15. Carson KR, Bartlett NL, McDonald JR et al. Increased body mass index is associated with improved survival in United States veterans with diffuse large B-cell lymphoma. J Clin Oncol 2012; 30: 3217–3222.
16. Coiffier B, Thieblemont C, Van Den Neste E et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010; 116: 2040–2045.
17. Pfreundschuh M, Trumper L, Osterborg A et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006; 7: 379–391.
18. WHO. Technical Report series 854. Physical status: the use and interpretation of anthropomorphy. Report of a WHO Expert Committee, 1995.
19. Fridrik MA, Petzer AL, Keil F et al. Non-pegylated liposomal encapsulated doxorubicin reduces cardiotoxicity in 1st line treatment of diffuse large B-cell lymphoma (DLBCL). Final results of a randomized trial. Blood 2011; 118: 1149.
20. Grossschadl F, Stronegger WJ. Regional trends in obesity and overweight among Austrian adults between 1973 and 2007. Wien Klin Wochenschr 2012; 124: 363–369.
21. Carella AM, de Souza CA, Luminari S et al. Prognostic role of gender in diffuse large B-cell lymphoma treated with rituximab containing regimens: a Fondazione Italiana Linfomi/Grupo de Estudos em Molestias Onco-Hematologicas retrospective study. Leuk Lymphoma 2013; 54: 53–57.
22. Griggs JJ, Mangu PB, Anderson H et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012; 30: 1553–1561.
23. Gregory SA, Trumper L. Chemotherapy dose intensity in non-Hodgkin's lymphoma: is dose intensity an emerging paradigm for better outcomes? Ann Oncol 2005; 16: 1413–1424.
24. Rodvold KA, Rushing DA, Tewksbury DA. Doxorubicin clearance in the obese. J Clin Oncol 1988; 6: 1321–1327.
25. Jager U, Fridrik M, Zeitlinger M et al. Rituximab serum concentrations during immuno-chemotherapy of follicular lymphoma correlate with patient gender, bone marrow infiltration and clinical response. Haematologica 2012; 97: 1431–1438.
26. Muller C, Murawski N, Wiesen MHJ et al. The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. Blood 2012; 119: 3276–3284.

Annals of Oncology 25: 176–181, 2014
doi:10.1093/annonc/mdt482
Published online 28 November 2013

The clinical features, management and prognostic effects of pathological fractures in a multicenter series of 373 patients with diffuse large B-cell lymphoma of the bone

S. Govi[1,†], D. Christie[2,†], C. Messina[1], M. Bruno Ventre[1], E. A. Gracia Medina[3], D. Porter[4], J. Radford[5], D. Seog Heo[6], Y. Park[7], G. Martinelli[8], E. Taylor[9], H. Lucraft[10], V. Ballova[11], E. Zucca[12], M. Gospodarowicz[13], A. J. M. Ferreri[1*] & on behalf of the International Extranodal Lymphoma Study Group (I.E.L.S.G.)

[1]Unit of Lymphoid Malignancies, Department of Onco-Hematology, San Raffaele Scientific Institute, Milan, Italy; [2]Department of Oncology Inland Dr., Premion and Bond University, Tugun, Australia; [3]Department of Medical Oncology, National Institute of Oncology and Radiobiology, La Habana, Cuba; [4]Department of Oncology Auckland, Auckland Hospital, New Zealand; [5]Department of Oncology, Christie Hospital, Manchester, UK; [6]Department of Oncology, Seoul National University Hospital, Seoul; [7]Department of Oncology, Korea Cancer Center Hospital, Seoul, Korea; [8]Division of Hematology, European Institute of Oncology, Milan, Italy; [9]Department of Oncology, Wesley Research Institute, Brisbane, Australia; [10]Department of Oncology, Northern Centre for Cancer, New Castle, UK; [11]Department of Oncology, National Cancer Institute, Bratislava, Slovakia; [12]Department of Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [13]Department of Radiation Oncology, Princess Margaret Hospital, Ontario Cancer Institute, Toronto, Canada

Received 3 July 2013; revised 16 September 2013; accepted 18 September 2013

Background: Pathological fractures (PFs) occur in 10%–20% of patients with diffuse large B-cell lymphoma (DLBCL) of the bone. The clinical features and the effects of this severe complication on management and prognosis have not been previously analyzed in a large series.

Patients and methods: The effects of PF on management and prognosis were reviewed in an international retrospective series of 373 patients with newly diagnosed bone DLBCL, comparing 78 patients with PF at presentation (group 'PF-BL') and 295 patients without PF ('controls').

*Correspondence to: Dr Andrés J. M. Ferreri, Unit of Lymphoid Malignancies, Division of OncoHematological Medicine, Department of OncoHematology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. Tel: +39-02-26437649; Fax: +39-02-26437625; E-mail: andres.ferreri@hsr.it

†These authors contributed equally.

Results: At a median follow-up of 53 months (range 3–246), PF-BL patients exhibited lower rates of overall response (ORR, 78% versus 85%; $P = 0.17$), 5-year progression-free survival (PFS, 53 ± 6% versus 61 ± 3%; $P = 0.02$) and 5-year overall survival (OS, 54 ± 6% versus 68 ± 3%, $P = 0.008$) than controls. Initial surgical stabilization of the PF did not change therapeutic outcome (5-year OS: 45 ± 9% versus 54 ± 10%; $P = 0.20$). PF-BL patients referred to irradiation of the fractured bone before chemotherapy exhibited a significantly poorer outcome than patients managed with the inverse sequence (ORR: 52% versus 92%, $P = 0.0005$; 5-year OS: 22 ± 14% versus 64 ± 9%, $P = 0.007$). Multivariate analysis confirmed the independent association between PF and worse survival and the negative effect of radiotherapy as initial therapy.

Conclusion: Fracture is an independent, adverse prognostic event in patients with bone DLBCL. Anthracycline-based chemotherapy followed by radiotherapy seems to be the better treatment sequence. Initial fracture stabilization does not seem to improve outcome; it should be used to improve patient's quality of life only if chemotherapy delays can be avoided.

Key words: diffuse large B-cell lymphoma, bone lymphoma, pathological fractures, bone fixation, radiotherapy, osteolymphoma

introduction

Bone lymphomas represent 3% of all primary bone malignancies, and <3% of all lymphomas in adults [1–3]. Bone lymphomas occur at any age, but with a predominance of elderly males and particularly affects the metaphysis and diaphysis of long bones [4–5]. Pain and swelling are the most common presenting symptoms [5, 6]. Between 66% and 90% of primary bone lymphomas are diffuse large B-cell lymphomas (DLBCL) [3, 7–9], usually presenting as limited-stage disease, and good prognosis when managed with modern combined therapies, with a 5-year OS OS rate of 70%–100% [3, 9, 10]. However, several biological, clinical and therapeutic questions remain open, mostly due to the fact that the related literature is almost exclusively based on small retrospective series.

Pathological fracture (PF) is one of the most frequent complications of bone lymphomas at presentation, varying in frequency between 10% and 20% [2, 9, 11]. However, no data on the clinical features or the effects of PF on management and prognosis are available. Questions remain regarding the best method of surgical stabilization to enable healing of the PF, the effect of radiotherapy as initial treatment and the optimal management for long-term local control of the disease.

To help answer some of these questions, we analyzed an international retrospective series of 373 patients with newly diagnosed DLBCL and skeletal involvement accomplished under the sponsorship of the International Extranodal Lymphoma Study Group (IELSG). The clinical features, management and outcomes of 78 patients with PF and of 295 patients without PF were compared.

patients and methods

study population

The members of the IELSG were invited to participate in a retrospective study focused on bone lymphomas (the IELSG #14 study). Selection criteria were histological diagnosis of non-Hodgkin's lymphoma, skeletal involvement, age ≥18 years and treatment carried out at the participating centers between 1980 and 2005. Questionnaires included personal data, clinical presentation, performance status (ECOG-PS), biochemical markers, diagnosis, stage, treatment, toxicity and outcome. Information about PF was specifically requested. The resulting database included information on 499 cases of bone lymphomas treated at 32 Cancer Centres in 14 countries (list of contributors at the end of the text). One hundred and eleven cases of lymphoma categories other than DLBCL and 15 cases of DLBCL without complete staging, clinical and treatment-related data were excluded; the remaining 373 patients with DLBCL with suitable data constituted the study population for this report. In order to investigate clinical features, therapeutic management and outcome of PF in these 373 assessable patients, the 78 patients with PF at presentation ('PF-BL'; pathological fracture in bone lymphoma) were compared with the 295 patients without PF ('controls'). The study conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards and ethics committees of the participating centers.

statistical considerations

A comparison of discrete variables was made by chi-square test or Fisher's exact test. Contributors defined responses as complete, partial, stable disease or progressive disease and response rates were recorded as either complete (CRR) or both complete and partial combined as overall response rates (ORRs). Recorded response regards all the lymphomatous lesions, and not only bone lesions, assessed after first-line treatment conclusion. Progression-free survival (PFS) was calculated from the date of the start of treatment to date of relapse, progression or death, or to the last date of follow-up. OS was calculated from the date of histological diagnosis to the date of death or last follow-up visit. Survival curves were estimated using the Kaplan–Meier method and compared by log-rank test. The Cox proportional hazards model was used for multivariate analyses and estimation of relative risks. All the probability values were two-sided. All analyses were carried out using the SPSS 13.0 statistical package for Windows (Lead Technologies Inc, 2004).

results

patients' characteristics

A comparison between study subgroups showed, as expected, that PF-BL patients had a significantly worse Eastern Cooperative Oncology Group-Performance Status (ECOG-PS, Table 1). Within the PF-BL group, there were 47 patients with unifocal disease (stage-IE disease), while 31 had multifocal disease (more than one lesion in the same bone) or polyostotic (lesions in more than one bone) disease. There were no differences in the number of involved bones and in extra-osseous disease, whereas distribution of affected bones was different between groups, with more common involvement of spine and limb bones in the PF-BL group (Table 1). Bulky disease and infiltration of regional and distant lymph nodes and extranodal organs were equally distributed between PF-BL patients and controls (Table 1).

Table 1. Clinical features of patients with bone DLBCL divided according to the presence of pathological fracture (PF)

	PF, *n* (%)	Without fracture, *n* (%)	*P* (X^2 test)
Number of patients	78	295	
Male	41 (53)	151 (51)	NS
Median age (range)	61 (18–93)	57 (17-85)	NS
ECOG PS >1	34 (44)	82 (28)	0.007
Ann Arbor stage III and IV	36 (46)	122 (41)	NS
Elevated LDH serum level[a]	25/49 (51)	107/209 (51)	NS
B symptoms	9 (11)	50 (17)	NS
Pain	68 (87)	251 (85)	NS
Swelling	24 (31)	117 (40)	NS
Involved bones			
Single	47 (60%)	189 (64%)	
Multiple	31 (40%)	106 (36%)	NS
Osseous sites			
Skull	6 (8)	52 (18)	0.03
Spine	30 (38)	77 (26)	0.03
Pelvis	13 (17)	73 (25)	NS
Upper limb	21 (27)	45 (15)	0.01
Lower limb	38 (49)	95 (32)	0.006
Extra-osseous sites			
Regional lymph nodes	9 (12)	50 (17)	NS
Distant lymph nodes	8 (10)	35 (12)	NS
Extranodal organs	20 (26)	74 (25)	NS

LDH, lactate dehydrogenase; IPI, International prognostic index.
[a]Relationship between patients with increased serum LDH levels and patients with available LDH level data.

antineoplastic treatment and management of PF

The initial treatment included surgery in 30 PF-BL patients. The surgical approach consisted of internal fixation, including intramedullary rod, ($n = 18$), laminectomy/decompression ($n = 4$), excision/joint replacement ($n = 4$) and arthroplasty/prosthesis/osteosynthesis ($n = 4$). Five patients underwent orthopedic intervention on the PF during or after chemo-radiotherapy, of these, two had internal fixation, two had amputations and one had a joint replacement. Within the PF-BL group, there were no differences in clinical presentation and disease characteristics between patients undergoing initial surgery and the others (data not shown).

Treatments received by PF-BL group and controls are summarized in Table 2. Sixty-seven PF-BL patients and 270 controls received chemotherapy, which consisted of an anthracycline-based regimen in 64 (96%) in the PF-BL group and 265 (98%) in the control group. Those few patients who did not receive anthracyclines were all over 70 years of age. Sixty-nine patients in the PF-BL group and 233 in the control group received radiotherapy as part of their first-line treatment, receiving a median dose of 36 Gy both for the PF-BL group (range 18–63) and the control group (range 4–56). The irradiated volume included the whole bone in 41 patients in the PF-BL group and 159 in the control group, but only part of the affected bone in 28 and 74 patients, respectively.

Among the 268 patients treated with combined treatment modality, 36 (80%) PF-BL patients and 163 (88%) controls received chemotherapy followed by radiotherapy (CT-RT), while the sequence was reversed (RT-CT) in 9 (20%) PF-BL patients and 21 (12%) controls; 14 PF-BL patients and 25 controls received concomitant chemo-radiotherapy (Table 2).

responses

Response rates after first-line treatment were not significantly different between PF-BL patients and controls. Fifty-three PF-BL patients achieved a CR (CRR = 68%; 95%CI = 58%–78%) and eight a PR, with an overall response rate (ORR) of 78% (95%CI = 69%–87%); 16 PF-BL group patients did not respond to treatment; response was unknown in one case. Two hundred and nineteen (74%) patients in the control group attained CR and 31 achieved PR, with an ORR of 85%; 33 patients in the control group did not respond to treatment, one died of toxicity, and the response was unknown in 11 controls.

Initial surgical stabilization of the PF did not appear to affect response rates: the CRR was 67% ($n = 20$) in the 30 PF-BL patients undergoing initial surgery and 69% ($n = 33$) in the 48 PF-BL patients who were not managed with initial surgery ($P = 0.84$). ORR rates were 77% and 79% ($P = 0.79$), respectively. Conversely, primary irradiation of the fractured bone followed by chemotherapy was associated with significantly lower response rates: CRR was 78% (28/36) for PF-BL patients treated with CT-RT and 43% (10/23) for PF-BL patients treated with RT-CT ($P = 0.007$), with an ORR of 92% and 52% ($P = 0.0005$), respectively. Importantly, all the PF-BL patients treated with RT-CT completed the planned radiation treatment (30–45 Gy), and the interval between RT conclusion and the first course of chemotherapy oscillated between 4 and 45 days (median 20). Likewise, all the PF-BL patients treated with CT-RT completed the planned radiation treatment (30–48 Gy), and the interval between the last course of chemotherapy and the first RT fraction oscillated between 0 and 80 days (median 23).

relapse and progression

At a median follow-up of 53 months (range 3–246), 38 patients in the PF-BL group and 106 in the control group experienced failure (relapsing or progressive disease), with a 5-year PFS of 53 ± 6% and 61 ± 3% ($P = 0.02$), respectively (Figure 1). One-third of failures observed in PF-BL patients involved the primary site of disease and the fractured bone; previously uninvolved bones and lymph nodes were sites of failure in 18% and 13% of the PF-BL group, respectively. One-third of failures consisted of disseminated disease with multi-organ involvement, including bones and lymph nodes. Two (5%) patients experienced central nervous system (CNS) dissemination (meninges, brain); they had respectively spine and skull involvement at presentation. Patterns of relapse among the control group were similar to those observed among the PF-BL group: 20% of failures involved the primary site of disease, 13% affected previously uninvolved bones, 12% previously uninvolved lymph nodes, 43% of failures consisted of disseminated disease with multi-organ involvement and 7% involved the CNS.

Initial surgical stabilization of the fracture did not influence PFS in PF-BL patients, with a 5-year PFS of 48 ± 10% and

Table 2. Treatment and outcome

	PF-BL group		Control group	
	N (%)	Five-year PFS	*N* (%)	Five-year PFS
Chemotherapy alone	9 (11)	56 ± 11%	61 (21)	46 ± 8%
Radiotherapy alone	10 (13)	33 ± 11%	24 (8)	46 ± 9%
Chemotherapy followed by radiotherapy	36 (46)	55 ± 10%	163 (55)	65 ± 4%
Radiotherapy followed by chemotherapy	9 (11)	44 ± 11%	21 (7)	49 ± 10%
Concomitant chemoradiation therapy	14 (18)	55 ± 10%	25 (8)	66 ± 10%
No therapy	0 (0)		1 (0.3)	

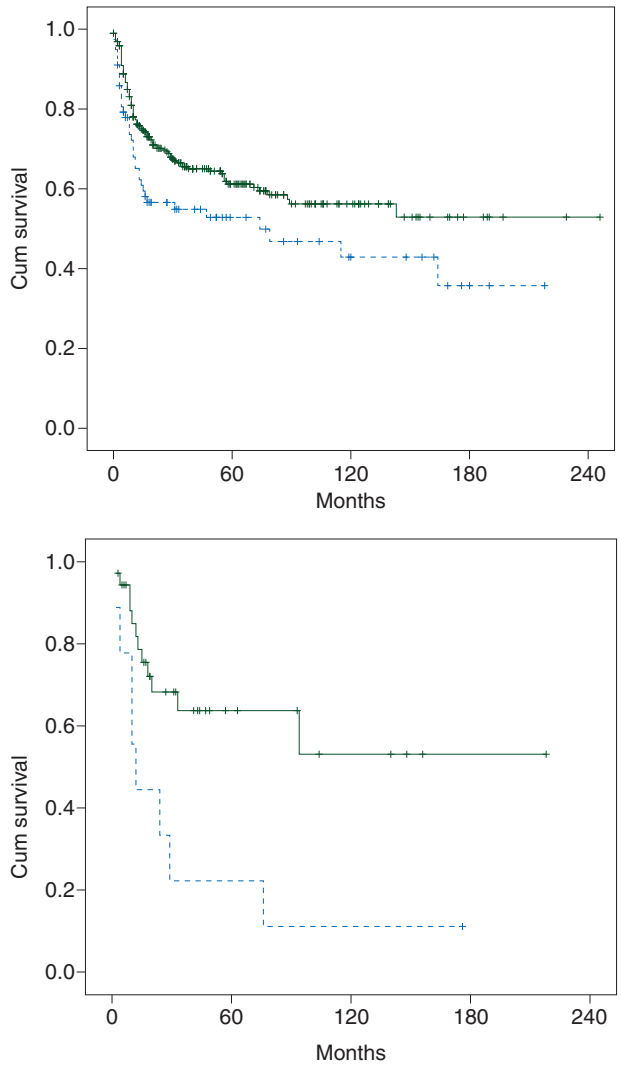

Figure 1. Upper graphic: progression-free survival (PFS) curves of the PF-BL group (dotted line) and control group (continued line). Lower graphic: OS curves for PF-BL group patients managed with primary chemotherapy followed by irradiation of the fractured bone (continued line) and with primary radiotherapy followed by chemotherapy (dotted line).

56 ± 8% ($P = 0.24$), respectively, for patients who underwent an initial surgical procedure and patients who did not. Conversely, sequence of combined treatment was associated with different 5-year PFS, which was 44 ± 11% for PF-BL patients treated with RT-CT and 55% ± 10% ($P = 0.07$) for PF-BL patients treated with CT-RT (Table 2).

survival

Forty-two patients in the PF-BL group and 204 in the control group are alive, with a 5-year OS of 54 ± 6% and 68 ± 3%, respectively ($P = 0.008$). Among the PF-BL group, 29 (81%) patients died of lymphoma, three died of therapeutic complications and four died of unrelated causes. Sixty-six (73%) patients in the control group died of lymphoma, five died of treatment complications and 20 died of unrelated causes.

Initial surgical stabilization of the PF did not change the outcome of the lymphoma treatment, with a 5-year OS of 45 ± 9% and 54 ± 10% ($P = 0.20$), respectively, for patients who underwent an initial surgical procedure and patients who did not. Irradiation of the fractured bone before chemotherapy was associated with poorer survival, with a 5-year OS of 22 ± 14% for PF-BL patients managed with RT-CT and 64 ± 9% ($P = 0.007$) for PF-BL patients treated with CT-RT (Figure 1).

A multivariate analysis on the whole series confirmed an independent association between PF and worse OS; advanced age, poor PS, advanced stage, high lactate dehydrogenase (LDH) serum level and chemotherapy without anthracyclines were also independently associated with worse OS, (Table 3; upper panel). A multivariate analysis limited to the 78 patients in the PF-BL group confirmed that the initial irradiation of the fracture, advanced age, poor PS, advanced stage and chemotherapy without anthracyclines were associated with poorer OS, whereas initial surgical stabilization was not (Table 3; lower panel). Among radiation variables, doses >30 Gy were independently associated with better OS, while the irradiation of the whole affected bone was not influential.

post-treatment sequelae and second PFs

Eight (10%) patients in the PF-BL group experienced a second PF after treatment, with a median interval between treatment conclusion and fracture diagnosis of 11 months (range 2–40), and including four patients treated with initial surgery. All these events but one occurred in the same bone that was affected by the original fracture. One patient suffered permanent disability of the affected limb, while severe transient disability was recorded in 12 patients; all these patients but one had a PF of the femur or pelvis at presentation. These sites of disease and the spine were more commonly associated with chronic persistent symptoms, which were usually mild, but affected 24%

Table 3. Multivariate analyses

Whole series ($n = 373$)	Subgroups	HR	95% CI	*P* values
Age	Continuous variable	1.04	1.02–1.05	<0.001
ECOG-PS	0–1 versus 2–4	2.61	1.79–3.78	<0.001
Stage of disease	I–II versus III–IV	1.97	1.38–2.81	<0.001
LDH serum level	Normal versus high	1.97	1.23–3.17	0.005
B symptoms	No versus yes	0.94	0.57–1.54	0.824
PF	Yes versus no	0.61	0.41–0.91	0.015
Use of anthracycline	No versus yes	0.40	0.17–0.92	0.032
PF-BL group ($n = 78$)	**Subgroups**	**HR**	**95% CI**	***P* values**
Age	Continuous variable	1.05	1.02–1.08	0.001
ECOG-PS	0–1 versus 2–4	2.34	1.08–5.07	0.030
Stage of disease	I–II versus III–IV	2.26	1.14-4-47	0.019
LDH serum level	Normal versus high	2.14	0.80–5.72	0.127
B symptoms	No versus yes	0.8	0.29–2.40	0.747
Initial radiotherapy	Yes versus no	0.31	0.12–0.77	0.012
Initial surgical stabilization	No versus yes	1.39	0.71–2.69	0.326
Fracture radiation dose	≤30 Gy versus >30 Gy	0.45	0.21–0.98	0.045
Radiation field	Whole bone versus partial bone	1.34	0.66–2.69	0.412
Use of anthracycline	No versus yes	0.15	0.04–0.47	0.001

($n = 10$) of survivors. Six patients had second cancers, three among the PF-BL group and three among the control group: malignancies were prostate cancer ($n = 2$), acute myeloid leukemia, gastric cancer, lung cancer and endometrial cancer.

discussion

This is the largest published report on the clinical features, prognostic impact and the management of PF in patients with DLBCL. Present results suggest that PF is an independent negative prognostic event in DLBCL patients, and that surgical stabilization as primary treatment does not contribute to improve outcome. Importantly, this study suggests that radiotherapy of fractured bone as initial treatment is associated with poorer survival. Accordingly, patients with DLBCL of the bone and PF should be treated with primary anthracycline-based chemotherapy followed by bone irradiation with 30–40 Gy. The use of large radiation fields was not associated with improved outcome.

The main limitations of this study are its retrospective nature, which, for instance, did not allow us to investigate pre- and post-treatment variables predicting the occurrence of a PF-like lysis of the cortex, tumor size and soft tissue infiltration, and the fact that most of registered patients were treated in a pre-rituximab and pre-positron emission tomography (PET) scan era. However, the impact of these limitations on the conclusions is unlikely to be significant, considering that the main goals of this study, that is the role of surgery or radiation therapy as initial management of PF in DLBCL patients, are independent of the use of rituximab and PET assessment. It may be hypothesized that the positive effect of the addition of rituximab might overcome the impact of some adverse prognostic variables (e.g. the radio-chemotherapy sequence); however, this is not the rule in large clinical trials on nodal lymphomas, where the individual prognosis-determining factors usually kept their validity. Consequently, we believe that drawn conclusions in this pre-rituximab and pre-PET study remain valid for patients with bone DLBCL currently managed with these important tools.

The goals of initial surgical stabilization of the fracture are usually not to provide cancer treatment but to preventing further bone destruction and displacement, to enable weight-bearing, to assist pain relief or healing and obtaining a better quality of life. While these are all important goals, there was no indication of an improved cancer-related outcome from initial surgery. Our data suggest that any initial surgery should be kept to a minimum, as the earlier that chemotherapy can be initiated, the better the cancer outcome is likely to be.

A PF or a high risk of fracture may lead the treating physician to start the treatment program with radiotherapy. This study suggests that irradiation of a fractured bone before chemotherapy does not improve disease control or survival, when compared with CT-RT sequence. Any conclusion about the sequencing of treatment should be made with caution as those patients having local treatments first may have been those presenting with more locally destructive lesions. However, in line with previous reports [6, 12], this study suggests that patients with PF should be managed like nodal DLBCL, including timely primary anthracycline-based chemotherapy followed by consolidation radiotherapy to the fractured bone. The use of radiation doses >30 Gy was associated with improved outcome, which is in line with recent prospective studies demonstrating that doses of up to 40 Gy are adequate after chemotherapy for aggressive lymphomas including extra-nodal sites. The optimal volume and dose of irradiation for these lymphomas remain suitable questions for future studies.

Although there was usually no long-term disability in the present series, involvement of femur, pelvis and the spine was more commonly associated with chronic symptoms, and a second PF after anti-lymphoma treatment was recorded in 10% of our patients. Both radiotherapy and chemotherapy have been implicated as incurring a higher risk of subsequent PF, in

particular, concomitant use of corticosteroids and high irradiation doses delivered to whole bones [13–15]. These and other high-risk factors, such as older age, female sex, osteoporosis, involvement of weight-bearing bones and the size of the biopsy defect should be accurately considered, and prednisone dose reduction to 50 mg/m^2 and reduction of radiation dose to 30 Gy when the whole bone is irradiated have been recommended [16]. With these measures, the only patients who experience late fractures seem to be those with fracture at presentation and biopsy-proven recurrence [16]. Subsequent fractures in these patients may be prevented limiting the size of the biopsy and achieving early control of local disease with adequate chemoradiotherapy.

In conclusion, with all the limitations of a retrospective analysis of pre-PET and pre-rituximab patients, this study, carried out on the largest international series, suggests that PF is a negative prognostic event in patients with DLBCL of the bone and provides useful recommendations for the management of this complication in everyday practice. Initial surgical stabilization does not contribute to control the lymphoma, and should be used to improve patient's quality of life and prevent bone disintegration only if chemotherapy delays can be avoided. Irradiation of the fractured bone as initial therapy is associated with a worse outcome, suggesting that patients with PF should be treated with primary anthracycline-based chemotherapy, restraining corticosteroid doses, followed by irradiation of the fractured bone, limiting as much as possible radiation volumes and doses.

list of participating centers with the number of registered patients/center

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, UK ($n = 30$); Korea Cancer Center Hospital, Seoul, Korea ($n = 28$); National University Hospital, Seoul, Korea ($n = 24$); M.D. Anderson Cancer Center, Houston, TX, 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, 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 ($n = 8$); Fundaleu, 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, UK ($n = 4$); Woden Walley, 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 ($n = 1$).

disclosure

The authors have declared no conflict of interest.

references

1. Limb D, Dreghorn C, Murphy JK et al. Primary lymphoma of bone. Int Orthop 1994; 18: 180–183.
2. Mikhaeel NG. Primary bone lymphoma. Clin Oncol (R Coll Radiol) 2012; 24: 366–370.
3. Cai L, Stauder MC, Zhang YJ et al. Early-stage primary bone lymphoma: a retrospective, multicenter Rare Cancer Network (RCN) Study. Int J Radiat Oncol Biol Phys 2012; 83: 284–291.
4. Lewis VO, Primus G, Anastasi J et al. Oncologic outcomes of primary lymphoma of bone in adults. Clin Orthop Relat Res 2003; 415: 90–97.
5. Chua SC, Rozalli FI, O'Connor SR. Imaging features of primary extranodal lymphomas. Clin Radiol 2009; 64: 574–588.
6. Baar J, Burkes RL, Bell R et al. Primary non-Hodgkin's lymphoma of bone. A clinicopathologic study. Cancer 1994; 73: 1194–1199.
7. Gianelli U, Patriarca C, Moro A et al. Lymphomas of the bone: a pathological and clinical study of 54 cases. Int J Surg Pathol 2002; 10: 257–266.
8. Jawad MU, Schneiderbauer MM, Min ES et al. Primary lymphoma of bone in adult patients. Cancer 2010; 116: 871–879.
9. Ramadan KM, Shenkier T, Sehn LH et al. A clinicopathological retrospective study of 131 patients with primary bone lymphoma: a population-based study of successively treated cohorts from the British Columbia Cancer Agency. Ann Oncol 2007; 18: 129–135.
10. Pellegrini C, Gandolfi L, Quirini F et al. Primary bone lymphoma: evaluation of chemoimmunotherapy as front-line treatment in 21 patients. Clin Lymphoma Myeloma Leuk 2011; 11: 321–325.
11. Alencar A, Pitcher D, Byrne G et al. Primary bone lymphoma—the University of Miami experience. Leuk Lymphoma 2010; 51: 39–49.
12. Barbieri E, Cammelli S, Mauro F et al. Primary non-Hodgkin's lymphoma of the bone: treatment and analysis of prognostic factors for Stage I and Stage II. Int J Radiat Oncol Biol Phys 2004; 59: 760–764.
13. Cabanillas ME, Lu H, Fang S et al. Elderly patients with non-Hodgkin lymphoma who receive chemotherapy are at higher risk for osteoporosis and fractures. Leuk Lymphoma 2007; 48: 1514–1521.
14. Lucraft HH. Primary lymphoma of bone: a review of 13 cases emphasizing orthopaedic problems. Clin Oncol (R Coll Radiol) 1991; 3: 265–269.
15. Stokes SH, Walz BJ. Pathologic fracture after radiation therapy for primary non-Hodgkin's malignant lymphoma of bone. Int J Radiat Oncol Biol Phys 1983; 9: 1153–1159.
16. Christie DR, Hulbert P, Christiansen P. Prosthetic devices within radiotherapy fields: planning implications and results. Australas Radiol 2001; 45: 528–530.