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Lymphoma

Clinical Features, Management, and Prognosis of an International Series of 161 Patients With Limited-Stage Diffuse Large B-Cell Lymphoma of the Bone (the IELSG-14 Study)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Diffuse large B-cell lymphoma • Bone lymphoma • Radiotherapy • Osteolymphoma • Central nervous system prophylaxis

Learning Objectives

Compare outcomes in patients with diffuse large B-cell lymphoma of the bone treated with different modalities.

Compare relapse rates and relapse sites in patients with diffuse large B-cell lymphoma of the bone treated with different modalities.

Abstract

Introduction. The clinical features, management, and prognosis of stage I–II diffuse large B-cell lymphoma of the bone (PB-DLBCL) included in an international database of 499 lymphoma patients with skeletal involvement were reviewed.

Methods. HIV-negative patients ($n = 161$) with diffuse large B-cell lymphoma of the bone (PB-DLBCL) after complete staging workup were considered. The primary objective of this study was to identify the most effective treatment modality; the secondary objectives were to define the contribution of irradiation fields and doses and the pattern of relapse.

Results. Median age was 55 years (range, 18–99 years), with a male/female ratio of 1:2; 141 (87%) patients had stage I, 14 (9%) had B symptoms, 37 (23%) had bulky lesion, 54 (33%) showed elevated lactate dehydrogenase serum levels, and 25 (15%) had fracture. Thirteen (8%) patients received chemotherapy alone, 23 (14%) received radiotherapy alone, and 125 (78%) received both treatments. The response to the first-line treatment was complete in 131 of 152 assessed patients (complete response rate, 86%; 95% confidence interval [CI], 81%–91%) and partial in 7, with an overall response rate of 91% (95% CI, 87%–95%). At a median follow-up of 54 months (range, 3–218), 107 (67%) patients remained relapse-free, with a 5-year progression-free survival of 68% (SE: 4). Four (2.5%) patients had meningeal relapse; 119 patients were alive (113 disease-free), with a 5-year overall survival of 75% (SE: 4). Patients managed with primary chemotherapy, whether followed by radiotherapy or not, had a significantly better outcome than patients treated with primary radiotherapy, whether followed by chemotherapy or not. The addition of consolidative radiotherapy after primary chemotherapy was not associated with improved outcome; doses >36 Gy and the irradiation of the whole affected bone were not associated with better outcome.

Conclusion. Patients with PB-DLBCL exhibit a favorable prognosis when treated with primary anthracycline-based chemotherapy whether followed by radiotherapy or not. In patients treated with chemoradiotherapy, the use of larger radiation fields and doses is not associated with better outcome. Central nervous system dissemination is a rare event in PB-DLBCL patients. ***The Oncologist*** 2014;19:291–298

Implications for Practice: Patients with limited-stage diffuse large B-cell lymphoma of the bone exhibit a favorable prognosis when treated with primary anthracycline-based chemotherapy whether followed by radiotherapy or not. In patients treated with chemoradiotherapy, the use of larger radiation fields and doses are not associated with better outcome. Central nervous system dissemination is a rare event in these patients, suggesting that specific prophylaxis is superfluous.

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Introduction

Primary bone lymphoma (PBL) is a rare disease, comprising approximately 7% of all malignant bone tumors, 4%–5% of all extranodal non-Hodgkin lymphoma, and less than 1% of all malignant lymphomas [1, 2]. Diffuse large B-cell lymphoma (DLBCL) is the most common histological type among all PBL, and most patients have limited-stage disease (stage IE-IIE) at presentation [3–5]. The available literature on diffuse large B-cell lymphoma of the bone (PB-DLBCL) consists of mostly small, monoinstitutional series, resulting in a vague description of clinical features, management, and prognosis. In the past 2 decades, the use of primary anthracycline-based chemotherapy followed by consolidative irradiation has been the most commonly used strategy for patients with PB-DLBCL [6–9], with good overall disease control and survival rates. However, the natural clinical behavior as well as some diagnostic and management issues have yet to be addressed. In particular, the role of different chemotherapeutic combinations, the impact on local disease control of radiation therapy, the contribution of irradiation fields and doses, the pattern of relapse, and the management of pathological fractures and long-term sequelae remain to be defined in an adequate number of patients.

Against this background and under the sponsorship of the International Extranodal Lymphoma Study Group (IELSG), we analyzed presentation, management, clinical behavior, and outcome of 161 cases of PB-DLBCL (stage IE-IIE DLBCL of the bone) included in a multicenter database of 499 lymphoma patients with skeletal involvement.

Materials and Methods

Study Population

The members of the IELSG were invited to participate in a retrospective study focused on PBL (the IELSG-14 study). A questionnaire requesting information about patient characteristics, clinical presentation, diagnosis, staging, International Prognostic Index (IPI) score, treatment, objective response, site and date of relapse, second-line treatment, long-term sequelae, and survival of patients with a histopathological diagnosis of non-Hodgkin lymphoma and bone involvement at presentation was sent to referring centers from November 1980 to January 2005.

In order to investigate clinical and therapeutic features of PB-DLBCL, we reviewed records of patients fulfilling the following criteria: (a) age ≥18 years old; (b) histological diagnosis of DLBCL; (c) stage IE and IIE disease according to the Ann Arbor staging system, that is a single bone lesion with (stage IIE) or without (stage IE) regional lymphadenopathies; (d) complete staging workup with at least enhanced total-body computed tomography scan and bone marrow biopsy; and (e) no evidence of HIV-1 infection (negative serologic tests; absence of epidemiological risk, opportunistic infections, or lymphocytopenia for patients diagnosed in the early 1980s) or other immunodeficiencies. The study conformed to the tenets of the Declaration of Helsinki and was approved by the institutional review boards of the participating centers.

Response Definition

Response to treatment was recorded as follows: a complete response (CR) was defined as the complete disappearance of all evidence of lymphoma, partial response (PR) was defined as ≥50% decrease in tumor size, progressive disease (PD) was defined as ≥25% increase in tumor size or the appearance of any new tumor lesion, and stable disease (SD) was defined when these criteria were not met [10].

Statistical Considerations

The primary objective of this study was to identify the most effective treatment modality; the secondary objectives were to define the contribution of irradiation fields and doses and the pattern of relapse. Clinical characteristics and response rates of the treatment subgroups were compared using the chi-square test or Fisher's exact test for categorical variables, according to the sample size. Survival curves were generated by the Kaplan-Meier method. Overall survival (OS) was calculated from the date of pathologic diagnosis to death or to the last date of follow-up, and progression-free survival (PFS) was calculated from the first day of treatment to relapse, progression, death, or to the last date of follow-up. Patients who did not progress or die at the last date of follow-up were censored, respectively, for PFS and OS analyses. Survival rates were reported as 5-year OS/PFS ± SE. Impact on survival of clinical and therapeutic variables was evaluated by comparing the survival curves by means of the log-rank test. Each patient was assigned to a therapeutic group according to the planned first-line treatment. The independent prognostic value of variables was analyzed using the Cox proportional hazard model. All the probability values were two-sided. Analyses were carried out using the SPSS 13.0 statistical package for Windows (LEAD Technologies, Inc., 2004; http://www.leadtools.com).

Results

Patient Characteristics

The database of the IELSG-14 study included 499 patients from 32 institutions in 14 countries (the list of participating centers with the number of registered patients/center appears at the end of the text). We excluded from analysis 110 patients with lymphoma categories other than DLBCL, 165 patients with advanced-stage DLBCL, 54 patients with incomplete staging workup, and 9 patients with unavailable therapeutic data. The remaining 161 patients with PB-DLBCL are the study population of the present study (Table 1). The median age of study population was 55 years (range, 18–99 years), with a male/female ratio of 1:2. At presentation, 141 (87%) patients had stage I and 20 (13%) patients had stage II, 14 (9%) patients had B symptoms, 37 (23%) had bulky lesion (>10 cm), 54 (33%) showed elevated lactate dehydrogenase (LDH) serum levels, 132 (82%) patients complained of pain as their main symptom, and 25 (15%) had fracture. The femur was the most commonly involved bone (Table 1); 145 (90%) patients had a solitary lesion, and 14 (9%) had multifocal lesions in a single bone. IPI score was 0–1 in 113 patients (70%), 2 in 36 (22%), and 3 in 7 (4%); it was unknown in 5 (3%).

Treatments

Patients were treated according to institutional guidelines, including chemotherapy alone (n = 13; 8%), radiotherapy

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Table 1. Patient characteristics

Parameter	Value
Patients, *n* (%)	161 (100)
Median age (yr) (range)	55 (18–99)
Age >60 years old, *n* (%)	62 (39)
Male gender, *n* (%)	90 (51)
Male/female ratio	1:2
Stage IIE, *n* (%)	20 (13)
B symptoms, *n* (%)	14 (9)
High LDH serum level, *n* (%)[a]	54/158 (34)
IPI risk group (score), *n* (%)	
Low (0–1)	113 (70)
Low intermediate (2)	36 (22)
High intermediate (3)	7 (4)
Unknown	5 (3)
Site, *n* (%)	
Femur	33 (20)
Spine	27 (17)
Pelvis	27 (17)
Skull	25 (15)
Lower limb, excluding femur	21 (13)
Upper limb, excluding humerus	11 (7)
Humerus	11 (7)
Others	6 (4)
Geographical region, *n* (%)	
North America	25 (16)
South America	13 (8)
Europe	70 (43)
Asia	13 (8)
Oceania	40 (25)
Year of diagnosis, *n* (%)	
1981–1985	7 (4)
1986–1990	30 (19)
1991–1995	40 (25)
1996–2000	47 (29)
2001–2005	37 (23)

[a]158 assessable patients.
Abbreviations: IPI, International Prognostic Index; LDH, lactate dehydrogenase.

alone ($n = 23$; 14%), or both ($n = 125$; 78%) (Tables 2 and 3). Of the 138 patients treated with chemotherapy, 118 (85%) received a doxorubicin-containing regimen, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) being the most commonly used ($n = 103$; 87%). No patient received rituximab as part of first-line treatment. Six patients received some central nervous system (CNS) prophylaxis with intrathecal chemotherapy or intravenous high doses of methotrexate (dose $\geq$1 g/m^2) and/or cytarabine (dose $\geq$2 g/m^2). Among the 148 patients treated with radiotherapy, the irradiated volume included the whole of the affected bone in 97 (65%) patients and only a part of the affected bone in 36 (24%); data on the irradiated volume were not available in 15 cases. The median dose was 40 Gy (range, 12–56 Gy), in 2.0-Gy fractions. Patients treated with radiotherapy alone had a higher median age, with a higher proportion of patients older than 60 years, and were more commonly diagnosed before 1996 (Table 2).

Response

The response after the first-line treatment was assessed in 152 patients: 131 patients achieved a CR (complete response rate [CRR] = 86%; 95% confidence interval [CI], 81%–91%) and 7 a PR, with an overall response rate (ORR) of 91% (95% CI, 87%–95%); 1 (0.6%) patient had SD and 13 (9%) patients experienced PD.

The response was assessed in 123 of the 125 patients treated with chemotherapy and radiotherapy: 107 patients achieved a CR (CRR= 87%; 95% CI, 81%–93%) and 6 a PR, with an ORR of 92% (95% CI, 87%–97%); 1 (0.8%) patient had SD and 9 (7%) experienced PD.

The response was assessed in 20 of the 23 patients treated with radiotherapy alone: 16 patients achieved a CR (CRR = 80%; 95% CI, 53%–97%) and 1 a PR, with an ORR of 90% (95% CI, 77%–100%); 3 patients experienced PD (15%).

The response was assessed in 9 of the 13 patients treated with chemotherapy alone: 8 patients achieved a CR (CRR = 89%; 95% CI, 69%–100%) and 1 patient experienced PD (11%).

Progression-Free Survival and Relapse Patterns

At a median follow-up of 54 months (range, 3–218 months), 107 (67%) patients remained relapse-free, and 54 (34%) patients experienced relapse, with a median PFS of 35+ months and a 5-year PFS of 68% $\pm$ 4% (Fig. 1). Failure (relapse/PD) involved the primary site of disease in 9 (17%) patients, and involved other bones in 11 patients (21%), regional lymph nodes in 1 (2%), other lymph nodes in 10 (19%), multiple sites in 7 (13%), meninges in 4 (8%), and other sites in 6 (11%). The relapse site was unknown in 5 (9%) patients. Forty-nine of 148 irradiated patients experienced relapse, which was inside the irradiated volume in 8 cases, invariably as exclusive site of relapse. The 4 patients with meningeal relapse originally had osteolytic lesions in the pelvic bones and did not receive CNS prophylaxis; all of them died of PD.

Forty-eight (34%) of the 141 patients with stage I disease and 6 (30%) of the 20 patients with stage II disease experienced failure, with a 5-year PFS of 68% $\pm$ 4% and 72% $\pm$ 11%, respectively.

Patients managed with primary chemotherapy, whether followed by radiotherapy or not, had a significantly better PFS (5 year: 73% $\pm$ 4% vs. 52% $\pm$ 8%, $p = .0001$) than patients treated with primary radiotherapy, whether followed by chemotherapy or not. Overall, 35 (28%) of the 125 patients treated with chemotherapy and radiotherapy, 4 (31%) of the 13 patients treated with chemotherapy alone, and 14 (61%) of the 23 patients treated with radiotherapy alone experienced relapse, with a 5-year PFS of 72% $\pm$ 4%, 67% $\pm$ 14%, and 51% $\pm$ 10%, respectively (Fig. 2).

The impact of consolidative radiotherapy was assessed by comparing patients managed with chemotherapy followed by radiotherapy with patients treated with chemotherapy alone (5-year PFS: 74% $\pm$ 5% vs. 67% $\pm$ 14%, $p = .47$).

The effect of radiation dose on disease control was analyzed in the 101 patients managed with primary chemotherapy followed by irradiation. There was no significant difference in PFS between the 47 patients irradiated with a dose $\leq$36 Gy and the 58 patients irradiated with >36 Gy (5 year: 72% $\pm$ 7% vs. 75% $\pm$ 7%, $p = .57$). Radiation volume

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Table 2. Patient characteristics according to treatment

Parameter	Combined treatment	Chemotherapy alone	Radiotherapy alone
Patients, *n*	125	13	23
Median age (yr) (range)	54 (18–99)	52 (27–68)	64 (27–85)
Age >60 years old, *n* (%)	43 (34)	2 (15)	14 (61)
Male gender, *n* (%)	66 (53)	9 (69)	14 (61)
Stage IIE, *n* (%)	15 (12)	2 (15)	3 (13)
B symptoms, *n* (%)	12 (10)	2 (15)	0 (0)
High LDH serum level[a]	46/123 (37)	6/12 (50)	2/23 (9)
IPI risk group (score), *n* (%)			
Low (0–1)	86 (69)	10 (77)	17 (74)
Low intermediate (2)	31 (25)	1 (8)	4 (17)
High intermediate (3)	4 (3)	1 (8)	2 (9)
Unknown	4 (3)	1 (8)	0 (0)
Site, *n* (%)			
Femur	27 (22)	3 (23)	3 (13)
Spine	20 (16)	2 (15)	5 (22)
Pelvis	20 (16)	3 (23)	4 (17)
Skull	16 (13)	3 (23)	6 (26)
Lower limb, excluding femur	19 (15)	0 (0)	2 (9)
Upper limb, excluding humerus	8 (6)	0 (0)	3 (13)
Humerus	9 (7)	2 (15)	0 (0)
Others	6 (5)	0 (0)	0 (0)
Geographical region, *n* (%)			
North America	19 (15)	2 (15)	4 (17)
South America	8 (6)	1 (8)	4 (17)
Europe	57 (46)	5 (38)	8 (35)
Asia	7 (6)	3 (23)	3 (13)
Oceania	34 (27)	2 (15)	4 (17)
Year of diagnosis, *n* (%)			
1981–1985	4 (3)	0 (0)	3 (13)
1986–1990	20 (16)	1 (8)	9 (39)
1991–1995	31 (25)	2 (15)	7 (30)
1996–2000	38 (30)	6 (46)	3 (13)
2001–2005	32 (26)	4 (31)	1 (4)

[a]158 assessable patients.
Abbreviations: IPI, International Prognostic Index; LDH, lactate dehydrogenase.

was irrelevant to disease control, with a similar PFS for patients with the whole of the affected bone irradiated compared with those with a part of a bone irradiated (5-year PFS: 76% ± 5% vs. 64% ± 9%, $p = .31$).

Survival

One hundred nineteen patients were alive (113 disease-free), with a 5-year OS of 75% ± 4% (Fig. 1). Forty-two patients died: 34 patients died of lymphoma, 1 died of toxicity, and 7 died of unrelated causes. The 5-year OS was 75% ± 4% for patients with stage I disease and 76% ± 10% for patients with stage II disease ($p = .96$).

Overall, patients managed with primary chemotherapy, whether followed by radiotherapy or not, had a significantly better OS compared with patients treated with primary radiotherapy, whether followed by chemotherapy or not (5 year: 84% ± 3% vs. 48% ± 9%, $p < .0001$). Patients treated with combined treatment showed a significantly longer OS than patients treated with radiotherapy alone (5 year: 81% ± 4% vs. 42% ± 11%, $p = .003$) (Fig. 2). In the subgroup of patients treated with combined modality, primary chemotherapy followed by radiotherapy was associated with a significantly better OS than the inverse sequence (5 year: 85% ± 4% vs. 58% ± 13%, $p = .001$).

In the subgroup of patients treated with primary chemotherapy, the addition of consolidation radiotherapy was not associated with better OS (5 year: 85% ± 4% vs. 83% ± 10%, $p = .88$) (Fig. 2); in these patients, the use of a radiation dose >36 Gy (5-year OS: 88% ± 5% vs. 82% ± 6%, $p = .11$) and the irradiation of the whole affected bone (5-year OS: 84% ± 4% vs. 82% ± 7%, $p = .51$) were not associated with better outcome.

Multivariate analysis on the whole series showed that age and primary chemotherapy were independently associated with OS (Table 4).

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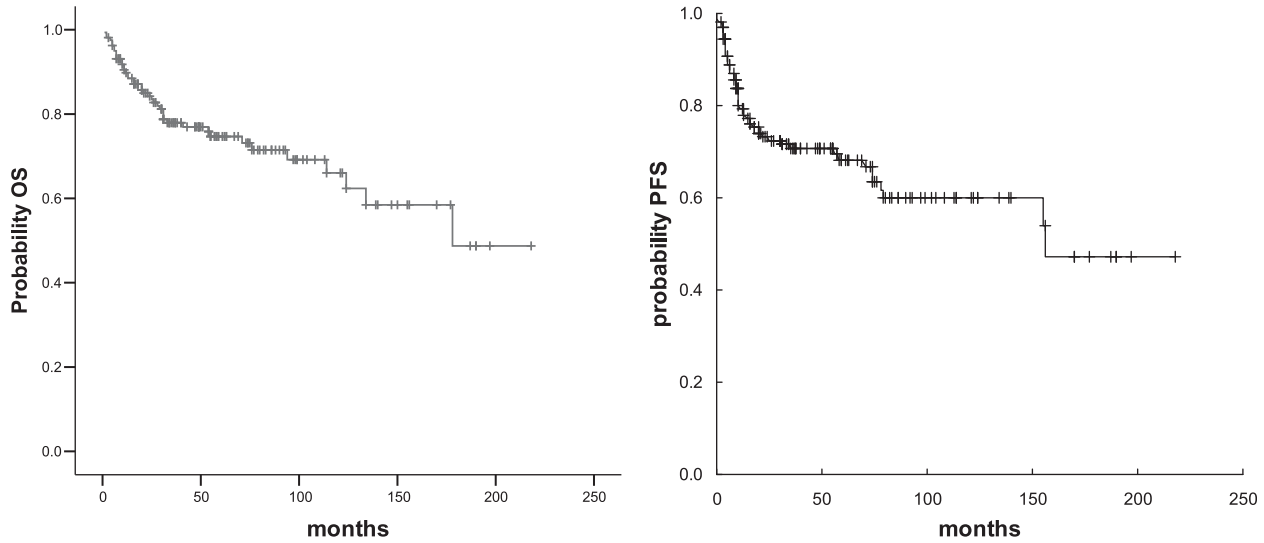

Figure 1. OS (left) and PFS (right) curves for the whole series.
Abbreviations: OS, overall survival; PFS, progression-free survival.

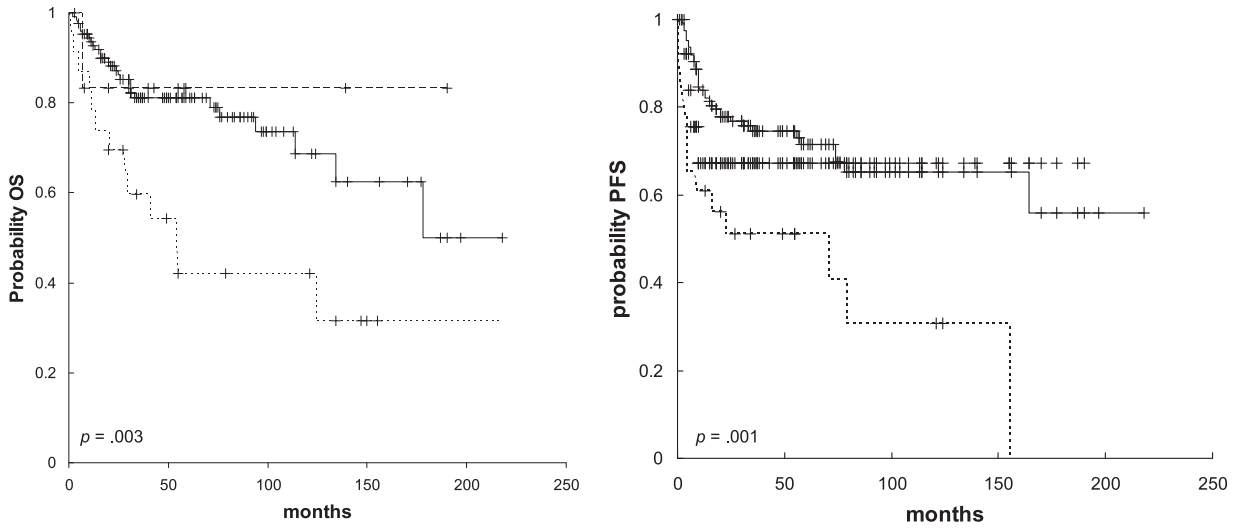

Figure 2. OS (left) and PFS (right) curves of the whole series by treatment: chemotherapy followed by radiotherapy (solid lines), chemotherapy alone (long dashed lines), and radiotherapy alone (short dashed lines).
Abbreviations: OS, overall survival; PFS, progression-free survival.

Discussion

This retrospective study, focused on the largest series of limited-stage DLBCL of the bone, shows that patients affected by these lymphomas exhibit a favorable prognosis when treated with primary anthracycline-based chemotherapy whether followed by radiotherapy or not, with an ORR >90% and a 5-year OS of 84%. This study demonstrates that this strategy produces significantly better results than primary radiotherapy whether followed by chemotherapy or not. Most patients had favorable prognostic factors at diagnosis, with increased age and poor performance status associated with a high risk of relapse and death. As expected for a good-risk cohort, CNS dissemination was recorded in 2.5% of patients, which is a lower rate than those reported in other DLBCL series in the pre-rituximab era.

The main limitations of this study were its retrospective nature, the lack of a formal central pathology review, and the fact that most patients were treated in a pre-rituximab and pre-positron emission tomography (PET) era. Despite a recent retrospective study suggesting that the addition of rituximab does not provide a clear survival advantage in patients affected by localized extranodal lymphomas [11], it is reasonable to expect a positive effect on disease control with the addition of this antibody, as reported for low-risk patients with DLBCL enrolled in the MInT prospective randomized trial [12]. The absence of a central pathology review poses a risk that misclassification has occurred and may be associated with bias. However, selected cases were reviewed at participating institutions, which are specialized centers with high levels of expertise in the management of lymphomas. Treatment was given per physician's discretion over a broad time period when patterns of practice may have evolved. Moreover, small numbers in some comparisons may be underpowered, and results should be interpreted with caution.

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Table 3. Treatment according to stage of disease

Treatment	Stage IE disease ($n = 141$)	Stage IIE disease ($n = 20$)	Whole series ($n = 161$)
Chemotherapy alone, *n* (%)	11 (8)	2 (10)	13 (8)
Anthracycline-based regimen, *n* (%)	11 (100)	2 (100)	13 (100)
CHOP regimen, *n* (%)	5 (45)	0 (0)	5 (38)
Median number of courses (range)	4 (1–8)	3; 4[a]	4 (1–8)
Radiotherapy alone, *n* (%)	20 (14)	3 (15)	23 (14)
Median dose (Gy) (range)	40 (30–55)	50 (40–56)	40 (30–56)
Whole affected bone, *n* (%)	14 (70)	1 (33)	15 (65)
Partial affected bone, *n* (%)	6 (30)	2 (66)	8 (35)
Chemoradiotherapy, *n* (%)	110 (78)	15 (75)	125 (78)
Chemotherapy → radiotherapy, *n* (%)	94 (85)	15 (100)	109 (87)
Radiotherapy → chemotherapy, *n* (%)	16 (15)	0 (0)	16 (13)
Anthracycline-based regimen, *n* (%)	95 (86)	11 (73)	106 (85)
CHOP regimen, *n* (%)	74 (67)	9 (60)	83 (66)
Median number of courses (range)	6 (1–8)	6 (3–8)	6 (1–8)
Median radiation dose (Gy) (range)	40 (30–56)	40 (35–50)	40 (30–56)
Whole affected bone, *n* (%)	78 (71)	9 (60)	87 (70)
Partial affected bone, *n* (%)	32 (29)	6 (40)	38 (30)

[a]No medians for only two patients.
Medians and ranges of the numbers of courses were estimated on patients treated with first-generation regimens (CHOP or CHOP derivatives).
Abbreviation: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

Table 4. Multivariate analysis

Variable	Subgroup	Odds ratio	95% CI	*p*
Age	Continuous	1.04	1.02–1.07	.0001
ECOG-PS	0–1	1.88	0.98–3.61	.057
	2–4			
Stage	I	1.27	0.44–3.67	.65
	II			
LDH	Normal	0.92	0.44–1.93	.83
	High			
B symptoms	No	1.25	0.37–4.27	.71
	Yes			
Fracture	No	0.87	0.41–1.85	.71
	Yes			
Primary chemotherapy	No	0.42	0.22–0.81	.009
	Yes			

Endpoint: overall survival. Odds ratios indicate the risk of death (mortality).
Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

DLBCL constitutes the vast majority of PBL, ranging from 68% in Japan [13] to 80% in Western countries [8, 14]. Nevertheless, PB-DLBCL remains a rare malignancy, whose natural history has been poorly established and therapeutic guidelines remain to be defined. The few published studies of PBL are limited by the absence of a uniformly accepted definition of PBL [15, 16]. Moreover, some authors considered together cases of primary and secondary bone lymphomas [17, 18], which further complicated the analysis and the reliability of the conclusions. Recently, the need to differentiate between limited-stage PBL and systemic disease with skeletal involvement was emphasized [19]. The current study contributes to our knowledge on the clinical presentation and natural behavior of PB-DLBCL in the largest reported, unselected series. Thus, PB-DLBCL can arise at any age, with equal distribution between genders, and it usually presents with favorable features, including the absence of B symptoms (91% of cases), normal LDH serum level (65%), and low or low-intermediate IPI (90%). Stage II disease is uncommon (13%), but this rate could be underestimated because of the lack of PET scanning in the staging workup. In any case, in the present study, local lymph node involvement was not associated with poorer outcome, suggesting that patients with either stage I or stage II disease should be treated with a similar strategy.

In the current study, patients with limited-stage DLBCL of the bone managed with chemotherapy, followed or not by

radiotherapy, had 5-year PFS and OS of 73% and 85%, respectively. These figures compare favorably with outcomes of patients with limited-stage DLBCL not otherwise specified treated with the same approach in previous trials, which have been 66% and 82% in the MInT trial [20]. Importantly, the MInT trial exclusively enrolled younger patients with IPI scores of 0–1, whereas, in the present series, 39% of patients were older than 60 years, and 26% of patients had IPI scores of 2–3, which suggests a negative selection. In line with previous studies [16, 21, 22], reported in the pre-rituximab era, patients treated with combined modality treatment had a significantly better response and survival rates than patients treated with radiotherapy alone. Among patients treated with combined modality, primary chemotherapy followed by radiotherapy was associated with significantly better outcome than patients treated with the reverse sequence. Interestingly, the addition of involved-field radiotherapy in patients treated with primary chemotherapy was not associated with an improved outcome, but this observation should be regarded with caution considering the retrospective nature of the study and the small number of patients managed with chemotherapy alone. However, our data confirm that primary anthracycline-based chemotherapy, whether followed by radiotherapy or not, is the first therapeutic choice for patients with PB-DLBCL.

The role of consolidation radiotherapy in limited-stage DLCBL remains to be defined, with a few randomized trials suggesting that it is superfluous in patients who achieve a CR after primary chemotherapy [23]. In some pre-rituximab trials, postchemotherapy consolidation with low-dose radiotherapy resulted in prolonged disease-free survival, but no OS benefit was observed [24]. In the rituximab era, the addition of consolidation radiotherapy significantly improved outcome in a large retrospective series treated with rituximab-CHOP combination [25]. Overall, the use of intensive immunochemotherapy without radiation therapy requires formal testing and validation in a randomized clinical trial before it can be used as an alternative treatment regimen for early-stage DLBCL. No studies addressing this issue in a large PBL series exist. As mentioned above, the present study suggests that postchemotherapy bone irradiation did not improve the outcome in PB-DLBCL. No differences were seen in relapse and survival rates between patients receiving radiotherapy to the whole bone and those patients with only part of the affected bone irradiated. In patients managed with chemoradiotherapy, radiation doses $>$36 Gy were not associated with better PFS than doses $\leq$36 Gy. Thus, if radiotherapy is to be given to the whole length of an affected bone, the dose should be limited to 36 Gy to avoid toxicity.

CNS relapse is an early and fatal event in DLBCL management, and it has been reported in approximately 5% of patients with DLBCL treated in pre-rituximab era [26]. Specific prophylaxis with systemic and/or intrathecal chemotherapy could prevent this severe event [27]. Skeletal involvement has been reported to be associated with a high risk of CNS dissemination in patients with DLBCL, mostly with advanced disease [28]. The present study demonstrates that limited-stage DLBCL of the bone is not associated with a high risk of CNS dissemination; this event was reported in 2.5% of cases, which is only half of the widely recognized risk of CNS dissemination in DLBCL patients [29–31]. CNS relapse consisted of meningeal lymphomatosis and was invariably fatal. These patients had bulky lesions in the pelvic bones and had at least one unfavorable indicator among increased LDH serum level, high IPI, bulky disease, and B symptoms, but the small number of events hampered the identification of reliable predictors. Nevertheless, the present study clearly suggests that CNS prophylaxis is unnecessary. Probably, this rate would be even lower with the addition of rituximab because CNS dissemination was halved in DLBCL patients treated with this antibody [32].

In conclusion, this study demonstrates that PB-DLBCL has specific features that define it as a separate entity, usually with favorable clinical features and good prognosis. These patients should be treated with primary anthracycline-based chemotherapy, whether followed by consolidative radiotherapy or not. In patients treated with chemoradiotherapy, the irradiation of the whole affected bone and the use of a radiation dose $>$36 Gy are not associated with better outcome. CNS dissemination is a rare event in these patients.

List of Participating Centers (Number of Registered Patients)

Princess Margaret Hospital, Ontario Cancer Institute, Toronto, Ontario, Canada (n = 97); San Raffaele Scientific Institute, Milan, Italy (n = 37); Auckland Hospital, Auckland, New Zealand (n = 30); Christie Hospital NHS Trust, Manchester, United Kingdom (n = 30); Korea Cancer Center Hospital, Seoul, Korea (n = 28); National University Hospital, Seoul, Korea (n = 24); MD Anderson Cancer Center, Houston, Texas, USA (n = 19); Istituto Europeo di Oncologia, Milan, Italy (n = 19); Westmead Hospital, Westmead, Australia (n = 19); Wesley Cancer Care Centre, Brisbane, Queensland, Australia (n = 18); Northern Centre for Cancer Treatment, Newcastle, United Kingdom (n = 16); Queensland Radium Institute, Brisbane, Queensland, Australia (n = 14); Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland (n = 13); National Cancer Institute, Bratislava, Slovakia (n = 13); North Shore Hospital, Sydney, Australia (n = 13); Royal Prince Alfred Hospital, Sydney, Australia (n = 13); Ospedale Policlinico Di Borgo Roma, Verona, Italy (n = 13); Victoria Geelong Hospital, Geelong, Australia (n = 10); Università Degli Studi La Sapienza, Roma, Italy (n = 8); Ospedale di Circolo Fondazione Macchi, Varese, Italy (n = 8); Fundacion Argentina Contra la Leucemia, Buenos Aires, Argentina (n = 7); Blokhin Cancer Research Center, Moscow, Russia (n = 7); Instituto de Enfermedades Neoplásicas, Surquillo, Lima, Perú (n = 6); East Coast Cancer Center, Tugun, Queensland, Australia (n = 6); Peter MacCallum Cancer Institute, Melbourne, Australia (n = 5); Prince of Wales Hospital, Sydney, Australia (n = 5); The James Cook University Hospital, Cleveland, United Kingdom (n = 4); Royal South Hants Hospital, Southampton, United Kingdom (n = 4); Woden Valley, Canberra, Australia (n = 2); National Institute of Oncology and Radiobiology, Havana, Cuba (n = 2); Ospedale Umberto I, Mestre, Italy (n = 2); Victoria Border Medical Oncology, Wodonga, Australia (n = 2); Royal Adelaide Hospital, Adelaide, Australia (n = 1); Saint Alphonsus Cancer Treatment Center, Boise, Idaho, USA (n = 1); Hospital Israelita, Buenos Aires, Argentina (n = 1); Azienda Ospedaliera "Maggiore della Carità," Novara, Italy (n = 1); Rabin Medical Center, Petah-Tiqwa, Israel (n = 1).

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