of them is bone marrow infiltration with malignant cells. Although bone marrow analysis is a basic part of the staging evaluation of NHL, reports on the influence of bone marrow (BM) infiltration on the prognosis of low grade non-Hodgkin’s lymphomas are controversial (6-9). BM infiltration is considered a prognostic parameter only in chronic lymphocytic leukemia (CLL) but not in some low grade NHL (10,11). The aim of the present study was to determine the incidence of BM involvement, detected by morphologic methods, in a series of 60 cases of low grade NHL classified according to the Working Formulation (WF) (4), and to assess its influence on the prognosis of the disease.

Material and Methods
A retrospective analysis of 160 patients with NHL in the period from 1978 to 1992 was performed. Seventy three of these cases were classified as low grade malignancy. Sixty of them, 33 men and 27 women (range 24 to 82 years of age), were followed for 6-179 months (median 41 months). All histopathological slides were reviewed by an experienced pathologist and graded according to the Working Formulation after lymph node or tissue biopsies (4). Patients were treated with either single alkylating agent chemotherapy or with a combined therapy with COP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclo- phosphamide, doxorubicine, vincristine, prednisone) protocol. In a few cases of stage I tumors, telecobalt (TCT) therapy was used.

Aspiration BM biopsies were performed in all patients. Trepan biopsy of the posterior upper iliac spine was performed in equivocal cases and in cases where the result of the biopsy could affect the treatment. Samples taken by aspiration biopsy were analyzed after May–Grünwald–Giemsa staining. Bone marrow infiltration was considered present if more than 5% of morphologically recognizable lymphoma cells were observed (mainly in follicular lymphomas) or when at least 30% of small lymphocytes or lymphoplasmocytes were found in the cases of lymphocytic and lymphoplasmocytic/plasmocytoid lymphomas. We set the cut-off point at 30% because it has been shown that normal bone marrow may have the lymphocyte content up to 25% (12). The groups with and without BM infiltration were compared for the following standard prognostic parameters: age, sex, stage of the disease, B-symptoms (13), presence of a large tumor mass (more than 5x5 cm), hemoglobin, leukocytes, and lactate dehydrogenase (LDH) levels.
Data were analyzed by the chi-square test. Life tables were calculated using the Kaplan-Meier method (14) and compared by the long-rank test.

Results

The highest percentage of BM involvement was seen in patients with lymphocytic lymphoma, but differences to other groups did not reach statistical significance (Table 1).

Table 1: Incidence of bone marrow (BM) infiltration in different histological types of 60 patients with low grade NHL. [view this table]
Table 2: Prognostic parameters in patients with low grade NHL with respect to the infiltration of bone marrow (BM) with tumor cells. [view this table]

Difference was also not observed for other standard prognostic parameters in patients with and without BM involvement at diagnosis, with the exception of stage distribution (Table 2). Patients with BM infiltration were all in the stage IV. Patients without B-symptoms predominated in both groups. The number of patients with anemia, high values of lactate dehydrogenase, leukopenia, and complete remission were nearly equal in both groups. Age was nearly the same in the two groups. Overall incidence of bone marrow infiltration was 47%. Actuarial survival of the patients with BM infiltration was 53% at 5 years and 31% at 10 years. Patients without BM infiltration had similar 5-year and 10-year survival (56% and 45%, respectively). There was no significant difference in survival between the two groups (Fig. 1).

Figure 1: Survival of the patients with a low-grade non-Hodgkin’s lymphoma according to the presence of bone marrow infiltration at diagnosis. Circles, patients with bone marrow infiltration; squares, patients without bone marrow infiltration; p>0.05. [view this figure]

Discussion

Although the histological examination of the trephine biopsy is a common method for the detection of BM infiltration in NHL patients, we used less aggressive aspiration biopsy and cytological examination. The overall incidence of BM involvement at diagnosis was 47% (28/60), which corresponds to the majority of the previously reported frequencies (6,15-18). Morra et al (6) found that the incidence of histological BM involvement at low grade NHL diagnosis was significantly higher than in other lymphoma groups, indicating that the majority of low grade NHL behave as systemic diseases from their onset. In a series of 172 patients with non-Hodgkin’s lymphoma classified according to the working formulation, they found a 39% incidence of BM infiltration at diagnosis: 59% for the low grade, 30% for the intermediate grade, and 25% for the high-grade malignant lymphomas (6).

Although a high percentage of BM involvement in the lymphocytic lymphoma in our study did not reach statistical significance, it is in accordance with the earlier observation of Hoerny et al (18), who also showed that lymphocytic lymphoma appeared to be the most disseminated low grade NHL. Stein et al (16) most frequently found involvement of the marrow in patients with poorly differentiated lymphocytic lymphoma (60%). Dick et al (15) found that nodular, poorly differentiated lymphocytic lymphoma more frequently exhibited marrow involvement than did diffuse, poorly-differentiated lymphocytic lymphomas.

Our finding that the survival of low grade NHL patients was not statistically affected by the presence or absence of the marrow disease at presentation is in agreement with some previous reports (6,7) but differs from the experience of Ben-Ezra et al (8) and Nabholtz et al (9). Morra et al (6) found that the survival curves of intermediate and high-grade patients presenting with BM involvement were significantly affected by the extent of marrow disease, whereas in low grade NHL cases, BM tumor mass did not influence prognosis. Hagberg et al (7) did not find a relationship between bone marrow involvement and survival in stages III and IV of non-Hodgkin’s lymphoma. Among the patients with small lymphocytic lymphoma, Ben-Ezra et al (8) found that the BM involvement independently influenced survival only in patients with leukocytosis but not in those without leukocytosis. Nabholtz et al (9) found that low grade NHL stage IV patients with BM involvement as the only extranodal manifestation had a 5-year survival of 71.9% which was similar to the anatomically least advanced stages. This was in marked contrast to the patients in stage IV with other sites of involvement, who had a 5-year survival rate of 12%, identical to the most unfavorable groups of high grade NHL. In conclusion, bone marrow infiltration by lymphoma cells at diagnosis did not affect survival in patients with low grade NHL.

References
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