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Treatment options in skeletal localizations of hairy cell leukemia: A systematic review on the role of radiation therapy

Andrea R. Filippi,[1]* Pierfrancesco Franco,[1] Carlo Marinone,[2] Corrado Tarella,[3] and Umberto Ricardi[1]

[1] Radiation Oncology Unit, Department of Medical and Surgical Sciences, University of Turin, Ospedale S. Giovanni Battista, Torino, Italy
[2] Department of Internal Medicine, Ospedale S. Giovanni Battista, Torino, Italy
[3] Department of Hematology, University of Turin, Ospedale S. Giovanni Battista, Torino, Italy

Skeletal localizations are a rare complication in hairy cell leukaemia patients, with an extimated incidence of 3%. These lesions, mainly osteolytic, can occur at various sites and are almost always symptomatic. Localized radiation therapy (RT) has been extensively used as effective palliative treatment in such cases, with different total doses and fractionation schedules. In this article, a systematic review of all reported cases with osseous complications is presented, to underline the role of RT and to define the most appropriate approach in this subset of patients. Am. J. Hematol. 82:1017–1021, 2007. © 2007 Wiley-Liss, Inc.

Introduction

Hairy cell leukemia (HCL) is an uncommon B-cell lymphoproliferative disorder, accounting for about 2% of all leukemias [1], first mentioned by N. Rosenthal and S. Lee in 1952 at the 31st meeting of the American Society of Clinical Pathologists in Chicago [2]. Diagnosis is made upon two main features: the peripheral-blood smear, which usually shows atypical mononuclear cells exhibiting clear cytoplasm with irregular cytoplasmatic projections (hairy cells), and histological pattern of bone marrow infiltration, showing a hypercellular marrow with a uniform population of mononuclear cells with moderate to abundant clear cytoplasm [3,4].

Splenomegaly is a common finding (80–90% of patients) [5,6]. A large number of patients present with pancytopenia, mainly because of hypersplenism, splenic pooling, bone marrow involvement, autoimmune mechanisms, and cytokine-mediated suppression [7]. Hepatomegaly is observed in fewer cases (30% of patients) [6,7]. One of the most prominent clinical features is immunodepression with an increased risk of developing infections, involving mainly lung, urinary tract, liver, and CNS. Unusual complications are represented by intrathoracic and intra-abdominal lymphadenopathy [8], cutaneous involvement [9–11], pleural and peritoneal involvement [12], ocular [13], meningeal [14], renal [15], hernial sac localizations [16], amyloidosis [17], and paraproteinemias [3,18–20].

While bone marrow infiltration is the rule in HCL, skeletal involvement with destructive bone lesions is quite uncommon. It was described for the first time in 1977, presenting as lytic or lytic/blastic, painful, isolated, or multiple lesions [21]. On the basis of available epidemiological data, the estimated incidence of skeletal involvement in HCL is ~3% [22,23]. The presenting symptom, in most patients, is localized pain. Occasionally, patients may complain of multiple painful sites, with localized or even diffuse arthralgia. Joint effusion may or may not be found. The majority of lesions occur within the femoral head and neck. Less frequently involved sites include the vertebral column, pelvis, skull, tibia, humeral head, and femoral diaphysis. The predominant radiologic finding is osteolysis with or without well-defined margins. Sometimes an osteoblastic component can be found, creating, with the lytic changes, a "mixed pattern." Areas of widespread or circumscribed demineralisation may be present, or zones of bony sclerosis. Other uncommon manifestations include aseptic necrosis of the femoral or humeral head and extensive osteoporosis [24].

Overview on clinical reports

Although bone lesions are infrequently seen, skeletal involvement is a well-established manifestation in HCL. Osseous localizations are rarely observed at presentation. Solitary skeletal involvement is an unusual manifestation in HCL [25]. In the last 30 years, only few cases have been reported in the medical literature. In those reports, most patients were treated with radiation therapy (RT). However, extremely heterogeneous fractionation schedules and doses were employed and detailed information concerning the role of RT in the management of bone lesions in HCL is still lacking. The most relevant papers on presentation and treatment of bone lesions in HCL are here summarized in Table I.

Early reports

The series and anectodal reports herein cited are chronologically located between the end of the seventies and mid-eighties, when HCL patients could benefit of mostly palliative treatments such as splenectomy, radiotherapy and steroids, and ineffective chemotherapeutic regimens.

- In the early case report of 1977 by Rhyner et al., painful bone involvement occurred at 2–3 years after diagnosis in three patients. Two of them were treated with RT: one received 60 Gy in 30 fractions, the other 8 Gy in a single fraction. Both patients responded well, with persistent pain resolution [21].
- Weh et al. described 5 cases of bone localization in a series of 150 patients. The femoral neck was the most common site of involvement (4/5); 4 lesions were lytic, sometimes associated with pathological fractures, and

*Correspondence to: Andrea R. Filippi, MD, Radiation Oncology Unit, University of Turin, Via Genova 3, 10126 Torino, Italy.
E-mail: afilippi@molinette.piemonte.it

Received for publication 7 November 2005; Accepted 17 July 2006

Am. J. Hematol. 82:1017–1021, 2007.

Published online 24 July 2007 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20785

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TABLE I. Systematic Review of All Reported Cases

Pt. n.	Involved sites	RT	Other therapies	Comments
1 [26]	Right femoral neck	None	NS	Alive at 15 months from BI
2 [26]	Left femoral neck	None	NS	Died 1 months from BI
3 [26]	Thoracic and lumbar vertebrae	None	Splen	Alive at 3 months from BI
4 [26]	Right femoral neck	None	NS	Bone lesion at presentation; alive at 3 mo from BI
5 [26]	Right femoral neck	None	NS	Bone lesion at presentation; died 30 mo from BI
6 [21]	Left femoral neck	60 Gy (30fr)	VCR, PDN	Alive at 18 mo from BI
7 [21]	Left femoral neck	8 Gy (1 fr)	NS	Alive at 9 mo from first BI; developing multiple compression fractures of thoracic spine
8 [21]	Parietal skull	None	NS	–
9 [27]	Right femoral head	34,5 Gy (23fr)	NS	Left hip involvement treated with RT (24 Gy)
10 [2]	Left femoral head	23 Gy	PDN, Splen	Relief of pain within 6 weeks
	Right femoral head and sacro-iliac region	22 Gy		Normalization of bone by X-ray examination
11 [28]	Right femoral neck	60 Gy (30fr)	Splen	Developed aseptic necrosis of right femour 1 year after first BI
12 [28]	Right femoral neck, L2	None	Splen, Chl	Developed additional vertebral bodies collapse and rib involvement 4 mo after Chl
13 [29]	Left humeral head	20 Gy	Splen	X-rays 2 mo after RT showed complete resolution of osteolysis; died of M. Kansasii dissemination 7 mo after BI
14 [29]	Right femoral head	25 Gy (10 fr)	Splen	Alive at 6 years from BI
15 [29]	Right femoral head	None	Splen, hip joint repl	Developed iperdensity in left femoral head 2 years after first BI
16 [29]	Several vertebral bodies	None	Splen, Dauno	No complaints of osseus pain 12 mo after Dauno
17 [30]	S-1	24 Gy	None	Concomitant right femoral osteolysis treated with total hip repl, alive at 14 mo from BI
18 [20]	Right femoral neck	20 Gy (5 fr)	Splen	Ig G κ class paraprotein present; developed scrotal involvement by HCL treated with RT and died 1 year after BI of cardiovascular accident
19 [20]	Right femoral neck	None	Splen	2 Ig G λ paraprotein present; died of P. Aeruginosa and A. Fumigatus pneumonia 2 mo after BI
20 [31]	Left femoral neck	Profilactic	Splen, hip joint repl	Generalized skeletal demineralization; splenic rupture occurred; died 4 mo after BI of S. Typhi sepsis
21 [32]	Neck, pelvis, upper, and lower extremities	None	Splen, PDN	Paraspinal mass due to HCL remitted with RT; bone pain disappeared with steroid treatment
22 [33]	NS	24 Gy	NS	–
23 [34]	Bilateral femoral head	30 Gy	Splen, CT, retroperitoneal RT	–
24 [24]	Right femoral head and neck, right pubic bone	None	Splen, total hip repl	Died 6 mo after BI of K. Pneumoniae meningitis and sepsis
25 [24]	Thoracic and lumbar vertebral bodies	Palliative	IFN	Osseous progression 2 years after first BI, involving both pubic bones, skull, entire spinal column, bilateral femura, right tibia, and humeral shaft
26 [23,35]	Right femoral head with subcapital fracture, left femoral head	30 Gy on left femoral head	Splen + total hip repl + Chl + IFN	Developed 2nd bone lesion 6 mo after Chl; alive and bone free 29 mo after IFN
27 [23,35]	Right femoral head	24 Gy	Splen, IFN	Alive and bone free 21 mo after first BI
28 [23,35]	Right femoral head	30 Gy	Splen, IFN	Alive and bone free 25 mo after first BI
29 [23,35]	Right femoral head and shaft	20 Gy	Splen, Chl, IFN	Alive and bone free 41 mo after first BI
30 [23,35]	Right femoral head	15 Gy	Splen, IFN	Developed two bone lesions during IFN; alive and bone free 31 mo after humeral involvement
	Left femoral head	15 Gy		
	Humerus	15 Gy		
31 [23,35]	Thoracic vertebrae with compression fractures	21 Gy	IFN, Chl, 2-dCF	Developed one additional bone lesion during IFN, another during Chl. Began 2-dCF for bone progression
	Lumbar vertebrae with compression fractures	21 Gy		

TABLE I. Continued

Pt. n.	Involved sites	RT	Other therapies	Comments
32 [23]	Right femoral head	20 Gy	Splen, IFN	Alive 3 mo after BI
33 [23]	Left distal tibia	20 Gy	Splen, Chl, PDN, VBL, Bleo, IFN	Developed bone lesion 3 mo after stopping IFN
34 [36]	Ribs, several vertebral bodies, pelvis, proximal femora	None	Splen,IFN,2-dCF	Alive 18 mo after BI; no change in X-rays appearance
35 [36]	Skull, pelvis, lumbar and thoracic spine, femora	None	Splen, Chl, Lithium carbonate, Oxymethalone	Died 8 years after BI of progressive pulmonary involvement with HCL
36 [37]	Ribs, several vertebral bodies, pelvis, femora	None	IFN	Slight improvement at X-rays after 8 mo of IFN
37 [38]	Bilateral knees, left distal tibia, left ankle	25 Gy (10 fr)	Splen, IFN, 2-dCF	IFN failed to improve symptoms; RT and 2-dCF reached for that goal
38 [25]	Left femoral neck, left proximal femur and bilateral great trochanters	None	2-CdA	Improvement in femoral lesions after 10 mo from 2-CdA, with two residual foci
39 [22]	Right femur, left tibia	None	Splen, IFN, 2-dCF, 2-CdA	Complete osseous remission after 2-CdA; mastectomy for breast cancer
40 [39]	Left humeral head	25 Gy (10 fr)	IFN, 2-CdA, Splen, Rit	Complete clinical response 2 mo after RT

Pt. n.: patient's number; RT: radiotherapy; BI: bone involvement; NS: not specified; mo: months; IFN: α-interferon; 2-dCF: pentostatin; 2-CdA: cladribrine; HCL: hairy cell leukaemia; PDN: prednisone; VCR: vincristine; VBL: vinblastine; Chl: chlorambucil; Bleo: bleomycin; Dauno: daunorubicin; repl: replacement; Splen: splenectomy; bone free: free from bone localizations; fr: fractions; Rit: rituximab.
We excluded Catovsky's et al. three cases of concurrent multiple myeloma [18].

1 lytic/blastic. None of these patients received systemic or local treatment [26]. One patient had a prothesis because of the fracture of the femoral neck while the other four were treated empirically with low doses of steroids, analgesics, and vitamin B.

- A case with bilateral hip pain in a series of 15 HCL patients was presented by Turner and Kjeldsberg. A lytic lesion was present on the right hip, and RT to a total dose of 34.50 Gy was administered to this site. On the contralateral hip 24 Gy were delivered, with "slow relief of pain over 5 months" [27].
- Demanes et al. reported on two cases with femoral neck and vertebral involvement. The first one was treated to a dose of 60 Gy, with hip pain resolution; the second only with chlorambucil, with modest and temporary pain relief. Interestingly, radiological findings showed osteonecrosis of the bone treated with 60 Gy [28].
- Quesada et al. described four cases, diagnosed at a median time of 15.5 months after initial evaluation, similarly to the Rhyner et al. experience. Predominant femoral localization and lysis were confirmed in this report. Two patients received RT, with doses of 20 and 25 Gy and pain resolution [21,29].

Systemic therapy era

Clinical data mentioned below belong to a period of time which starts from the end of the eighties and reaches the present days. Highly effective systemic treatments options, namely interferon (IFN) and, mostly pentostatin (dCF) and Cladribine (2-CdA) have been introduced during that period. The characteristics and epidemiological distribution of skeletal localization of HCL may be affected by the routinary use of these purine analogues, able to induce long-lasting complete remission in the majority of patients with HCL.

- One of the largest published series is by Lembersky et al. in 1988. They reviewed 267 HCL patients and found eight cases of skeletal involvement, with a median time from diagnosis to the discovery of the skeletal complication of 20 months. All patients were treated with radiation, with doses varying from 15–30 Gy. Pain control was obtained in all patients regardless of the fractionation schedules employed. Most of these patients received systemic treatment with IFN α-2b within 4 months of the initial bone lesion. Five of seven achieved a partial response defined as normalization of the peripheral blood counts with at least a 50% improvement in the percentage of hairy cells in the bone marrow biopsy. No recurrence of any skeletal lesion was detected with a median follow-up time of 29 months. The authors suggested that bone lesions appear to be associated with higher tumor burdens, and that patients treated with RT and systemic treatment apparently are at lower risk of developing other bone lesions [23].
- VanderMolen et al. described one HCL patient whose radiographs revealed diffuse osteosclerosis of the ribs, vertebral bodies, pelvis, and proximal femora. He responded to combination therapy with both dCF and α-IFN with an improvement in peripheral blood counts, while her bone disease remained radiographically unchanged [36].
- Lal et al. focused on a 45-years-old male, complaining of severe pain in the left proximal thigh, with bone marrow replacing lesions involving bilateral femura at MRI scan. Interestingly, no evidence of disease could be detected elsewhere, with bilateral posterior iliac crest bone marrow aspirate and biopsy, immunophenotyping by flow citometry and chromosome analysis interpreted as normal. The patient underwent a 7-day infusion of 2-CdA, with clearing of the lesions after 10 months at MRI scan. No pain recurred [25].
- The most recent paper, to our knowledge, is by Jehn et al. who reported on a case of skeletal localization in a HCL patient previously treated with multiple lines of chemotherapy, including IFN and purine analogs like dCF. A very good clinical and radiological response after a single course of 2-CdA could be obtained without irradiation [22].

Discussion

It appears clear that probably all patients affected by HCL with bone involvement are symptomatic, and that RT is a very efficient local treatment modality in terms of long-term pain relief. In all series, a clinical response was seen even after low doses. From a radiobiological point of view, considering also the efficacy of radiotherapy in reducing splenomegaly in HCL, probably low doses RT are adequate for disease control [40]. Leukemic clones of B-cell origin like HCL are extremely radiosensitive, with a surviving fraction after 2 Gy (SF2) in vitro of $\sim$0.2 to 0.3. Taking into account these SF2 values, a dose of 20–25 Gy given with conventional fractionation is theoretically sufficient to reduce to 1 a clone of 10^9 cells. Indeed, a very low toxicity is expected with these treatments, allowing different fractionation "adapted" to the patient's characteristics. A complete radiological work-up including CT and MRI is very useful in defining treatment volumes. Rarely complete radiological responses after RT are reported, similarly to the findings obtained in primary bone lymphomas after chemo-radiotherapy. Several studies have been published, providing information about long-term outcome of HCL patients treated either with dCF or 2-CdA. Both of those drugs are characterized by high effectiveness either as first-line therapy or after other treatment modalities, achieving an overall response rate of about 96%, with 80% being complete responses (CRs) and a disease-free survival at 5 years of about 85% for dCF [41,42] and an overall response rate up to 100%, with 95 % being CRs, and an overall survival rate of about 95% at 9 years for 2-CdA [43,44]. Analyzing patient characteristics of these large cohorts of patients, no mention about skeletal localizations is made, while in the previous reports this complication seemed to be more frequent. In the era of effective systemic therapy, osseous localizations seem to be extremely rare either at disease presentation and at time of relapse, which is usually located within bone marrow, peripheral blood, or spleen. It could be hypothesized that purine analogues have some sort of "protective effect" towards developing bone involvement, even in long-term survival. At relapse, patient could be successfully retreated with the same drug used as first-line therapy, with high response rates or switched to the other purine analogue, suggesting a possible lack of crossresistance between the two drugs. To our knowledge, only five cases of skeletal involvement treated with purine analogues are reported upto now. While isolated bone progressions are reported after chlorambucil or interferon [Table I], skeletal localizations seem to have high responsiveness rates if treated with purine analogues, even if few cases are reported within the scientific literature. Focusing on the clinical reports cited in this review, the correlation between disease burden and bone localizations is not clear: some patients develop lesions while in complete hematological remission, other patients have bone involvement as a single site of disease. At any rate, skeletal involvement does not appear to affect prognosis. Even if uncommon, this event may occur several months or years following diagnosis. The long median survival currently expected in HCL patients and the rate of complete haematological remission obtained with systemic treatments has probably modified the characteristics of bone manifestations, but occurrence of localized symptomatic lesions in haematological complete remission or in heavily pretreated patients can still be expected. In these cases, local RT with an "adapted" dose and fractionation schedule, in the range of 20–30 Gy, seems to be a reasonable treatment option, with an expected high response probability, a long lasting symptom control, and a limited toxicity.

Acknowledgments

The authors disclose no personal interests with any organization potentially involved in materials discussed.

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