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Clinical Investigation: Lymphoma

Early-Stage Primary Bone Lymphoma: A Retrospective, Multicenter Rare Cancer Network (RCN) Study

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Summary

Primary bone lymphoma (PBL) is a rare form of extranodal lymphoma. This study by the Rare Cancer Network retrospectively analysed patients treated with radiotherapy and /or chemotherapy, in Stage I and II disease. Local recurrence was observed in only 10% and distant recurrence in 17% of patients. IPI score, RT dose, complete response to treatment, and use of chemotherapy were independent favorable prognostic

Purpose: Primary bone lymphoma (PBL) represents less than 1% of all malignant lymphomas. In this study, we assessed the disease profile, outcome, and prognostic factors in patients with Stages I and II PBL.

Patients and Methods: Thirteen Rare Cancer Network (RCN) institutions enrolled 116 consecutive patients with PBL treated between 1987 and 2008 in this study. Eighty-seven patients underwent chemoradiotherapy (CXRT) without (78) or with (9) surgery, 15 radiotherapy (RT) without (13) or with (2) surgery, and 14 chemotherapy (CXT) without (9) or with (5) surgery. Median RT dose was 40 Gy (range, 4−60). The median number of CXT cycles was six (range, 2−8). Median follow-up was 41 months (range, 6−242).

Results: The overall response rate at the end of treatment was 91% (complete response [CR] 74%, partial response [PR] 17%). Local recurrence or progression was observed in 12 (10%) patients and systemic recurrence in 17 (15%). The 5-year overall survival (OS), lymphoma-specific survival (LSS), and local control (LC) were 76%, 78%, and 92%, respectively. In univariate analyses (log−rank test), favorable prognostic factors for OS and LSS were International Prognostic Index (IPI) score ≤ 1 ($p = 0.009$), high-grade histology ($p = 0.04$), CXRT ($p = 0.05$), CXT ($p = 0.0004$), CR ($p < 0.0001$), and RT dose >40 Gy ($p = 0.005$). For LC, only CR and Stage I were favorable factors. In multivariate analysis, IPI score, RT dose, CR, and CXT were independently influencing the outcome (OS and LSS). CR was the only predicting factor for LC.

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factors. Early stage PBL treated with combined RT and chemotherapy has an excellent prognosis.

Conclusion: This large multicenter retrospective study confirms the good prognosis of early-stage PBL treated with combined CXRT. An adequate dose of RT and complete CXT regime were associated with better outcome. © 2012 Elsevier Inc.

Keywords: Primary bone lymphoma, Early stage, Radiotherapy, Combined treatment modality

Introduction

Primary bone lymphoma (PBL), either in adults or children (1), is a rare presentation of non-Hodgkin lymphoma, accounting for less than 1% of all malignant lymphomas, for about 5% of all primary malignant bone tumors, and for 4−5% of all extranodal non-Hodgkin lymphomas (2−4). PBL was first described as a distinct clinical entity by Parker and Jackson in 1939 (5), and defined in the 2002 World Health Organization (WHO) classification of tumors of soft tissue and bone, as a single skeletal tumor with, or without regional lymph node involvement, or multiple bone lesions, without visceral or lymph node involvement (6).

Almost 90% of PBL patients present with diffuse large B-cell lymphoma histological subtype, which may have a better prognosis than that of the less common T-cell lymphoma subtype (7−9). The most commonly affected parts of the skeleton are within the metaphysis and diaphysis of the long bones (10). The clinical characteristics are nonspecific, making a proper diagnosis difficult at the outset. Pain, swelling, and pathologic fractures are the most common presenting symptoms.

Local radiotherapy (RT) was established as the standard treatment in the 1960s with a local relapse rate of 10−20%, but with a distant relapse rate of about 50% and a 5-year survival rate ranging between 55% and 65% (11−13). The 5-year survival rate has been improved to about 70−90% with the addition of chemoradiotherapy (CXRT) in early-stage disease (11, 14−17).

The role of RT was recently challenged (18, 19), as chemotherapy alone appeared to be quite effective, especially with the development of new agents such as rituximab. The purpose of our Rare Cancer Network (RCN; http://www.rarecancer.net) study was to collect substantial information from a large number of patients to more properly define the disease profile, therapeutic approach, and outcome and prognostic factors of this disease.

Patients and Methods

Patients

We collected 116 eligible patients from a total of 136 cases of PBL treated between 1987 and 2008 in 13 institutions of the RCN. Inclusion criteria included: age >16 years, confirmed pathological diagnosis of bone involvement, Stages I and II according to the Ann Arbor staging system (20), and a minimum of 6 months' follow-up after treatment. After a review of all clinical and pathological records, 20 cases were excluded from the analysis because of disseminated disease (12 cases) and multiple bone involvement (8 cases). All the medical records were reviewed for age, gender, symptoms, physical examination, laboratory examination, imaging, pathological diagnosis, involved sites, stage, International Prognostic Index (IPI) (21), treatment modality, response, site of relapse, treatment-related complications, time to death, and date of last follow-up. In this study, all investigators obtained their own Institutional Review Board approval for patients' data collection.

All pathology reports were reviewed and "translated" into the WHO classification. The workup of individual patients included medical history, physical examination, complete blood count, lactate dehydrogenase, erythrocyte sedimentation rate, complete metabolic profile, bone marrow biopsy and plain bone X-ray in all patients. Bone computed tomography, magnetic resonance imaging, positron-emission tomography, or whole body computed tomography scan were performed according to each institution's policy. Stage was established with the Ann Arbor staging system. Single localized bone lesions were classified as Stage IE, and in case of lymph node involvement on the same side of the diaphragm, patients were considered to have Stage IIE. IPI score was established based on the medical records.

Patients were treated according to each hospital's local policy. The modality of treatment included chemotherapy, RT, surgical resection, or a combination of these. Most patients had a biopsy only (100); however, 16 underwent surgery. Of these, 13 had some form of local excision or curettage, 2 had a laminectomy with partial excision, and 1 had a total hip replacement.

Response was evaluated according to lymphoma-adapted Response Evaluation Criteria in Solid Tumors (22, 23). Early and late treatment toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) V3.0 (24).

Statistical methods

Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death from any cause. Lymphoma-specific survival (LSS) was calculated from the date of diagnosis to the date of lymphoma-related death. Local control (LC) was calculated from the date of diagnosis to the date of local recurrence. Survival curves were constructed using the Kaplan-Meier method, differences were considered significant if the p value was ≤ 0.05 (two-tailed log−rank test). Multivariate analysis (Cox model) was used to determine the independent prognostic factors. All prognostic factors identified in the univariate analyses with p value <0.20 were included in the multivariate analyses.

Results

Patient and treatment characteristics are presented in Table 1.

Median age was 51 years (range, 17−93 years), and there were 69 males (59%) and 47 females (41%).

The majority of patients (75%) received combined CXRT. Treatment sequences were chemotherapy followed by