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## ORIGINAL ARTICLE

# Primary Non-Hodgkin's Lymphoma of Bone: a Rare Cause of Lytic Bone Lesion

**M Tong,[1] TK Yau,[1] WC Wu,[2] JJ Lam,[2] AWM Lee[1]**

*[1]Department of Clinical Oncology and [2]Department of Orthopaedics and Traumatology, Pamela Youde Nethersole Eastern Hospital, Hong Kong*

## ABSTRACT

***Objective:*** *To review the clinical behaviour and treatment outcome of patients with localised primary lymphomas of bone.*

***Patients and Methods:*** *The medical records of patients with primary lymphomas of bone managed at the Pamela Youde Nethersole Eastern Hospital, Hong Kong, from 1994 to 2001 were retrospectively reviewed. Five Chinese patients with this condition were identified. All patients had diffuse large cell lymphomas (New Working Formulation) of B-cell phenotype and were classified as stage IE/IIE by Ann Arbor staging. Four of the 5 patients presented with lytic bone lesions in the long bones of the lower limbs and the remaining patient presented with a lytic lesion in the vertebrae. All patients were treated with anthracycline-based combination chemotherapy, followed by radiotherapy of 40 to 44 Gy.*

***Results:*** *The median follow up was 60 months (range, 28 to 73 months). All patients achieved complete remission after treatment and remained disease-free up to the last assessment. One patient had a complication of fracture during chemotherapy but no late adverse effects on bone healing due to radiotherapy were identified.*

***Conclusions:*** *These results suggest that combined chemotherapy and radiotherapy for localised primary lymphomas of bone can provide excellent local and systemic disease control. Radiotherapy following chemotherapy at doses of approximately 40 to 44 Gy appears to be sufficient for local control of the tumour, with no significant adverse effects on bone healing observed.*

***Key Words:*** *Bone neoplasm, Bone tumour, Chemotherapy, Extranodal lymphoma, Radiotherapy*

## INTRODUCTION

Lymphomas only rarely present as a primary osseous lesion. It was not until 1939 that Parker and Jackson described 17 patients with "primary reticulum cell sarcoma" and established primary non-Hodgkin's lymphoma (NHL) of bone as a distinct clinical entity.[1] Primary NHL of bone comprises approximately 3% to 7% of all extranodal NHLs, and approximately 7% of primary bone tumours.[2-9] As primary lymphoma of bone (PLB) is a highly curable disease, differentiation from other causes of lytic bone lesion such as secondaries from carcinomas and other primary bone tumours is important.

***Correspondence:*** *Dr M Tong, Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong.*
*Tel: (852) 2595 4175; Fax: (852) 2904 5216;*
*E-mail: macytong@hkcr.org*

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The optimal management of PLB remains controversial. Due to its rarity, only a few retrospective studies have been published addressing the prognosis and treatment of PLB (Table 1).[3-14] Most of the studies had small patient numbers retrospectively collected over a long time span, resulting in a heterogeneous group of patients with different staging methods and a great diversity of treatment approaches. Moreover, histologic classifications of lymphomas have been subjected to repeated modifications, lack of reproducibility, and inherent limitations of morphologic study alone. In this study, we retrospectively evaluated the clinical outcome of patients with PLB treated at the Pamela Youde Nethersole Eastern Hospital from 1994 to 2001. Since this small series was collected over a relatively short period of time, the staging method, histopathological diagnosis, and treatment approaches were more uniform and might aid in the future management of patients with PLB. The clinical pattern and management issues are also reviewed and discussed.

## PATIENTS AND METHODS

Patients were eligible for this retrospective review if they had NHL involving a single osseous site (with or without regional lymphatic involvement) and received primary treatment (chemotherapy and/or radiotherapy) at the Pamela Youde Nethersole Eastern Hospital. Patients with non-contiguous polyostotic sites, involvement beyond regional nodes, or prior history of lymphomas were excluded as it is difficult to confirm the primary sites in these patients.

Between January 1994 and June 2001, 10 patients with lymphoma with bony involvement were identified in the departmental data registry. Five patients were excluded from the study — 4 had Ann Arbor stage III and IV disease at presentation and 1 had incomplete staging and was treated with palliative intent only. The remaining 5 patients were included in this study.

### Demographic Data and Clinical Features

The demographic and clinical data of the 5 patients are summarised in Table 2. All 5 patients were Chinese. The median age at diagnosis was 54.7 years (range, 44.7 to 63.8 years). There was a slight male preponderance (male-to-female ratio, 1.5:1). Except for a patient with a T10 vertebral lesion, all patients had their primary sites in the long bones of the lower limbs. All patients presented with bone pain at diagnosis and 2 had associated localised swelling as well.

### Pretreatment Evaluation

One patient (patient 2) had the diagnosis made only after total hip replacement for suspected avascular necrosis. The other 4 patients had histological diagnoses made by open bone biopsy. All specimens underwent immunostaining for sub-classification, including immunostaining for L26 (B cell marker) and CD3 (T cell marker). All

**Table 1.** Publications for primary bone lymphoma.

| Authors | Year of studies | Number of patients | Stage | Treatment modalities | Summary of findings |
|---|---|---|---|---|---|
| Heyning et al[10] | 1943-1996 | 60 | I-IV | NA | 5-year OS: 61% |
| Dosoretz et al[11] | 1950-1978 | 30 | NR | RT | 5-year OS: 63%, 5-year LC: 86%<br>No local failure for RT dose >50 Gy |
| De Camargo et al[8] | 1955-1999 | 24 | NR | CT, CMT | 5-year OS: 71%, no difference between CT and CMT |
| Marshall et al[6] | 1962-1997 | 28 | I-II polyostotic | RT. CMT | LC: 100%, 5-year OS 60% |
| Dubey et al[5] | 1967-1992 | 45 | I-II | RT, CT, CMT | 5-year OS: 72%, no difference between CMT and RT |
| Fairbanks et al[4] | 1970-1989 | 63 | I | RT, CT, CMT, Surgery | 5-year DFS: 90% for CMT, 57% for RT, RT >40 Gy improves OS |
| Fidias et al[7] | 1970-1995 | 37 | I | CMT | 5-year OS: 91% |
| Bacci et al[12] | 1972-1982 | 30 | NR | RT, CMT | 88% NED at 87 months |
| Baar et al[3] | 1975-1992 | 17 | I-IV | RT, CT, CMT | 76% NED at 29 months |
| Christie et al[13] | 1979-1993 | 70 | NR | RT, CMT | 5-year OS: 82%, 5-year LC: 59% |
| Stein et al[9] | 1979-2000 | 10 | I | CT, CMT | 90% NED at 71 months |
| Sothi and Spooner[14] | 1985-1996 | 19 (stage IE) | I-IV | CMT, CT | LC: 100%, 5-year OS: 85% (for stage IE) |

*Abbreviations:* NA = not available; NR = not reported; RT = radiotherapy; CT = chemotherapy; CMT = combined modality treatments; OS = overall survival; LC = local control rate; DFS = disease-free survival; NED = no evidence of disease.

**Table 2.** Demographic data and summary of clinical features.

| Patient number | Sex | Age at diagnosis (years) | Site | AA stage | Histology | Surgery | Chemotherapy | RT — all in 2 Gy daily fractions | Bony complications | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 44 | Tibia | IAE | B-DLCL | IM nailing (for fracture during chemotherapy) | CEOP x 8 | 44 Gy | Pathological fracture | |
| 2 | M | 40 | Femoral head | IAE | B-DLCL | THR | CEOP x 6 | 40 Gy | | |
| 3 | F | 58 | Spine | IBE | B-DLCL | Hemi-laminectomy + wiring | CEOP x 3 | 40 Gy | Collapsed T10 | Poor marrow tolerance |
| 4 | F | 63 | Tibia | IAE | B-DLCL | Nil | CEOP x 5 | 44 Gy | | Hepatitis B reactivation after chemotherapy |
| 5 | M | 54 | Tibia | IIBE | B-DLCL | Nil | CHOP x 6 | 40 Gy | | |

*Abbreviations:* AA = Ann Arbor; B-DLCL = diffuse large B cell lymphoma; RT = radiotherapy; IM nailing = intramedullary nailing; THR = total hip replacement; CEOP/CHOP = chemotherapy schemes used (refer to Table 4).

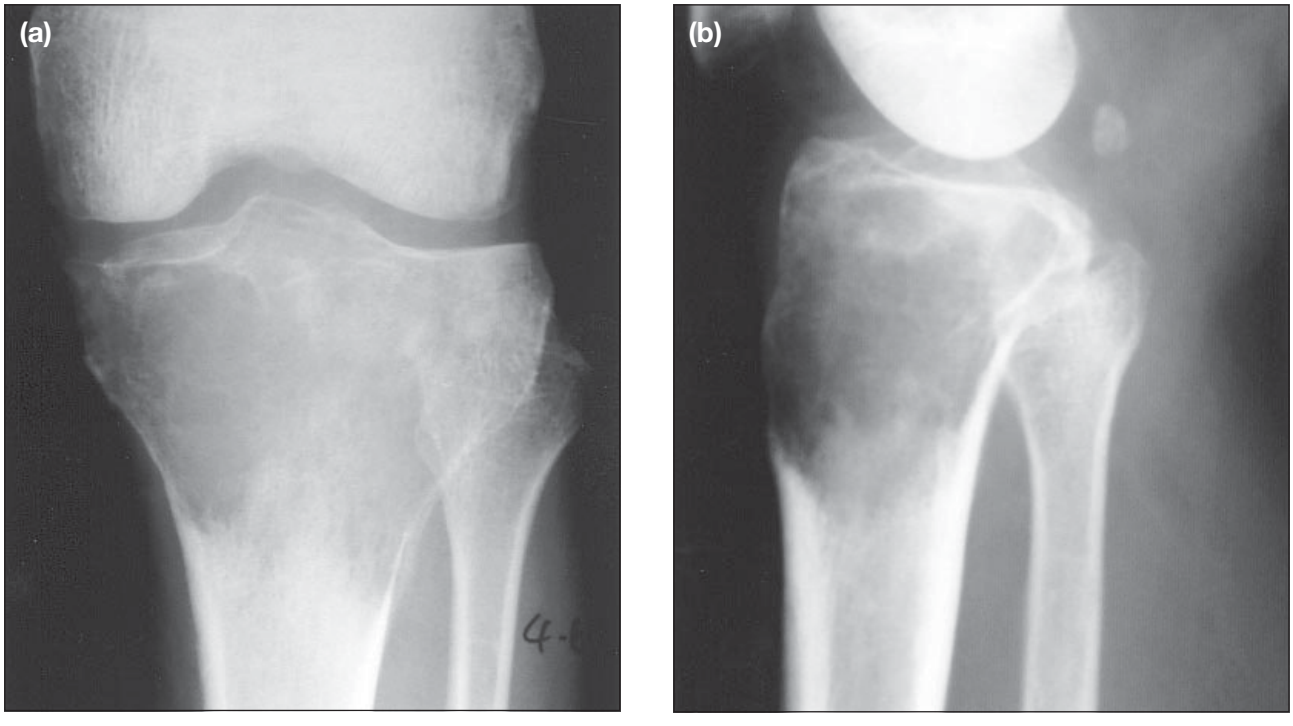


**Figure 1.** (a) Anteroposterior and (b) lateral radiographs show a proximal tibia primary lymphoma at the time of diagnosis with lytic bony destruction with periosteal reaction.

5 patients had diffuse large cell lymphoma (New Working Formulation) of B-cell phenotype.

Apart from baseline blood tests, including serum lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR), staging evaluation included chest X-ray (100%), computed tomography (CT) scan of the abdomen and pelvis (100%), bone scan (100%), CT scan or magnetic resonance imaging (MRI) of the primary involvement site (100%), marrow trephine biopsy over the iliac crest (80%), and gallium scan (60%).

## Imaging Characteristics

Plain X-rays showed lytic destruction with or without periosteal reaction in all patients (Figures 1a and 1b). All patients had associated soft tissue extension and marrow involvement seen on CT scan or MRI (Figure 2). The involved primary sites showed strong positive uptake of radionuclide in all 5 patients with baseline technetium bone scans (Figure 3) in the 3 patients who had baseline gallium scans performed.

# RESULTS

Overall, 4 patients were staged as Ann Arbor stage IAE and 1 patient was staged as IIBE. Based on the modified criteria from the international NHL prognostic index (IPI),[15] of which Dubey et al had reported the validity as a prognostic tool for PLB,[5] only 1 patient had no risk factors and was classified into the low risk category (Table 3). Four patients had 1 or 2 risk factors and were classified into the high risk category.

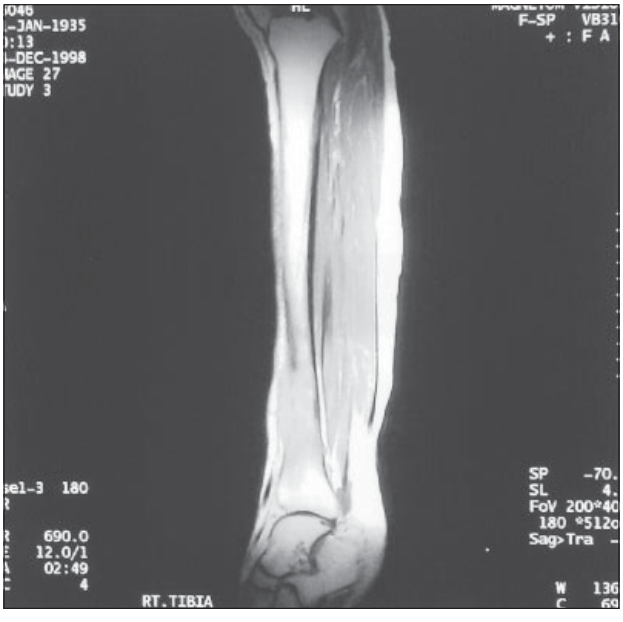


**Figure 2.** Magnetic resonance imaging shows a distal tibial lymphoma of bone with adjacent soft tissue extension.

## Treatment

All patients were treated with combination chemotherapy followed by radiotherapy. Two patients had surgery prior to commencement of chemotherapy. One

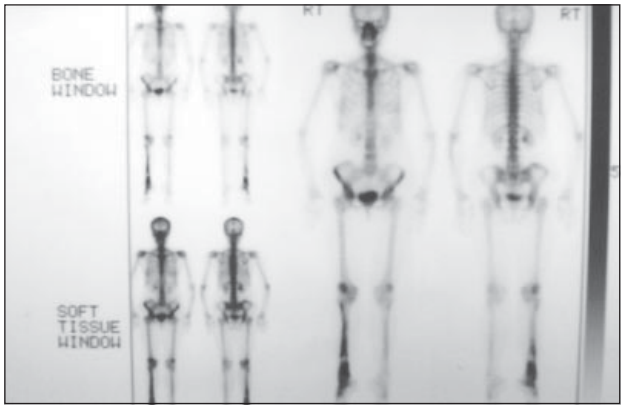


**Figure 3.** Whole body bone scan shows a distal tibial lymphoma of bone with intense uptake of radionuclide at the right tibia.

patient (patient 3) had hemi-laminectomy and wiring performed for vertebral collapse. The other (patient 2) had total hip replacement for suspected avascular necrosis and fracture of the femoral neck (before the diagnosis of lymphoma was made). Another patient (patient 1) sustained a compound pathological fracture of the involved tibia 1 week after the first cycle of chemotherapy. Surgical fixation and intramedullary nailing was performed with no interruption of subsequent chemotherapy.

All patients were initially treated with combination chemotherapy. Originally, it was planned to give 6 to 8 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or its variant CEOP (with doxorubicin replaced by epirubicin). The schedules and dosages are listed in Table 4. Three of the 5 patients had World Health Organization (WHO) grade 3/4 neutropenia during chemotherapy. One patient (patient 3) had chemotherapy stopped after the third cycle because of poor marrow tolerance and repeated neutropenic fever despite growth factor support. Another patient (patient 4) had chemotherapy stopped after the fifth cycle because of viral hepatitis B reactivation. The hepatitis gradually subsided after cessation of chemotherapy.

All patients showed good clinical response to chemotherapy at physical assessment. Post-chemotherapy MRI or CT scans were done for 2 patients who showed resolution of soft tissue swellings. Another 2 patients had progress radionuclide scan done — both showed marked reduction of radionuclide uptake at the original tumour site. For the patient with PLB of the spine, progress CT scan was done but failed to produce meaningful assessment, mainly because of the severe artifacts generated by the alloy instruments. Consolidation radiotherapy was given to all patients after completion of chemotherapy. The whole bone was covered with radiation doses ranging from 40 to 44 Gy, using 2 Gy daily fractions. All patients tolerated the radiotherapy well and treatments were completed uneventfully. In all patients, differentiation of healing bone from residual active tumour by progress imaging after treatment was difficult.

**Table 3.** International Prognostic Indices.

| Patient number | International Prognostic Indices | | | |
|---|---|---|---|---|
| | Age >60 years | ECOG performance status >2 | Serum lactate dehydrogenase >1 x upper normal limit | Total number of risk factors |
| 1 | - | - | + | 1 |
| 2 | - | - | - | 0 |
| 3 | - | - | + | 1 |
| 4 | + | - | + | 2 |
| 5 | - | - | + | 1 |

*Abbreviation:* ECOG = Eastern Cooperative Oncology Group.

**Table 4.** Combination chemotherapy regimens.

| Scheme | Drug | Dose | Schedule |
|---|---|---|---|
| CHOP | | Repeat every 3 weeks | |
| | Cyclophosphamide | 750 mg/m$^2$ IV | Day 1 |
| | Doxorubicin | 50 mg/m$^2$ IV | Day 1 |
| | Vincristine | 1.4 mg/m$^2$ (maximum 2 mg) IV | Day 1 |
| | Prednisolone | 100 mg oral | Days 1 to 5 |
| CEOP | | Repeat every 3 weeks | |
| | Cyclophosphamide | 750 mg/m$^2$ IV | Day 1 |
| | Epirubicin* | 50-60 mg/m$^2$ IV | Day 1 |
| | Vincristine | 1.4 mg/m$^2$ (maximum 2 mg) IV | Day 1 |
| | Prednisolone | 100 mg oral | Days 1 to 5 |

*Abbreviation:* IV = intravenous.
* Dose of epirubicin was 50 mg/m$^2$ for patients aged >60 years.

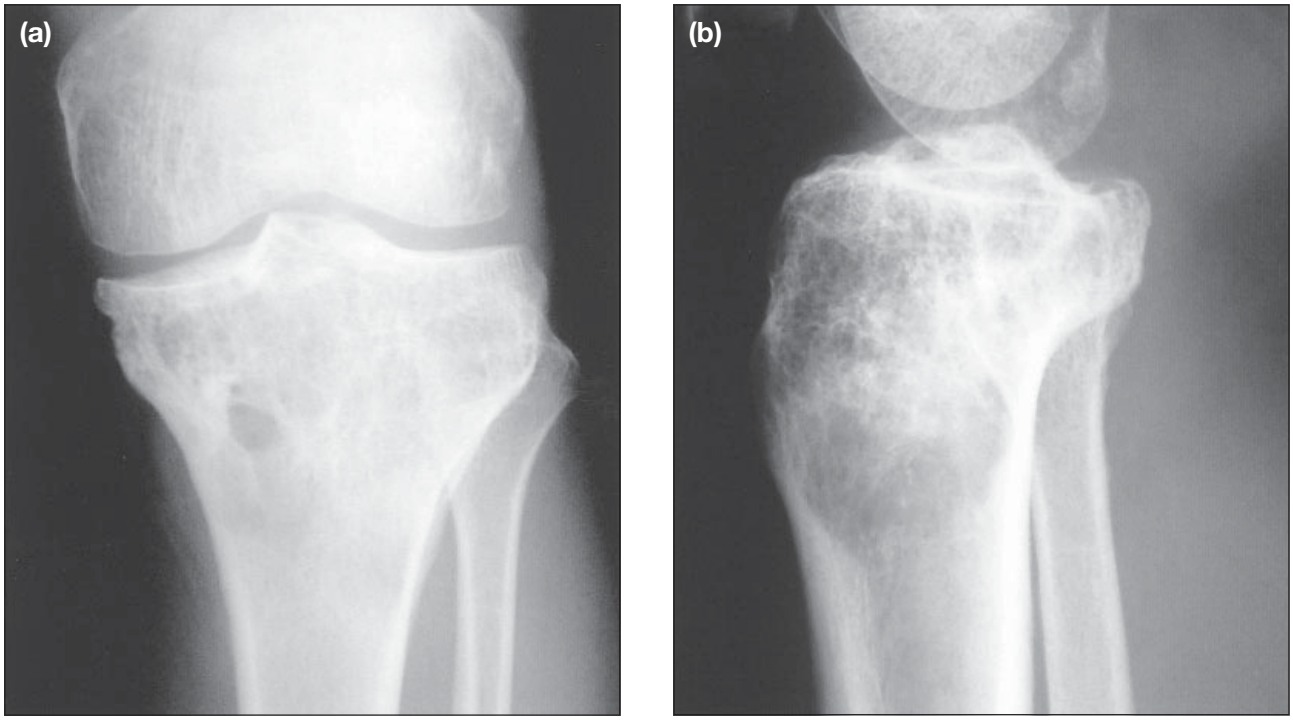


**Figure 4.** (a) Anteroposterior and (b) lateral radiographs show a proximal tibia primary lymphoma 1 year after completion of treatment with areas of new bone formation within areas of previous destructive site.

The median follow up duration is 60 months (range, 28 to 73 months). All patients remain alive and relapse-free. Both relapse-free survival and overall survival at 4 years were 100%. The patient who had the complication of compound fracture of the tibia during chemotherapy had good bone healing and the nail was removed 43 months after treatment completion. The other 2 patients with tibial primary lesions also had good bone healing after treatment (Figures 4a and 4b) with no late complications to date.

## DISCUSSION

Since PLB is a rare disease entity, the case series in the literature are all retrospective, non-randomised studies with patients collected over a long period of time (Table 1). From these studies, PLB affected a wide range of ages with the peak incidence in the fifth decade of life. There was a slight male predominance. Most patients presented with bone pain and localised swelling but without systemic symptoms.[2,3,5-7] The commonest histological subtypes of PLB were B-cell lymphomas with a diffuse mixed-cell or diffuse large cell histology, but other histologies such as small non-cleaved cells have been reported.

The IPI has been shown to be a useful prognostic tool for NHL. Since patients with stage III or IV and greater than 1 extranodal site of involvement are excluded from PLB studies, there are only 3 evaluable parameters: age, serum LDH, and performance status. Dubey et al had reported that the IPI, based on these 3 factors, was a valid prognostic tool for PLB.[5] The 10-year disease-free survivals for a score of 0 versus a score greater than 0 were 85% and 43%, respectively.

The role of surgery in PLB is limited to the diagnostic biopsy and management of fractures arising before, during, or after definitive treatment. The mainstays of definitive treatment are radiotherapy and chemotherapy. Due to limited clinical data, it is unclear whether combined chemotherapy and radiotherapy is superior to either chemotherapy or radiotherapy alone.

In 1983, Dosoretz et al presented the treatment results of 30 patients with localised PLB treated with radiotherapy alone from 1950 to 1978.[11] The 5-year relapse-free survival and overall survival were 53% and 63%, respectively. The local control rate was 86% and there was no local failure observed for patients who received radiotherapy doses higher than 50 Gy.

In 1987, Mendenhall et al reported their experience with 21 patients — 9 received radiotherapy alone, 1 received chemotherapy alone, and 11 received combined chemotherapy and radiotherapy (55 Gy in approximately 30 fractions).[16] Different chemotherapy schemes were

used, ranging from single agents, such as cyclophosphamide or chlorambucil, to multi-agent regimens. However, nearly half of the patients were treated without an anthracycline component, which was probably suboptimal by modern standards. Six of 9 patients (67%) who received radiotherapy alone failed either locally or regionally, while 6 of 11 patients (55%) who received combined therapy failed distally. The only patient who received chemotherapy alone relapsed locally. Overall, 5-year survival was only 56%. More recently, these researchers analysed their treatment results of exclusively stage IE PLB patients. Among 28 patients treated with radiotherapy alone or combined chemotherapy and radiotherapy, the local control rate was 100%. The cause-specific 5- and 10-year survivals were 60% and 53%, respectively. Multivariate analysis suggested age 60 years or older, lack of aggressive chemotherapy, and site of origin other than the long bones may influence the likelihood of survival. In the study, an aggressive regimen was defined as at least 75% of optimal doses of either an anthracycline-containing regimen given for at least 3 cycles, or mechlorethamine, vincristine, procarbazine, and prednisone, or cyclophosphamide, vincristine, procarbazine, and prednisone given for at least 6 cycles.[6]

In 1994, Fairbanks et al reported 63 patients with stage IAE PLB.[4] Fifty patients were treated with radiotherapy alone, 10 patients were given combined therapy, 2 patients had chemotherapy alone, and 1 had surgery alone.[4] Univariate analysis suggested an improved 5-year disease-free survival for patients treated with combined treatment versus radiotherapy alone (90% versus 57%) but multivariate analysis showed neither treatment resulted in a superior outcome with respect to overall survival. However, radiotherapy doses higher than 40 Gy resulted in improved overall survival compared with lower doses.

In 2002, Stein et al reported their experiences of 10 patients with stage IE-IIE PLB treated with doxorubicin-based chemotherapy (mostly CHOP for 6 cycles).[9] Seven patients had consolidation radiotherapy to the primary tumour with generous margins. For patients with stage IIE disease, the regional lymph nodes were irradiated as well. The mean radiotherapy dose was 39.89 Gy. The outcome was impressive — 9 patients were alive without evidence of disease relapse. No patients had severe late side effects. Only 1 patient died due to metastatic small cell lung cancer while in complete remission from the lymphoma. These authors concluded that they had adopted the combined modality approach in their institution based on their excellent results.

Apart from the usual treatment complications of chemotherapy and radiotherapy, bone fracture, either before or after treatment, is a significant complication.[2,5-7,12,16-18] This is due to either bone damage by tumour, radiotherapy, or disuse atrophy due to pain. For lesions in weight-bearing bones, risk of fractures ranging from 50% to 85% has been reported. It has been suggested that radiation doses of 50 Gy or higher did not increase the probability of local control but appeared to contribute to the risk of fracture following radiotherapy.[5-7,16-18]

It is clear that no definite conclusions about optimal management of PLB can be drawn from these retrospective studies. Interpretation is further complicated by the fact that chemotherapy schemes used in many of these studies are also suboptimal by modern standards. Due to the rarity of this disease, there are no ongoing or completed randomised controlled studies to address this issue. However, from large prospective studies of other lymphomas, there is growing evidence of improved treatment outcomes with combined chemotherapy and radiotherapy. From the result of the Southwest Oncology Group randomised study, superior progression-free survival and overall survival were demonstrated with combined CHOP chemotherapy (3 cycles) and involved-field radiotherapy, when compared with 8 cycles of CHOP chemotherapy alone.[19] It thus appears logical to apply the same approach to PLB.

The excellent clinical outcome of our patients lends further support to the combined approach, and radiotherapy doses of 40 to 44 Gy appear sufficient after induction chemotherapy. We favour the addition of routine consolidation radiotherapy as it is difficult to differentiate residual tumour from regenerating bone in these patients. From the experience of other lymphoma studies,[19] it is likely that a shortened course of chemotherapy may be sufficient.

## CONCLUSION

These results suggest that combined chemotherapy and radiotherapy can provide excellent local and systemic disease control for primary malignant lymphoma of bone. Radiotherapy with doses of approximately 40 to 44 Gy appears to be sufficient for local control of the tumour and has no significant adverse effect on healing of the involved bone.

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