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Primary non-Hodgkin's lymphoma of bone: treatment and outcome

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Background. *This study was performed to assess the characteristics, management and outcome of patients with primary Non-Hodgkin's lymphoma of the bone that were diagnosed and treated at Roswelll Park Cancer Institute.*

Patients and methods. *Eighteen patients were presented to us with the criteria, for diagnosis with histopathological and immunohistochemical confirmation, of Non-Hodgkin Lymphoma with adequate bone biopsy between 1970-1996. Twelve patients received combined treatment with anthracycline based chemotherapy and localized radiation, 5 received localized radiation alone and 1 had chemotherapy alone.*

Results. *There were fifteen patients with stage IEA, and three patients were staged IVEA. The histopathological examination revealed 13 patients with intermediate - grade diffuse, large cell, 2 patients were intermediate-grade diffuse mixed small and large cells, 2 patients were intermediate-grade diffuse small cleaved cell type, and 1 patient had an anaplastic large cell type. Five patients treated with combined treatment and one patient treated with localized radiation alone are without evidence of the disease at a median follow-up of 13 years. Six patients who had combined treatment with radiation and chemotherapy and 3 patients who had radiation alone died from progression of their disease. Two died from other causes, one with combined treatment with radiation and chemotherapy and the other with radiation alone. One patient with combined treatment was disease free at one year but was lost to follow -up.*

Conclusions. *This study suggests that patients presenting with early-stage primary Non-Hodgkin's Lymphoma of bone can be treated with curative intent with the combination treatment of localized radiation and systemic chemotherapy. However, confirmation needs to be verified in larger and prospective studies.*

Key words: lymphoma non-Hodgkin-drug therapy-radiotherapy, bone neoplasms, anthracyclins; treatment outcome

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Introduction

Primary non-Hodgkin's lymphoma of the bone (PLB) is a rare form of lymphoma. With such rare neoplasms, information on treatment and outcome is difficult to obtain in a controlled, prospective manner.[1,2] Treatment is generally based on the extent of disease. Patterns of failure for early stage disease have been thought to be more local than distant. However, more recently, these patients are thought to have a risk of both local and distant failure. In fact, lymphoma presenting in bone may often be a sign of disseminated disease. As a result, initial treatment with curative intent has evolved from local irradiation alone to combination local radiation and systemic chemotherapy.[3-6] This study relates our experience in the diagnosis and treatment of this rare clinical entity.

Primary malignant lymphoma of bone presents both diagnostic and therapeutic problems.[7] The Non-Hodgkin's lymphomas encompass over 29 types of lymphoma. The group of cancers under the general term lymphoma is quite broad. Over the years, different classification systems have been used to differentiate lymphomas including Rappaport classification (used until the 70's) the National Cancer Institute Working Formulation and most recently, the National European-American Lymphoma Classification (REAL) system.[8-10] Additionally primary non-Hodgkin's Lymphoma of bone (PLB) constitutes approximately 5% of all extranodal non-Hodgkin's Lymphoma (NHL) and 7% of primary bone tumors.[11] With PLB being rare disease, there has been paucity of publications on its treatment and outcome while the clinicopathologic staging has changed several times over the last 30 years.

Patients and methods

Patients

Between January 1, 1970 and December 31. 1996, eighteen patients met the criteria for a histologically confirmed diagnosis of non-Hodgkin's Lymphoma of the bone (PLB) by biopsy of the bony lesion. These were then classified according to the Working Formulation and The Revised European-American Lymphoma (REAL) classification.[9,10] To have a diagnosis of PLB, patients needed a primary focus in a single bone, with or without locoregional adenopathy. However, multiple bony lesions were allowed if there was no evidence of lymphomatous involvement outside of bone.

Staging

All patients were staged according to the Ann Arbor Staging Classification.[13] Patients were evaluated with a complete history and physical examination. Staging investigations included a minimum of a chest X-ray with X-rays of the bone lesion(s) and /or a skeletal survey. Ten patients had computed tomography (CT) scans of the chest, abdomen, and pelvis; three patients had gallium scans, one patient had magnetic resonance imaging (MRI); all patients had a bone marrow aspirate and / or biopsy.

Treatment and assessment of the response

Twelve patients received combined treatment with anthracycline based chemotherapy and localized radiation, 5 received localized radiation alone using 6 Megavoltage with doses range from 2000 cGy to 5000 cGy in 200 cGy per fraction and 5 treatments per week, and 1 had chemotherapy alone as their initial curative treatment.

A complete response was defined as disappearance of all evidence of lymphoma documented by a normal physical examination,

Table 1. Patients and tumor characteristics

Patient	Gender	Age	Site	Stage	Histology
1	F	49	Ulna, Metatarsal	IVE	DSC
2	M	44	L-spine	IE	DLC
3	F	68	Sacrum	IE	ALC
4	M	24	Femur	IE	DLC
5	M	21	Tibia	IE	DMC
6	M	64	Ileum	IE	DLC
7	M	24	Femur	IE	DLC
8	M	35	Femur	IE	DLC
9	M	29	Scapula	IE	DLC
10	F	68	L-spine	IE	DLC
11	F	57	T-spine	IE	DLC
12	M	32	Humerus	IE	DLC
13	M	84	Clavicle, C-spine	IVE	DLC
14	M	70	Sternum	IE	DMC
15	F	87	L-spine	IE	DLC
16	F	27	Ileum	IE	DLC
17	F	73	L-spine	IE	DSC
18	F	41	Femur, Ileum	IVE	DLC

M = male; F = female; DLC = diffuse large cell, DSC = diffuse small cell, DMC = diffuse mixed small and large cell, ALC = anaplastic large cell.

blood tests, and radiographic imaging. A partial response was defined as a decrease in more than 50% in size with residual radiographic abnormalities, which are sometimes considered as fibrosis or bone remodeling after treatment. No response was defined as less than a 50% reduction in size of known disease. Progressive disease was defined as an increase in the size of known disease or the appearance of new sites of involvement. Survival was measured from the date of diagnosis.

Results

Patients characteristics

Of the 18 patients, there were 8 females and 10 males. The mean and median age was 50 years and 49 years respectively (range 21 - 87). Fifteen patients were staged as IEA, 3 patients were staged IVEA. The most common presenting symptom was pain at the involved site. None of the patients presented with B symptoms. The histopathology included 13 patients with intermediate-grade diffuse large cell, (Diffuse large B-cell, in REAL) 2 patients were intermediate-grade diffuse mixed small and large cell, (Angioimmunoblastic T -cell lymphoma, in REAL) 2 patients were intermediate-grade diffuse small cleaved cell type, (Angiocentric lymphoma, in REAL) and 1 patient had an anaplastic large cell type (Anaplastic large cell (CD 30+), in REAL). Sites of involvement were long bone (7), flat bone (4), spine (6) and pelvis (5). Two patients had more than one bone involved. Patients and tumor characteristics are summarized in Table 1.

Outcome

Of the eighteen patients, 6 patients are without evidence of disease at a median follow-up of 13 years; 5 of these 6 patients received combined treatment with chemotherapy and radiation, while 1 patient had only localized radiation. Nine out of 18 patients died from progression of their disease; 2 were stage IVEA; 3 of these 9 had radiation alone as initial treatment, and the other 6 had combined modality treatment with radiation and chemotherapy. Of the remaining 3 patients (2 of whom had combined treatment with radiation and chemotherapy, and 1 with radiation alone), 2 died from other causes and were found to be free of disease; 1 patient was disease free at one year but was lost to follow-up. Table 2 outlines the treatment given and outcome after completion of treatment.

Discussion

Our series had similar patient and tumor characteristics as those with PLB reported in the literatures. The majority of patients however appear to have B cell tumors with inter-

Table 2. Treatment and outcome

Patient No.	Radiation cGy/#frxs	Chemotherapy Regimen x (#courses)	Initial Response	Status
1	3750/15	CHOP X 6	CR	ANED
2	4500/25	CHOP X 6	CR	DOD
3		CHOP X 8	CR	DWD
4	4000/20	MACOP- B X 6	CR	ANED
5	4000/20	CHOP X 3	CR	ANED
6	3600/18	CHOP X 6	CR	ANED
7	4400/22		CR	ANED
8	4000/20	CHOP X 6	CR	ANED
9	5000/25	CYTOXAN / PREDNISONE	CR	DOD
10	3200/16		CR	DOD
11	4000/20		CR	DOD
12	4000/20	CHOP X 6	CR	DOD
13	3000/10	CYTOXAN / PREDNISONE	CR	ANED*
14	3000/10	MCOP X 6	CR	DOD
15	2000/10		CR	DWD
16	4000/20	MCOP X 6	PR	DOD
17	3600/18		CR	DOD
18	3000/10	CYTOXAN	CR	DOD

cGy = centigray; frxs =fractions; ANED = alive without evidence of disease; ANED*= alive without evidence of disease but lost to follow-up at 1 year; DOD = dead of disease; DWD = dead without disease; CR = complete response; PR = partial response; MCOP = methotrexate, cyclophosphamide, vincristine, prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin

mediate-grade mixed small and large cell lymphoma and the intermediate-grade diffuse large cell lymphoma.[12,14,15] A minority in literatures were a small non-cleaved (non-Burkitt's) lymphoma and an immunoblastic lymphoma[7] according to the Working Formulation. Our series had 13 patients with intermediate-grade diffuse large cell type; 2 patients with intermediate-grade diffuse mixed small and large cell; 2 with intermediate -grade diffuse small-cleaved cell; and 1 patients with an anaplastic large cell type.

The peak incidence of PLB is reported to be in the fifth decade with the median age 44 years and a male predominance. The most common symptom was localized bony pain and swelling with the majority of the cases involving the lower half of the body.[16,17]

Suryanarayan et al.,[18] studied the group of 31 children of PLB and reported the primary sites were the femur (9), tibia (8), with the remainder involving the upper half of the body. Twenty-one of the cases were classified as intermediate-grade large cell lymphoma. In our study, the age was ranging from 21 years to 87 years with the median age was 50 years. The most common presenting symptom was pain at the involved site. None of our patients had B symptoms and 12 patients had disease in the lower half of the body (4 flat bone, 6 spine).

Most pervious studies indicate the majority of the patients with PLB present with early stages. Vassallo et al.,[19] reported 7 of 8 cases presenting with stage IE disease, whereas 18 of 21 cases reported by Mendehall et al.,[20] presented with stage IE or IIE disease. Additionally two other studies, one by Baar et al.,[7] found 13 out of 17 patients with localized, stage IEA disease and the other by McIntyre et al.,[21] reported 18 out of 22 with stage IE disease. Similar to these studies, our series had 15 patients with stage IEA and only 3 patients with stage IVEA.

The rarity of non-Hodgkin's lymphoma of the bone and the misleading histologic features because of similarity to other small round cell tumors can cause considerable difficulty in diagnosing this entity. Additionally assessment of response after treatment is challenging because of the persistent radiologic abnormalities. Multiple bone biopsies are generally required as result. Hatori et al.,[22] concluded that flow cytometry, in conjunction with morphologic and other molecular techniques, can provide a rapid and accurate means of diagnosing of this disease. Ascoli et al,[23] found that clinical data, radiographic findings and cytohistological correlation led to a final diagnosis of primary non Hodgkin's lymphoma of the bone, confirmed by immunopositive staining for leukocyte common antigen CD45 and B-cell associated antigen CD20.

The best treatment of primary NHL of the bone remains unknown. All patients in our

series with stage IV and 9 patients with stage IEA received localized radiation and chemotherapy (with or without anthracycline based regimens). Our results with such treatment appear similar to that reported by others.

Ferreri et al.,[24] studied 20 patients with PLB, 12 patients with monostotic disease (stage I and II) and 8 patients with polyostotic disease (stage IV), all patients received adriamycin-containing chemotherapy in association with radiation therapy to 45 Gy. All patients with monostotic disease achieved complete remission (CR). After a median follow-up period of 50 months, 10 patients were alive and relapse-free, 1 other patient was alive following relapse and 1 patient died with relapse free.

The survival rate for the patients in this study were 92% at 50 months but the survival rate with the patients staged IV was 25% at 40 months. They concluded that the treatment of patients with early stage PLB with adriamycin- containing chemotherapy and whole bone irradiation to 45 Gy, prevented local relapse and produce more favorable outcome. Baar et al,[16] reported on 17 patients treated for early-stage PLB with combined modality treatment with chemotherapy and radiotherapy. They noted that 13 of 17 (76%) patients were disease free at a median of 29 months. Of these 13 patients, all patients received chemotherapy with anthracycline based regimen with 9 receiving adjuvant radiotherapy to the primary site of the disease. Of the 4 patients who relapsed, 2 received chemotherapy alone; 1 received radiotherapy alone; and 1 received chemotherapy plus radiation to the primary site. The authors concluded that combined treatment with chemotherapy and radiation improves outcome over single modality treatment of either radiation or chemotherapy for localized Non-Hodgkin's lymphoma of the bone.

One study reported by Tondini et al.,[25] demonstrated a 5-year relapse-free survival and total survival of 83% for patients with stage I and II disease with a short chemotherapy course of cyclophosphamide, doxorubicin, vincristine, and prednisone followed by locoregional irradiation.

In another study, Bacci et al.,[26] observed 30 patients treated for PLB over a 10- year period. Four patients were treated with radiation at a dose of 3000-4500 cGY in 15-23 fractions to the whole bone with the boost of 1000-1500 cGy in 5-8 fractions to the primary lesion and 26 patients were treated with radiotherapy plus adjuvant chemotherapy with one of two anthracycline-containing regimens. There were 3 systemic relapses in this group and local relapse was observed in one of the four patients treated with radiotherapy only. The overall disease-free survival was 88% at a mean follow-up period of 87 months.

In contrast to these very positive results, Mendenhall et al.,[20] described their experience with 11 patients who received combined -modality therapy, 9 patients who received radiotherapy alone and 1 patient who received chemotherapy alone. There were 13 relapses in 21 evaluate cases. Six of 9 patients who received radiotherapy alone relapsed either regionally or distantly and 6 of 11 patients who received combined chemotherapy and radiotherapy treatment relapsed distantly. The patient who received chemotherapy alone relapsed locally. Overall 5-year survival was 56%. In this series, no treatment modality demonstrated and clear-cut advantage in the management of PLB.

In summary, our experience would suggest that those patients presenting with early-stage primary Non-Hodgkin's Lymphoma of bone can be treated with curative intent and do best with combination treatment consisting of localized radiation and systemic chemotherapy. Patients with advanced stage disease, however, have a poor prognosis despite aggressive combination treatment and should be considered for treatment on protocols. However, because our small patient numbers and heterogeneity of patients dis-

ease definite conclusions can not be drawn but warrant future investigation in a multi-institutional setting to accrue enough patients for prospective, randomized studies.

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