Primary bone lymphoma: Tunisian multicentric retrospective study about 32 cases.

Lymphome osseux primitif: étude rétrospective multicentrique Tunisienne à propos de 32 cas.

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RÉSUMÉ

Objectif: Etudier les caractéristiques épidémiologiques et cliniques, les modalités thérapeutiques, et le pronostic des lymphomes osseux primitifs (LOP) sur une série Tunisienne rétrospective.

Méthodes: Nous avons recueilli des cas de LOP histologiquement confirmé dans trois départements d'oncologie médicale du nord et du centre de la Tunisie et nous avons analysé leurs caractéristiques épidémiologiques, le protocole thérapeutique et les résultats.

Résultats: Nous avons colligé de Janvier 1990 à juillet 2014, 32 patients dont l'âge médian était de 53 ans. Les LOP touchaient surtout les os longs, fémurs, tibias et humérus avec une atteinte plurifocale dans 3 cas/32. Il s'agissait le plus souvent de stades précoces I et II et dans 91% de lymphomes B à grandes cellules. Tous les patients ont eu une chimiothérapie (CT) en majorité de type CHOP, associée au rituximab pour les 9 cas les plus récents. 14 patients/32 patients ont reçu une radiothérapie loco-régionale et un patient a eu une résection chirurgicale de type résection-reconstruction. Le taux de réponses objectives cliniques-radiologiques après CT était de 90%. Avec un suivi médian de 38,5 mois (1-192 mois), Le taux de survie globale (OS) à 5 ans était de 63%, 14 patients sont vivants en rémission et 18 ont présenté des rechutes loco-régionale et/ou systémiques.

Conclusion: Les LOP restent une maladie rare, encore tardivement diagnostiquée en Tunisie. Cependant, la majorité des patients restent diagnostiqués à des stades précoces. Les progrès de la CT, en particulier depuis l'introduction du Rituximab, permettent d'obtenir un taux élevé de réponses objectives et une amélioration de la survie.

Mots-clés

Lymphome, non hodgkinien, primitif, os, classification, stade, chimiothérapie, réponse objective, survie.

SUMMARY

Objective: To report the epidemiologic, clinical features, treatment modalities and prognosis of primary bone lymphomas (PBL) within a retrospective Tunisian series.

Methods: We collected cases of histologically confirmed PBL in 3 medical oncology departments from northern and central Tunisia andwe analyzed their characteristics.

Results: From January 1990 to July 2014, we collected 32 patients with histologically proven PBL, having a median age of 53 years. They affected mainly the long bones and diagnosed at early stages. 91% of the PBL were large cell B lymphoma.All patients received CHOP or CHOP-likeChemotherapy (CT), associated to Rituximab in the last 9 cases, with 14/32 patients received loco-regional radiotherapy and one patient had a resection-reconstruction surgery. We observed 90% of objective responses after primary CT.With a median follow-up of 38.5 months (1 to 192), the 5-year overall survival OS rate was 63%.18 patients relapsed and 14 remain alive in complete remission.

Conclusion: PBL remains a rare disease lately diagnosed in Tunisia. However, most of the patients had early stages tumors. Furthermore, the efficacy of CT and introduction of Rituximab leads to a high rate of complete/objective responses, improving the survival rate.

Key-words

Lymphoma, bone, primary, B-cell, chemotherapy, rituximab, radiotherapy, response, survival.

Primary non Hodgkin lymphomas of bone or PBL are rare, accounting for less than 1-2% of adult Non Hodgkin Lymphomas (NHL) and less than 7-10% of primary bone tumors(1,2).PBL is defined as a lymphoma localized in an osseous site without evidence of disease elsewhere for at least 6 months. The presence of regional lymph nodes does not exclude the diagnosis of PBL [1]. Treatment is based on chemotherapy (CT), with Rituximab for B-cell lymphomas (DLBC), but loco-regional radiotherapy (LRT) and more rarely orthopedic reconstructive surgery could be indicated.

We report the results of a retrospective study concerning patients treated in three university hospitals in Tunisia, with histologically confirmed PBL during a 24 years period.

METHODS

We collected patients with histologically-confirmed PBL treated over a 24years period at northern and central Tunisia (1990-2014) in Tunis from Salah Azaiez Institute, Abderrahman Mami Hospital and in Sousse from Farhat Hached university hospital. Staging investigations included: physical examination, performance status, laboratory tests (complete blood count, lactate deshydrogenase (LDH) and complete metabolic profile), thoraco-abdominal computed tomography (CT-scan) and bone marrow biopsy. PBL cases were classified according to Ann Arbor: stage I consisted in single localized bone lesion, stage IIE consisted in bone lesion with lymph node involvement on the same side of the diaphragm,stage III consisted in bone lesion with distant lymph nodes involvement and stage IV included multiple bone lesions or a single large bone lesion. All patients assigned a score using the Age Adjusted International Prognostic Index (IPI)system including 3 of the above factors: Stage, LDH and Performance status, the sum of the points allotted correlates with the following risk groups: Low risk (0 points), Low-intermediate risk (1 point), High-intermediate risk (2 points) and High risk at 3 points. We grouped patients by IPI score into group 1 including those with scores 0-2 and group 2 for those with scores >2. All patients received CT mainly by CHOP (Doxorubicin, Cyclophosphamide, Vincristine and Prednisone) or CHOP-like protocols such as ACVBP(Adriamycin, Cyclophosphamide, Vincristine, Bleomycine and Prednisone) and in relapsing patients ICE(Ifosfamide, Carboplatin and Etoposide) and DHAP(Dexamethasone, Cisplatin, high dose Aractyin). Since its availability in 2004, patients with DLBC received Rituximab in addition to CT.Radiotherapy(RT) was prescribed in emergencies at a dose of 30 Gy in 10sessions in case of severe pain and/or spinal cord compression) or in stage I diseaseat doses from 46 to 54 Gy in 15 to 27 sessions.Surgery was performed in situation of pathologic fractures. Response to CT and/or CT was evaluated clinically and radiologically at the end of the protocol.Complete response was defined as total control of bone pain, normal LDH level and disappearance of bones lesions with reconstruction. Partial response was defined as control of bone pain and regression of more than 50% of bone lesions. We analyzed the epidemiological, clinical, histological features, treatment protocols and therapeutic results.

RESULTS

We collected thirty-two (32) patients, with a median age of 53 years (20 to 87 years) and a 1.6 sex-ratio. Bone pain was the major symptom (53% of patients) andmean time to diagnosis was 9 months (2-24 months). PBL predominates in long bones (66%), while axial location was seen in 13 cases; lesions being were exclusively osteolytic (Figures 1 and 2).Regional lymph nodes and soft tissue involvement were seen respectively in 10 and 2 cases. All patients had high grade lymphomas of B-cell lineage in 91% of cases, the resting 9% being T-cell type or anaplastic. Patients were classified according to Ann Arbor classification as stage I, II and IV in respectively 13, 9 and 10 cases. 68% of patients were staged in group 1 IPI score and 32%(10 patients) in group 2 IPI score.Patients received CHOP-CT in 28 cases and ACVBP in 4 cases, associated to Rituximab in 9 cases. Two patients scored 2 IPI, had an intensification and autologous stem cell after objective responses to ACVBP.

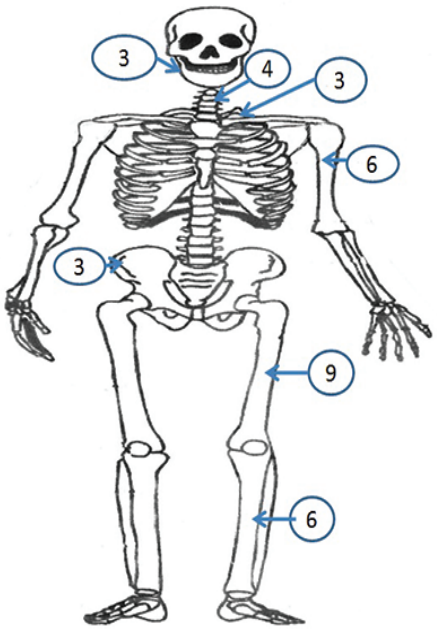

Figure 1 : Bone anatomic localizations

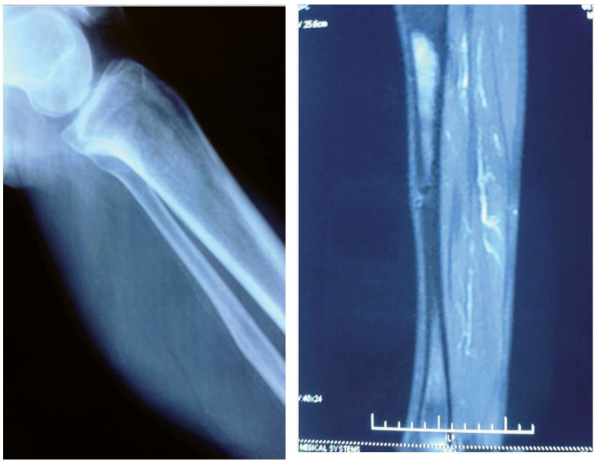

Figure a: Standard radiology Figure b: MRI

Figure 2: Imaging of bone lesions

Loco-regional RT was used in 14/32 patients, curative in 6 cases and for pain and spinal cord compression in respectively 5 and 3 cases. One patient complete responder after 6 cycles of ACVBP, had a resection-reconstruction of his femoral PBL due to an initial pathologic fracture. Histologic examination showed a complete histologic response (pCR) in the resected femoral tumor. After primary CT, we observed 80% of complete clinical and radiological response rate (CRCR) and partial in 10 cases. With a median follow-up of 38.5 months, varying from 1 to 192 months, the 5-year OS was at 63%.3 patients died by severe sepsis after grade IV-induced neutropenia, 14 (43%) presented local relapses in bones, 4 (12%) had distant relapses in testis, lymph nodes, orbit and pericardium. Salvage treatment consisted on CT in 6 patients and LRT in 3 cases. One of our patients who presented a bone relapse treated by CT (RGEPD: Rituximab, Gemcitabine, Etoposide, Prednisone and Doxorubicine) is still alive in complete remission and he has two babies. By the time of our study 11 patients remain alive in complete remission.

DISCUSSION

We collected from 3 university hospitals in Tunisia, 32 cases of PBL, over a 24 years period confirming the rarity of this disease that represents in literature less than 1% of primary bone tumors [1,2]. PBL affects the middle-aged to elderly population, with a slight predominance in men [1,2]. The mean age in our series was 53 years.We compared them to 3 large series of PBL, from Memorial Sloan-Kettering cancer center [3], British Columbia Cancer Agency [4] and Multicenter Rare Cancer Network [5] that concerned respectively 82, 131 and 116 patients (Table I and II). We observed for our patients prolonged median delay to at 9 months, PBL diagnosis being rarely suggested initially because symptoms of bone and/or articular pain aren't specific nor pathognomonic, and general symptoms (fever, night sweats) are rare. Most patients have repeated consultations and treatment by anti-inflammatory and analgesics prescribed by first line physicians and orthopedics/rheumatologists. PBL arises in flat and axial bones, but long bones can be also affected [7,4]. Radiologic lesions are mostly osteolytic, without any specific aspect in imagery [8]. Lesions can be multifocal (4 of our cases). Histology, based on fine needle biopsy for all our patients concluded to high grade B-cell lymphomas in 29/32 patients, comparable to literature data [4, 5, 7, 9]. PBL is more often diagnosed in early stage, even when diagnosis is delayed[4, 10].

Table 1 : PBL Patients characteristics compered to others international series

	Our serie	Ramadan(3)	MSKCC(4)	Cai et al(5)
Number	32	131	82	116
Mean age	53	63(18-87)	48 (11-83)	51(17-93)
Sex-ratio	1.6	1.4	1.1	1
Initial symptoms				
Pain	53%			78%
bone Fracture	6%			17%
B symptoms	6%	31%	5%	17%
Localisation				
Spine	12%	32%	9%	28%
Pelvis	9%	14%	15%	20%
Humerus	18%	11%	12%	10%
Femur	28%	12%	27%	14%
Other sites	9%	23%	8%	
Histology				
DLBCL	91%	79%	80%	78%
Follicular lymphoma	0%	6%		6%
DLTCL	9%	10%		
Classification according to Ann Arbor				
IE	40%	26%	78%	80%
IIE	28	20%	4%	20%
IV	31%	54%	19%	
IPI score				
0-2	68%	64%	88%	70%
>2	28%	36%	11%	30%

DLBCL= diffuse large B cells lymphoma, DLTCL= diffuse large T cells lymphoma, IPI = International Prognostic Index.

Table 2 : PBL Therapeutic results of PBL

	Our serie	Ramadan(3)	MSKCC(4)	Cai et al(5)
Radiotherapy	43%	48%	46%	87%
Surgery	3%			14%
Protocol				
CHOP	59%	79%		
R-CHOP	21%	21%	50%	87%
ACVBP	6%			
R-ACVBP	6%			
OS	63%	60%		
DFS		56%	88%	76%

CHOP= Doxorubicin, Cyclophosphamide, Vincristine and Prednisone; RCHOP= Rituximub- CHOP;ACVBP= Adriamycin, Cyclophosphamide, Vincristine, Bleomycine and Prednisone; RACVBP= Rituximub- ACVBP; OS= 5 year's overall survival, DFS= disease-free survival.

Additionof Rituximab to chemotherapy was an important progress in the treatment of high grade B-cell NHL. In Tunisia, Rituximab was approved since 2004. All the patients were treated with anthracyclin based chemotherapy (CHOP or ACVBP), with an objective response rate of 90%, and 10% of complete response. We indicated, as salvagetreatment, intensification for 2 high-risk IPI patientsand they're still alive in complete remission. Loco-regional RT was used in 14/32 patients for isolated bone lesions in early treated patients and/or in case of emergency or pain. In the literature, the role of radiation therapy is still a matter of debate. Ramadan et al. found that addition of RT to CT deteriorates survival rate [5]. However, Ling Cai and Barbieri,showed that RT was associated with a better 5-year survival in patients with early stage PBL [6, 11, 12]. A recent publication reported the results of a retrospective study concerning 70 patients with PBL, treated between 1985 and 2013 by CT alone (45/70) or combined CT-RT in 24 patients (11). RT concerned bulky disease or incomplete response to CT. Despite no difference in term of 5 year survival patients that received RT were more likely to experience fracture healing (p = 0.01) and have a higher risk for fracture in the post-treatment period observed in 5/24 pts (p = 0.0375).

Despite the high response rate after primary CT, median time to relapse was shorter than in US and Asian series of PBL [4, 13].Indeed, in recent studies, most PBL are treated with combined radiotherapy, chemotherapy and Rituximab. Also, the majority of studies reported early staged lymphoma.

CONCLUSION

PBL is a rare disease andDLBCL is the most frequent subtype. It has a fairly good prognosis. The role of CT is central in its treatment and the addition of Rituximab improved outcomes. However, radiotherapy's role is steel not well established. Larges prospective studies are needed to develop the appropriate treatment and recommendations.

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