Primary Lymphoma of Bone: Experience of 39 Cases at the Tata Memorial Hospital, India

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Primary lymphoma of bone (PLB) is an uncommon clinical entity and a rare presentation of non-Hodgkin's lymphoma. At the Tata Memorial Hospital, over a period of 10 years from 1976 to 1985, 39 cases with a diagnosis of PLB were seen. Twenty-seven cases completed the prescribed treatment and were evaluable for treatment response. Eight patients (21%) presented in clinical stage I (E), four patients (10%) in stage II (E), and 27 patients (69%) in stage IV (E). All of the evaluable patients except two were treated with combination chemotherapy, which consisted of cyclophosphamide, vincristine, and prednisolone in 18 patients, and seven patients received Adriamycin in addition. The majority of patients received six courses of chemotherapy extending over 8 to 12 months. External radiotherapy was given to all except one patient, who had surgery as local treatment. Five patients had generalised relapse, one of which had in addition a local relapse. Five were resistant to treatment. Overall and disease-free survival by Kaplan-Meier method at 60 months are 66% and 56%, respectively.

KEY WORDS: malignant bone lymphoma, radiotherapy, chemotherapy

INTRODUCTION

Primary lymphoma of bone (PLB) is a distinct, well-recognized clinicopathological entity, accounting for approximately 5% of all extra nodal lymphomas [1]. It is histologically identical to lymphoma arising in lymphoid or soft tissue, but it is present initially as a localized or multifocal bone lesion. This tumour has a significantly different clinical course and a much better prognosis than non-Hodgkin's lymphoma (NHL) secondarily affecting bone [2].

Radiotherapy is an effective modality for good local control due to its radioresponsiveness but distant failures occur in approximately 50% of initially localised bone tumours [3]. Thus, employment of adjuvant systemic chemotherapy in a multimodal approach is warranted for the improvement of results [2,4–6].

This study reviews 39 cases of PLB and discusses the present treatment policy at the Tata Memorial Hospital.

MATERIAL AND METHODS

Over a period of 10 years, from January 1976 to December 1985, a total of 2,749 patients of biopsy-proven NHL were registered at the Tata Memorial Hospital, Bombay; 934 patients (34%) presented with extranodal disease, of which 39 (4.2%) involved the bone primarily.

The mean and median age at presentation was 37 years (range 3 to 67 years; Fig. 1). Twenty-eight patients (72%) presented in the 3rd to 5th decades; 31 (79%) were males and eight (21%) females with a male-to-female ratio of 4.9:1 (Fig. 1).

All patients presented with persistent, localized bony pain and swellings from 1 month to 6 months' duration. Eleven patients (28%) presented with multiple bony in-
Fig. 1. Age distribution of patients with primary lymphoma of bone. The youngest patient was 3 years old, the oldest 67 years (median 37 years).

volvement in noncontiguous sites at initial presentation; four (10%) had lymphadenopathy at the regional drainage sites, away from the primary focus. Only two patients (5%) presented with fever of 1 month's duration.

All patients underwent a thorough sequential work-up to rule out systemic lymphoma. This evaluation included complete blood counts and chemistry, chest and bone radiographs, biopsy of tumour to give tissue diagnosis and bone marrow aspiration, and biopsies at sites other than known areas of disease. In addition, eight had bipedal lymphography and 26 had radionuclide bone scans. Computed tomography (CT) scan evaluation was not carried out because it was not available in our hospital at the time of this study.

The clinical, radiological, and isotopic bone scan revealed multiple bony site involvement in 27 patients (69%), whereas 12 (31%) showed singular bone involvement. The site distribution of disease appears in Figure 2. Bones of the pelvis, namely ilium and ischium, were involved in 12 patients (17%), followed by vertebral involvement in nine (13%) and that of the skull bones in six patients (9%). Among the appendicular bones, the humerus and femur were most commonly involved, in seven patients each (10%), followed by the tibia in six patients (9%). In all 39 patients, a total of 69 bony lesions were seen, 44 (64%) in the axial skeleton and 25 (36%) in the bones of the extremities.

The histopathology was interpreted according to the modified Rappaport's classification for NHL [7]. All patients had unfavourable histological subtypes: 26 patients (67%) had diffuse histiocytic (DH), ten (26%) diffuse poorly differentiated lymphocytic (DPDL), and three (7%) undifferentiated (UD) lymphoma.

Of the special investigations for lymphoma, bipedal lymphography showed positive retroperitoneal nodes in only three of the eight patients subjected to it (38%). Bone marrow involvement was seen only in two patients (5%), whereas isotopic bone scan revealed multiple involvement in 16 of the 26 patients (62%) in which it was undertaken.

The clinical staging was undertaken in accordance with Ann Arbor Staging System [8] (Table I). Eight patients (21%) were found to be in stage IA (E), four (10%) in IIA(E), and the remaining 27 (69%) in stage IV(E). Of the total patients, only 27 completed the prescribed treatment and are the subject of analysis of treatment response in the present study.

Twenty-four patients (89%) received combination of multidrug chemotherapy and radiotherapy. Two patients (7%) in stage IA(E) had only localized radiotherapy, and one patient had surgery followed by postoperative adjuvant chemotherapy (Table II). All patients who received radiotherapy were simulated and treated to single bony site or multiple areas of involvement, either by telecobalt or by 6 MV linear accelerator. Radiation fields encompassed the entire bone in which the tumour originated and a margin of soft tissue around the clinically and radiographically defined lesion. The total dose of radiotherapy varied from 30 to 45 Gy according to the site and volume of the tumour, age of the patient, and skin tolerance. Wherever indicated, a localized "boost" of an additional 10 Gy was delivered to the original tumour area. In lesions of extremities, individual shaping of fields was undertaken, leaving a strip of normal tissue to preserve lymphatic and venous drainage of the affected
chemotherapy and irradiation offered no major problem who completed prescribed treatment is disease free at 82
Clinical stage  

A patient with a primary lesion of the sternum; this pa-

patients.

| TABLE I. Histopathological Correlation With Clinical Stage* |
|-----------------|---------------|---------------|
| HP/CS           | I (E)         | II (E)        | IV (E)        |
| DH              | 5             | 4             | 17            |
| DPDL            | 3             |               | 7             |
| UD              |               |               | 3             |

*DH = diffuse histiocytic; DPDL = diffuse poorly differentiated
lymphocytic; UD = undifferentiated lymphoma. Total number = 39

<table>
<thead>
<tr>
<th>TABLE II. Result of Treatment</th>
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<tr>
<td>Clinical stage (no. of patients)</td>
</tr>
<tr>
<td>I (E) (2)</td>
</tr>
<tr>
<td>II (E) (4)</td>
</tr>
<tr>
<td>IV (E) (19)</td>
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<tr>
<td>IV (E) (1)</td>
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<tr>
<td>Total (27)</td>
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</tbody>
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*RT = radiotherapy; S = surgery; CT = chemotherapy; REC = recurrence; RES = residual disease.

Among the stage IV(E) patients, 20 completed the
treated with chemotherapy, and 11 (55%) are disease free 53 to
According to the Kaplan-Meier method at 60 months were 66% and 56%

RESULTS

In stage IA(E), of the six patients that completed the
prescribed treatment, four (67%) were disease free at 40 to 134 months after diagnosis. One patient who was
treated with only radiotherapy died of an unrelated cause at 9 months after diagnosis. The tumour was resistant in
a patient with a primary lesion of the sternum; this pa-
tient died of disseminated disease at 12 months of diag-

18 patients (72%) were treated with a regime
using cyclophosphamide, vincristine, and prednisolone
(COP), as shown in Table III. In seven patients (28%),
Adriamycin was given in addition to the above regime
(CHOP). Chemotherapy in either regime was carried out
for six courses in the majority of patients. However,
patients in the former schedule received two to four
courses in addition. Thus, the duration of chemotherapy
was 8 to 12 months in most of the cases. Concomitant
chemotherapy and irradiation offered no major problem
of administration and did not lead to interruption of ther-
apy in the majority of patients.

1.8

1.4

CHOP (7 patients)

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VCR 1.4 mg/m² days 1-15
PRED 40 mg/m² days 1-15

*CTX = cyclophosphamide; VCR = vincristine; PRED = predni-
solone; ADRIA = Adriamycin. Total number = 25 patients.

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12 to 20 months after having completed six courses of COP and
local radiotherapy. Two of the latter also had central
nervous system involvement. All were treated with fur-
ther radiotherapy and chemotherapy but died of disease at 24 to 91 months after diagnosis. In four patients
(20%), sustained progression of disease was observed
despite combined modality therapy comprising COP in
three and CHOP in the fourth patient; all died of dissem-
nated disease within 12 months of diagnosis. Three of
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A comparison of the clinical efficacy of the poly-

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the tibia 6 months after initiation of therapy and was subjected to palliative amputation. The operative specimen confirmed the absence of any residual disease.

**DISCUSSION**

In 1939, Parker and Jackson [9] drew attention to the existence of a special bone tumour, namely, primary reticulum cell sarcoma of bone. Since then there have been sporadic reports in the literature of this rather uncommon and obscure tumour. Lately it has been recognised as a separate clinicopathological entity [6]. It is a moderately radiosensitive tumour, and radiotherapy can impart a good local control [6,10,11].

Dosoretz et al. [10] demonstrated that in a significant proportion of patients PLB presented as a localized disease, whereas Reimer et al. [12] felt that the majority present in a disseminated form. Newall and Friedman [13] found PLB unpredictable and to have a potential for metastases to any part of the body. In an analysis of 17 cases of PLB seen over a specific period at our institution, Dinshaw et al. found only 24% in stage I, the remaining being clinically advanced at presentation [4]. In the present study, which includes some cases from the above study, 80% cases have presented in stage II and beyond. All patients included in both of these studies had unfavourable histological subtypes, with diffuse histiocytic lymphoma being the most common. The high frequency of diffuse histology in this group of patients is similar to that seen in patients with other extranodal lymphomas [14–17].

Sweet et al. [18] emphasize the inclusion of staging laparotomy in the pretreatment work-up, whereas Reimer et al. [12] detected the presence of disseminated disease in the majority of patients without the necessity for staging laparotomy. In the present study, 62% of the patients presented in clinical stage I(E) and, after complete pretreatment workup, only 20% remained in that stage. We are thus of the opinion that, due to the majority of patients presenting with unfavourable histology and disseminated disease in bones, staging laparotomy is not warranted in the pretreatment workup of PLB.

Conventionally, radiotherapy has remained the mainstay of treatment of PLB as against surgery, whereas the adjunctive rather than palliative value of chemotherapy has been appreciated only lately. Wang and Fleischli [19] reported a 5 year cure rate of 50% with radiotherapy or radical surgery; Shoji and Miller [20] achieved a 5 year survival of 44% with these modalities. That a combination of surgery and radiotherapy does not impart a more significant benefit in survival than the use of either modality alone is also supported by the experience of Boston et al. [3].

The dramatic improvement in long-term disease control of PLB with organised adjuvant chemotherapy programmes is sufficiently documented in recent literature [2,6]. The clinical superiority of Adriamycin-based chemotherapy schedules for the more unfavourable lymphoma has been acknowledged by various workers [5,21,22]. In the present series, 25 (93%) patients were treated with combination chemotherapy, only seven of which included Adriamycin. Of the former group, 15 (60%) are disease free for a mean period of 66 months following therapy (range 40 to 142 months). The remaining 10 (40%) died of uncontrolled disease. Of the patients who received the CHOP schedule, five (71%) are alive and well, whereas among those treated without Adriamycin, eight (44%) succumbed to disease.

Of the two patients in stage IA(E) who were treated with radical radiotherapy, one remains controlled without disease at 88 months; the other died of an unrelated cause at 9 months after therapy. Although in both of these cases the tumour dose employed was 40 Gy, we would recommend irradiation doses in the range of 40 to 55 Gy in 4 to 6 weeks, as also suggested by other authors [20,23], along with adjuvant Adriamycin-based chemotherapy. Megavoltage therapy with multiple fields and irradiation of all fields per session and shrinking field technique would allow delivery of doses in the higher dose range mentioned above. The likelihood of therapy-related fractures as expressed by Stokes and Walz [24] would, in our opinion, be remote with the use of the aforementioned radiation technique.

The incidence of extension of lymphoma to the central nervous system from remotely stationed primary disease needs further investigation. In an analogy to the management of aggressive NHL, cranial prophylactic therapy could help augment the chances of long-term control in specific cases. Further clinical trials are thus necessary to throw light on this aspect.
CONCLUSION

PLB usually presents in a disseminated form and with an unfavourable histology requiring combined modality therapy. An optimal management scheme would comprise Adriamycin-based chemotherapy and individually tailored megavoltage radiotherapy to doses of 45 to 55 Gy in 4 to 6 weeks.

REFERENCES