

Primary bone lymphoma: experience with 52 patients

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Background and Objectives. A retrospective analysis was performed to assess the efficacy of various treatments of non-Hodgkin's primary bone lymphomas (PBL).

Design and Methods. Fifty-two consecutive, previously untreated PBL patients were seen between the years 1982 and 1998. Information was obtained regarding each patient's presentation and clinical course. Histology was reviewed in all cases. Modern immunohistochemical stains were performed on each case.

Results. Regarding therapeutic approach, we observed a complete response (CR) in 35/41 (85%) patients treated with chemotherapy with/without radiation therapy and in 7/11 (64%) patients who received radiation therapy alone. Relapses were observed in only 2/35 (6%) patients after chemotherapy (with/without radiation therapy), as compared with 4/7 (57%) patients after radiation therapy alone ($p = 0.004$); the relapse-free survival curves of these two subsets were significantly different. At both univariate and multivariate analysis only type of front-line therapeutic approach (chemotherapy with/without radiation therapy vs. radiation therapy alone) turned out to have a significant prognostic influence.

Interpretation and Conclusions. Our data indicate that in PBL use of chemotherapy or combined-modality therapy seems to provide more durable CRs than radiation therapy alone.

Key words: primary bone lymphoma, chemotherapy, radiation therapy.

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Although non-Hodgkin's lymphoma (NHL) is primarily a disorder of lymph nodes, it can also arise from extranodal sites. As many as 20-40% of NHL may be extranodal, and the incidence seems to have been increasing over the last two decades. Since secondary involvement of the bone marrow (a common event in nodal lymphoma) only rarely results in localized bone lesions, such lesions are usually considered as primary bone lymphomas (PBL) even when there is some evidence of dissemination.

PBL accounts for approximately 3% of all malignant bone tumors¹ and 4-5% of all extranodal NHL.^{2,3} There is a slight male preponderance, and most patients are over 45-50 years of age. Patients commonly present with local bone pain, soft tissue swelling, and a mass or a pathologic fracture. Although PBL can arise in any part of the skeleton, long bones are the most common site of presentation, followed by the pelvis and spine, with the scapula, maxilla and mandible accounting for most of the remaining cases. On full staging evaluation, approximately 60% of presentations turn out to be primary (stage IE) and 40% to be advanced (stage IV). Nodal involvement is uncommon. Histopathologically, according to the R.E.A.L. classification,⁴ the majority of PBL are diffuse large B-cell lymphomas,⁵⁻¹² while - with the exception of in one Japanese series¹³ - T-cell lymphomas are much rarer.

Even though cure of PBL by surgery alone has been recorded, this approach is no longer considered appropriate. Unlike with other bone tumors, the role of surgery in PBL is now limited to the diagnostic biopsy and to the repair of fractures that either present at initial diagnosis or arise during the peri- or post-treatment period. Management of limited, stage I or II PBL has traditionally been based on radiation therapy to the involved bone and draining lymphatics.¹⁴⁻¹⁶ However, a combination of chemotherapy and radiation therapy has recently been suggested.^{6-11,17-19} Herein, we report the outcome of 52 consecutive, previously untreated PBL patients treated between 1982 and 1998.

Design and Methods

Between March 1982 and June 1998, 52 consecutive, previously untreated cases of PBL were diagnosed at the Seràgnoli Institute of Hematology in Bologna, at the Operative Unit of Anatomic Pathology and Diagnostic Cytopathology in Cardarelli Hospital of Napoli and at the Institute of Pathology of Pavia. In all cases, pathologic

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material was obtained from the involved bone by an open biopsy or fine needle aspiration. Diagnostic specimens of all patients have been reviewed and classified (by SAP) according to the REAL classification.⁴ Tissue samples were fixed in 10% buffered formalin for 24 hours, decalcified and processed routinely. Three-micron-thick sections were cut from the paraffin blocks and stained with hematoxylin and eosin, Giemsa and Gomori silver impregnation for reticulin fibers. Further sections were cut and used for immunohistochemistry, which was carried out by applying optimized antigen retrieval methods,²¹ the APAAP technique,²² and specific antibodies against the following molecules: CD45/LCA, CD3/anti-CD3 polyclonal antibody, CD79a/JCB117, CD20/L26, Bcl-2/anti-Bcl-2, Bcl-6/PG-B6, CD10/270, CD30/Ber-H2, CD5/54/F6, CD138/M115, Ki-67/Mib-1, Oct-2 and BOB.1.

In all patients, staging evaluation included initial hematologic and chemical survey, in addition to chest X-rays, abdominal ultrasonography, computed tomography of the chest and abdomen, and bone marrow biopsy. For a diagnosis of PBL, patients had to present with a primary focus in a single bone, with or without locoregional adenopathy. Multiple bone lesions were acceptable as long as there was no evidence of non-osseous lymphomatous involvement. Bulky disease was defined as a tumor mass \geq 6 cm. Cases were staged according to the Ann Arbor staging system.²⁰

Patients' characteristics

Table 1 summarizes the clinical characteristics of the 52 patients described in this review (30 males, 22 females; median age, 58 yr, range 14–82). The most common presenting symptom was pain (38/52, 73%). The most frequently involved sites were the extremities (50%), particularly the femur. Forty-one (79%) patients presented disease in only one bone site and 11 (21%) had multifocal bone involvement. Only 2 (4%) patients had B symptoms at initial presentation.

Various treatment strategies were employed. Thirty-three patients were treated with combined modality therapy with variable sequencing of the chemotherapy relative to the radiotherapy; chemotherapy was delivered before radiation therapy in 29 cases and afterwards in 4. Eight patients were treated with chemotherapy alone. Eleven patients were treated with radiation therapy alone. All patients treated with radiation therapy received doses between 35 and 45 Gy. The chemotherapy regimens employed were CHOP or CHOP-like in 28 patients and MACOP-B or MACOP-B-like in 13 patients.

Response

Assessment of PBL patients' response to treatment is commonly hampered by the persistence of

Table 1. Patients' characteristics (n=52).

Sex	M/F	30/22
Age	Median Range	58 14-82
<i>Sites</i>		
Extremities		26 (50%)
Femur		14
Tibia/fibula		6
Humerus		5
Ulna/radius		1
Axial skeleton		23 (44%)
Scapula		5
Spinal		9
Pelvis		7
Ribs		2
Skull		3 (6%)
Mandible		2
Maxilla		1

abnormalities on bone scans, gallium scans, and magnetic resonance imaging after successful treatment. Thus without multiple open biopsies, it is not possible to be absolutely certain of complete response (CR). For the purpose of this report, CR was defined as disappearance of all evidence of lymphoma, as documented by a normal physical examination, blood tests, and radiologic imaging. When residual radiographic abnormalities were consistent with normal bone reformation, patients were considered in CR if no other possible signs of disease were present. Partial response (PR) was defined as $>50\%$ reduction in tumor burden without CR after completion of treatment, and no response as anything less. For those patients who achieved a CR, patterns of failure were assessed. Local failure was defined as failure in the initial bone site and/or in adjacent lymph nodes. Failure anywhere outside these confines was considered to be distant.

Survival curves and statistical analysis

Relapse-free survival (RFS) was calculated as the survival from the achievement of CR until relapse or death. Overall survival (OS) was calculated from the time of diagnosis until death from any cause. Survival curves were calculated by the actuarial method of Kaplan and Meier.²³ Log rank analysis was used to assess the significance of differences between patient group of patients.²⁴ Cox multivariate regression analysis²⁵ was used to assess the prognostic significance (with respect to disease-free survival and OS) of the following co-variables: type of treatment, disease site (long bone, flat bone or pelvis),

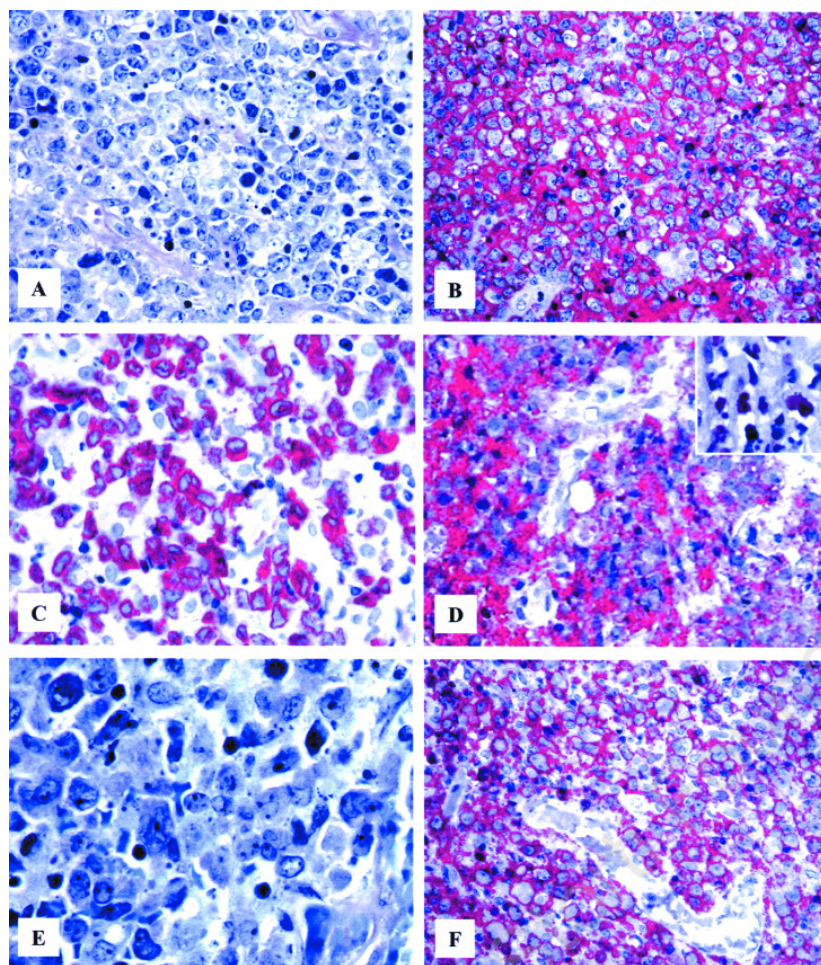


Figure 1. [A] Diffuse large B-cell lymphoma: marked cellular pleomorphism of the neoplastic cells (Giemsa; $\times 400$); [B-C-D] Diffuse large B-cell lymphoma: CD20, Bcl-2, CD10 and Bcl-6 (inset $\times 500$) positivity (immunoalkaline phosphatase technique in paraffin sections; $\times 400$); [E-F] Anaplastic large cell lymphoma (Giemsa; $\times 500$): strong expression of CD30 molecule both at the membrane level and in the Golgi area (immunoalkaline phosphatase technique in paraffin sections; $\times 400$).

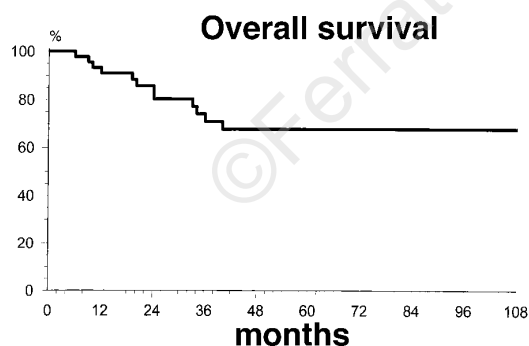


Figure 2. Projected overall survival curve of all 52 PBL patients.

number of involved bone sites, presence of bulky mass, age (<60 yr. vs. ≥ 60 yr.), sex, presence of B symptoms, and histology.

Results

Of the 52 patients studied, 42 (81%) fulfilled the criteria for CR and 5 (9%) for PR, giving an overall response rate of 90%. The remaining 5 (10%) were considered resistant to treatment. Of the 42 patients who obtained CR, 36 (86%) are still in remission; the median duration of CR is currently 40 months (range 6-99 months). The 5 patients who achieved PR maintained this status for a median of 20 months (range 6-29 months).

At microscopic evaluation, 44 cases were diffuse large B-cell lymphomas (DLBCLs) (Figure 1, A-D), 2 atypical Burkitt's tumors (ABTs), 2 ALK anaplastic large cell lymphomas of T-cell derivation (T-ALCL) (Figure 1, E, F), 2 follicular lymphomas (FLs), and 2 small B-cell lymphomas (SBCLs). According to these data, an obvious prevalence of aggressive lymphomas over indolent lymphomas was found, as was a striking prevalence of B-cell tumors over T-cell ones. On immunohistochemistry, not all cases showed optical antigen preservation, due to the harsh decalcification procedures applied in some instances: however, most of them showed a suffi-

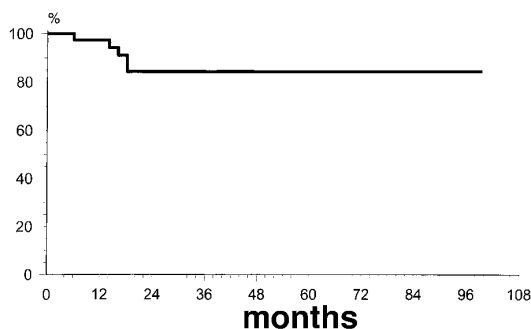


Figure 3. RFS curve of CR patients.

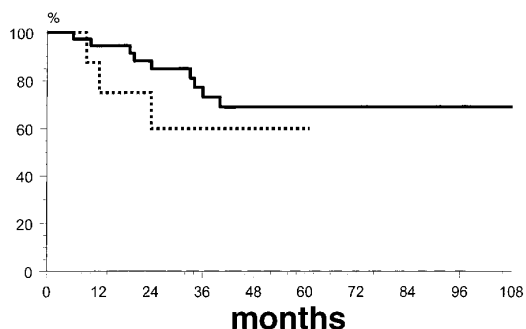


Figure 4. OS curves comparing single (—) vs multiple lesion (---) subsets.

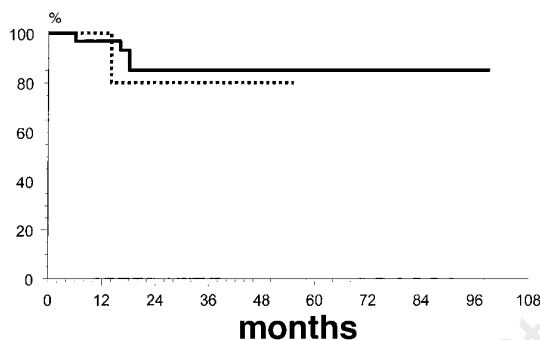


Figure 5. RFS curves comparing single (—) vs multiple lesion (---) subsets.

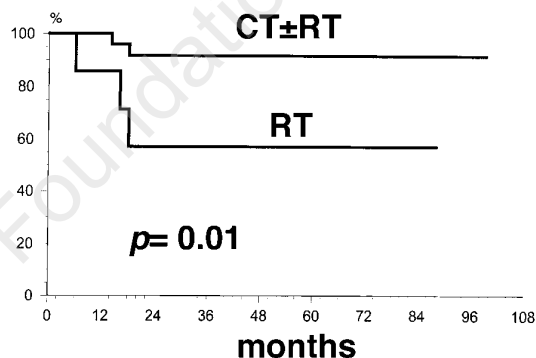


Figure 6. RFS curves comparing chemotherapy (with/without radiation therapy) (CT±RT) vs radiation therapy alone (RT). $p=0.01$

ciently preserved phenotypic profile. Thus, B-cell (CD20 and CD79a) and T-cell (CD3) markers were detected in all instances, as were CD45 and transcription factors Oct-2 and BOB.1. Both T-ALCLs expressed CD30. ABTs, FLs and SBCLs had the proper phenotype according to the criteria of the REAL classification.⁴ Among DLBCLs – which represented the largest group within the series – 23 out of 32 evaluable cases expressed the Bcl-2 protein, 16/37 CD10, and 16/30 the Bcl-6 gene product. In addition, one case (CD10-) revealed weak CD5 staining. The Ki-67/Mib-1 marking was always high with a mean value of 70%. CD30 and CD138 were expressed by a small minority of the neoplastic cells in some cases, thus confirming the impression that none of the DLBCLs evaluated had anaplastic or immunoblastic morphology. Based on these findings, more than 50% of evaluable DLBCLs showed a phenotypic profile consistent with a germinal center derivation. Among DLBCLs no significant dif-

ferences, regarding response to therapy, overall survival and relapse-free survival, were observed on the basis of CD10, Bcl-6 and Bcl-2 positivity.

The projected OS at 108 months was 68% (Figure 2) with a median follow-up of 50 months (range, 6-108 months). The probability of RFS for CR projected at 96 months (Figure 3) was 84%. As regards the number of bone lesions at presentation, the overall response and CR rates were 89.5% and 81.5%, respectively, in the single bone-lesion subset and 87.5% and 75% in the multiple bone-lesion subset. Figures 4 and 5 show the OS and RFS of the single and multiple bone lesion subsets, respectively. With regard to therapeutic approach, we observed CR in 35/41 (85%) patients treated with chemotherapy with/without radiation therapy (in particular, 85% (28/33) in the chemotherapy + radiation therapy subset and 87.5% (7/8) in the subset treated with chemotherapy alone) and in 7/11 (64%) patients who received radiation therapy alone. Relapses were

recorded in only 2/35 (6%) patients who achieved CR after chemotherapy with/without radiation therapy [1 (3.5%) in the combined subset and 1 (14%) in the chemotherapy alone subset], as compared with 4/7 (57%) patients who had CR after radiation therapy alone ($p=0.004$); the RFS curves of these two subsets of patients were significantly different ($p=0.01$) (Figure 6). At both univariate and multivariate analysis, only the type of front-line therapeutic approach (chemotherapy with/without radiation therapy vs. radiation therapy alone) turned out to have a significant prognostic influence ($p=0.02$ and $p=0.01$, respectively).

Discussion

NHL only very occasionally presents as a primary bone lesion. Although PBL is a well-defined clinico-pathologic entity, because of its rarity it has been difficult to establish specific treatment guidelines. The relatively few published studies on PBL span many years, during which time staging techniques and treatment modalities have evolved, and the histologic classification of NHL has been significantly refined. Clinical protocols for PBL have thus been formulated on the basis of meta-analyses of retrospective studies of differently treated patients. Traditionally, treatment has been based on radiation therapy alone. This approach seems to provide high levels of local control within the radiation field, but unacceptable rates of locomarginal failure (probably related to underestimation of tumor extent and bulk) with a systemic failure rate approaching 50%. There is no clear preponderant risk of failure in the CNS or bone, both being possible. No increased incidence of second tumors has been recorded either in the bone or soft tissue as a result of primary therapy.

In our series of patients, the principles relevant to the treatment of nodal NHL were applied to extranodal PBL. Miller and Jones²⁶ previously demonstrated that the use of an anthracycline-containing chemotherapeutic regimen can affect both response and long-term survival rates in the treatment of early-stage NHL of unfavorable histology. In their studies, the role of radiation therapy remained undetermined.

In our series, we recorded a CR rate of 85% (35/41) among the patients treated with chemotherapy or combined modality therapy (chemo- and radiation therapy), as compared with 64% (7/11) in the small group of patients treated with radiation therapy alone. Significantly, the relapse rate was then much higher among the patients who achieved CR after radiation therapy alone (57% [4/7] vs. 6% [2/35]; $p=0.004$). Moreover, use of chemotherapy was the only prognostically advantageous factor that emerged at univariate/multivariate survival analysis.

In conclusion, our series primarily indicates that use of chemotherapy (with/without radiation therapy) seems to provide more durable CRs than radiation therapy alone. On the other hand, our data do not allow us to draw any conclusion as to whether the addition of radiation therapy confers any advantage. Other unresolved questions include the optimum number of chemotherapy courses and the dose and volume of any radiation therapy. Some authors^{10,18} have suggested that all PBL patients should be treated with combined-modality therapy, an assertion supported by strong evidence that this approach provides significant benefits in the treatment of localized NHL. However, only phase III, randomized, controlled clinical trials will determine whether combined modality treatment is indeed superior to chemotherapy alone in the treatment of PBL.

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Pre-publication Report & Outcomes of Peer Review

Contributions

PLZ was the principal investigator involved in the conception of the study, its design, and the writing of the paper. GC, SA, MP, ES, RB, SAP were involved in the histological review. GC, EB, MT, VS and LP collected the study data. MB, ST and SAP critically revised the paper and gave the final approval for its submission. PLZ: primarily responsible for the publication; PLZ: primarily responsible for Table 1 and Figures 2-6; SAP: primarily responsible for Figure 1.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received June 14, 2002; accepted January 23, 2003.

In the following paragraphs, the Editor-in-Chief summarizes the peer-review process and its outcomes.

What is already known on this topic

Primary bone lymphoma is a rare disorder, so that few data are available on the efficacy of different treatment modalities.

What this study adds

This study suggests that chemotherapy or combined-modality therapy is preferable to radiotherapy in patients with PBL.

Caveats

This is a retrospective study.