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Critical Review

Use of Radiation in Extramedullary Leukemia/Chloroma: Guidelines From the International Lymphoma Radiation Oncology Group

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Survival times for patients with leukemia generally have improved in recent decades, and this improvement has been attributed to an enhanced understanding of the genetics driving the cause of the disease and improved combinations of chemotherapy and targeted therapy. Durable control of systemic disease in blood and bone marrow has significantly improved survival, but extramedullary relapse can pose therapeutic challenges for which radiation therapy can have an important role. This report discusses the current role of radiation therapy for patients with leukemia, specifically the extramedullary manifestations of leukemia. © 2018 Published by Elsevier Inc.

Introduction

Extramedullary manifestations of acute leukemia include a variety of clinically significant phenomena, which often pose therapeutic dilemmas. Chloroma and leukemia cutis represent 2 well-known extramedullary manifestations that have a range of clinical presentations. Chloroma (also known as granulocytic sarcoma or myeloid sarcoma) is a rare extramedullary tumor of immature myeloid cells. Soft tissue deposits of lymphoid leukemias can also occur and are typically managed in the same way as chloroma. Leukemia cutis specifically refers to the infiltration of the epidermis, dermis, or subcutis by neoplastic leukocytes (leukemia cells), resulting in clinically identifiable cutaneous lesions.

Chloroma: Presentation, Work-up, and Rationale for Radiation

Chloroma most often develops in the setting of acute myeloid leukemia (AML), but it can occur in association with chronic myeloid leukemia during the accelerated phase, myelodysplastic syndrome, and, rarely, in the absence of marrow involvement (1-4). Chloroma occurs in approximately 10% of patients with AML (2, 5, 6). The clinical manifestations of

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chloromas are diverse, given their various sites of occurrence (Fig. 1A and B). The most common locations include soft tissue, bone, periosteum, and lymph nodes; however, other sites have been described as well (3). Given the variety of sites at which chloroma develops, the use of imaging can facilitate diagnosis and help gauge treatment response. Chloroma lesions often appear as soft tissue masses that are easily visualized by computed tomography (7). Positron emission tomography can be performed to detect chloroma lesions and is useful in excluding additional sites of involvement. Positron emission tomography is also helpful for planning radiation therapy (RT) and for monitoring responses to treatment (Fig. 1D).

RT should be considered for patients with isolated chloroma and inadequate response to chemotherapy and isolated recurrence after hematopoietic stem cell transplantation (HCT), and for palliation in circumstances that require rapid symptom relief because of vital structure compression (8). RT results in excellent, rapid, and durable local control at the targeted site (9) (Fig. 2).

Radiation Dose and Technique

Few studies have addressed the role of RT in the management of chloroma (9, 10). The selection of dose is a function of the clinical scenario. A low-dose RT regimen of 24 Gy in 12 fractions can be used for most patients and produces excellent disease control and minimal morbidity (9). However, lower doses, ranging from 6 to 20 Gy, also given in 2-Gy fractions, can provide symptomatic relief and minimize disease burden if a more protracted course of radiation is not feasible.

A margin of 0.5 to 1 cm can be placed around gross disease, including any osseous involvement or changes on the bone window setting of the computed tomography scan, without the need for elective regional irradiation (Fig. 3). The immobilization technique and need for image guidance are functions of the anatomic site to be treated. Although three-dimensional conformal RT techniques can be used in most cases, intensity-modulated RT may be beneficial for treating leukemia involving the head and neck to minimize associated toxicity. Notably, RT within the dose ranges noted above does not preclude using total body irradiation as an HCT conditioning regimen or vice versa.

The timing of RT for extramedullary disease in the setting of transplantation is a function of the clinical scenario and the preference of the bone marrow transplant team. At some institutions, radiation is used before the transplantation to minimize disease burden. In such cases, dose to the optic structures, central nervous system, and lungs should be minimized and accounted for by using a conformal planning approach. However, at other centers, radiation is used after transplantation to eradicate any residual disease, and in those cases, the total body irradiation dose to be used must be factored into treatment planning.

Leukemia Cutis: Presentation, Work-up, and Rationale for Radiation

Leukemia cutis is reported in 10% to 15% of patients with AML and less commonly in cases of chronic leukemias

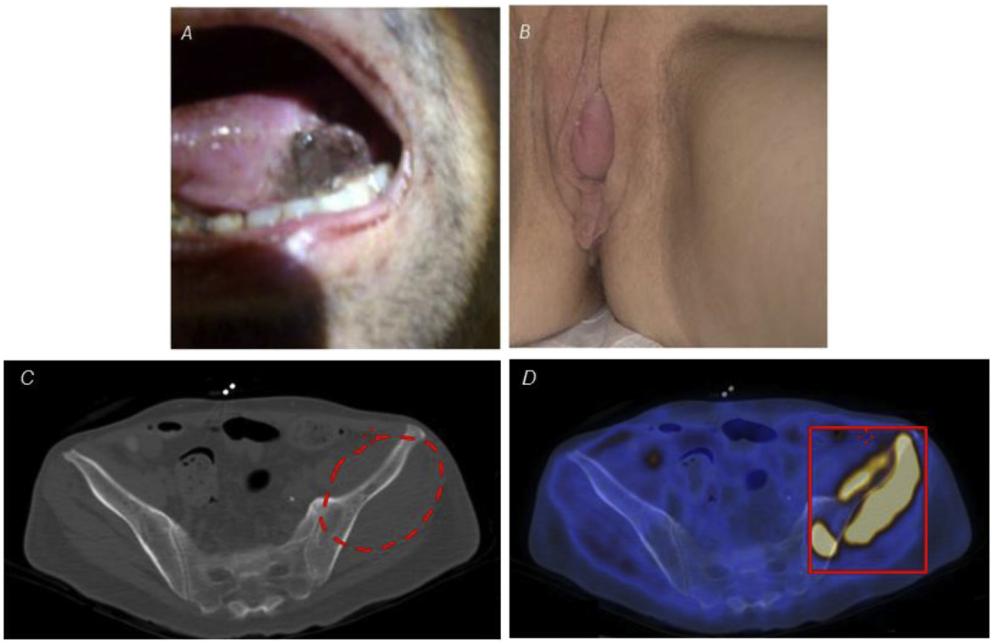

Fig. 1. Clinical and radiographic appearance of chloroma in the oral cavity (A) and vulva (B). An axial CT scan (C) and positron emission tomography scan (dashed line) (D) show a chloroma in the left hemipelvis (rectangle). *Abbreviation:* CT = computed tomography

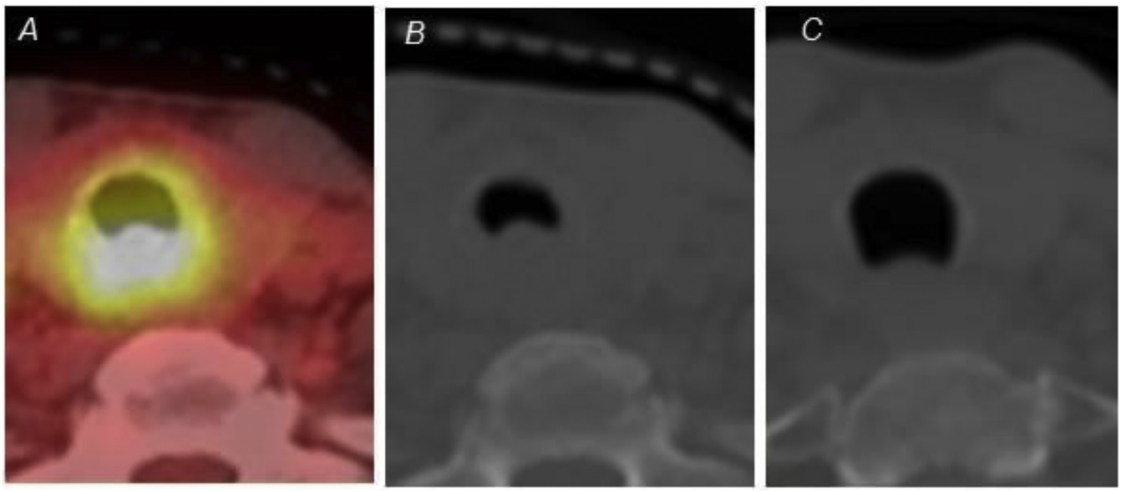

Fig. 2. Clinical appearance of chloroma on PET (A) and CT (B) scans in patient with stridor who was treated with 24 Gy and experienced rapid symptomatic relief and radiographic response immediately after completing radiation therapy (C). *Abbreviations:* CT = computed tomography; PET = positron emission tomography.

(11, 12). Leukemia cutis can develop concomitantly after or, rarely, before the onset of systemic leukemia (13). The cutaneous lesions produced by different leukemia subtypes have remarkable clinical uniformity (Fig. 4); however, distinctly different morphologies can develop over the course of the disease (14, 15). The lower extremities are the anatomic locations most commonly involved, followed by the upper extremities, back, trunk, and face (16). Patients with suspected leukemia cutis should always undergo biopsy (unless contraindicated), because skin lesions similar to leukemia cutis have a wide range of causes.

Control of cutaneous involvement is essential for long-term disease control because blasts from the skin may reseed the marrow, resulting in relapse. Therefore,

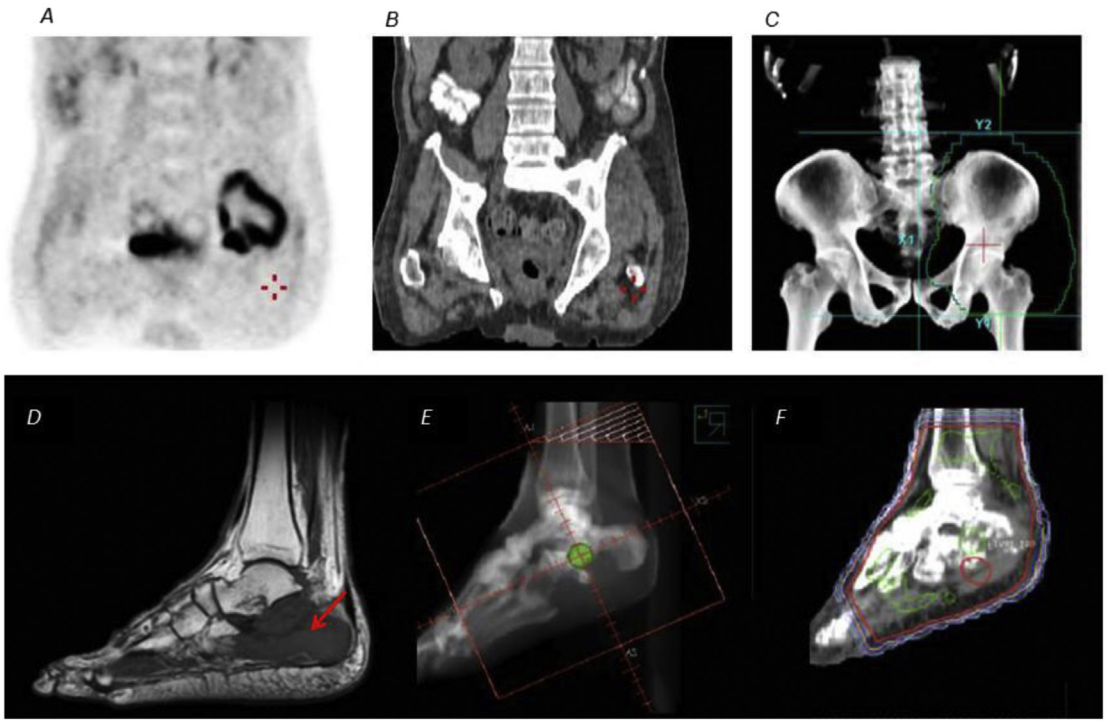

Fig. 3. (A) Chloroma in the left pelvis on positron emission tomography and (B) coronal computed tomography scans. (C) Radiation treatment field (green line). (D) Chloroma in the calcaneus as seen on a T1 magnetic resonance imaging scan (arrow). (E) Radiation treatment fields. (F) Dose distribution. Red line represents the 20-Gy isodose line. (A color version of this figure is available at www.redjournal.org.).

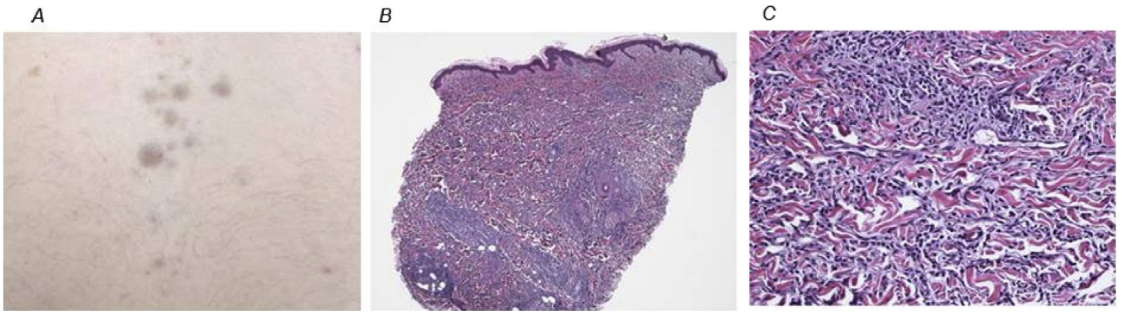

Fig. 4. (A) Clinical appearance of leukemia cutis consisting of clustered indurated papules on the back of a patient with acute leukemia. (B) Hematoxylin and eosin stain of a skin biopsy demonstrating a dense monomorphic infiltrate involving the dermis on low power with sheets of atypical myeloid cells intercalating between collagen bundles on high power (C) consistent with leukemia cutis.

skin-directed therapies like RT can be an important part of treatment (17-20). From a radiation perspective, therapy is definitive only in the setting of marrow remission because leukemic cells in the marrow will continue to reseed the skin if they are not eradicated. By contrast, patients with active marrow disease at the time of RT should be treated in a palliative manner, with RT directed at symptomatic lesions only. In such cases, radiation provides rapid relief of lesion-associated pain and pruritus. Total skin electron beam therapy is not appropriate for patients with bone marrow involvement, unless the disease is diffuse and symptomatic.

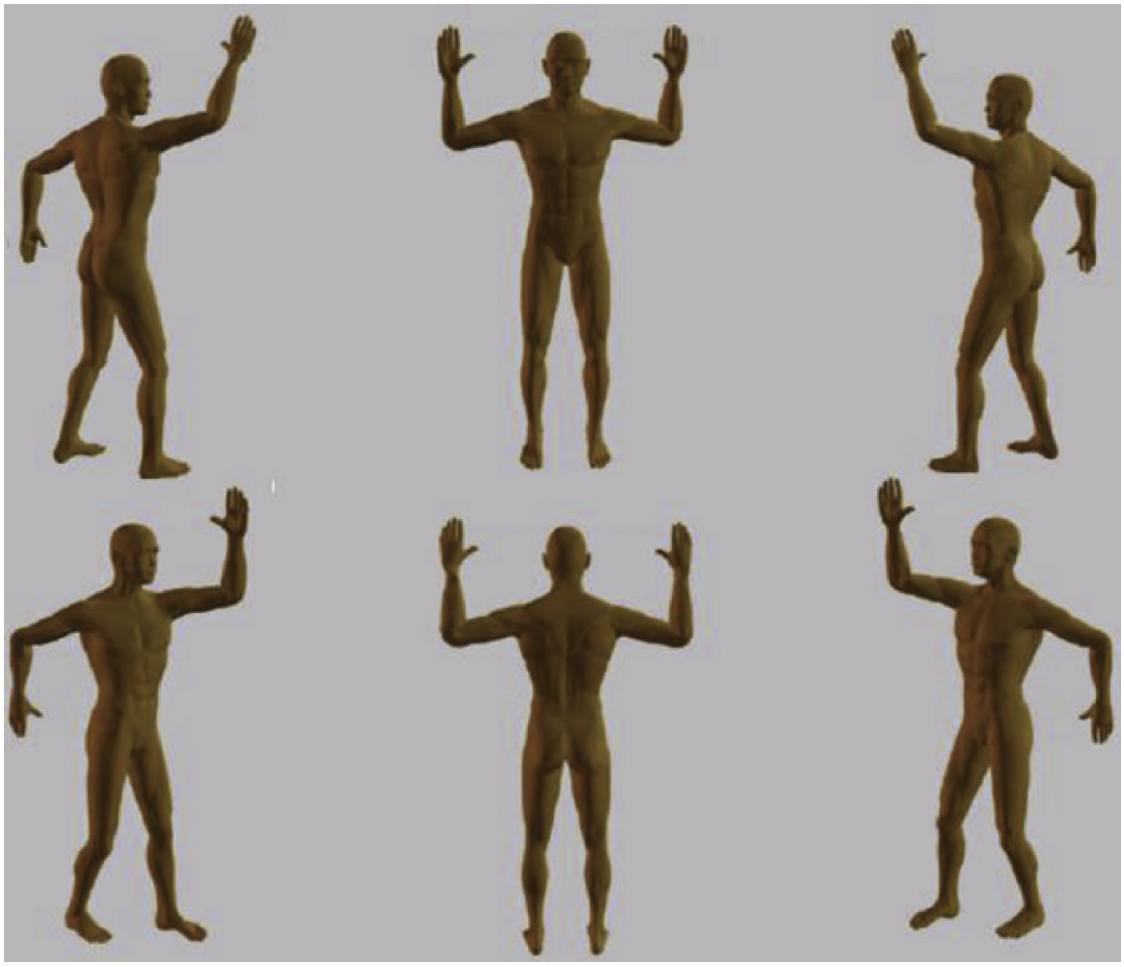

Fig. 5. Views of the 6 positions in which patients stand during total skin electron beam therapy.

Fig. 6. Hyperpigmentation and desquamation in the axilla (A) and genitalia (B) consistent with a radiation recall reaction after gemcitabine administration.

Radiation Dose and Technique

When leukemia cutis involvement is diffuse and the bone marrow shows no evidence of disease, total skin electron beam therapy can be appropriate to ensure maximum disease control. A clear dose-response relationship has not been identified, and complete responses have been seen after doses as low as 6 Gy and cutaneous failures at 24 Gy (21). The techniques used for total skin electron beam therapy vary from institution to institution (22), and this procedure should be done only at centers that routinely use it. Several techniques can be used (22), among the more common is a modified Stanford technique (Fig. 5).

In the more common clinical scenario of a symptomatic cutaneous lesion, clinically set-up electron therapy with bolus can be used in most cases. A regimen of 24 Gy in 2-Gy fractions can provide durable symptomatic relief. However, lower doses can be used for patients with poor life expectancy, as complete responses have been seen after as little as 6 Gy (21, 23).

Toxicity and Follow-up Care

Although electron beam therapy is generally well tolerated, both medical and radiation oncologists should be aware of the risk of developing subacute severe skin toxicity, especially when doxorubicin is given near the time of RT (24, 25). Although some suggest that high-dose cytarabine should be used instead of anthracyclines when chemotherapy is to be given in conjunction with RT (24), recall reactions have been noted after administration of gemcitabine and clofarabine as well as of cytarabine (Fig. 6) (21). Therefore, caution is advised when any chemotherapy will be given shortly after RT, particularly total skin electron beam therapy. Following radiation for chloroma, a repeated scan can be performed 2 to 3 months post treatment to gauge response. Patients with extramedullary involvement may be predisposed to extramedullary relapses; therefore, any new or suspicious soft tissue or skin abnormality should always be biopsied (26).

Consensus Statements

- The 2 most common extramedullary manifestations of leukemia are *chloroma* and *leukemia cutis.*
- Radiation is recommended for patients with isolated chloroma and inadequate response to chemotherapy, with isolated recurrence after hematopoietic stem cell transplantation (HCT), and for palliation of symptomatic vital structure compression.
- A low-dose RT regimen of 24 Gy in 12 fractions using conventional techniques is recommended, with lower doses (6-20 Gy) used when the clinical scenario does not allow a more protracted course.
- For symptomatic leukemia cutis, isolated skin lesions can be treated with a similar dose regimen with conventionally set-up electrons with bolus dose.
- In the rare clinical scenario of persistent diffuse leukemia cutis with no evidence of disease in the bone marrow, total skin electron beam therapy to a dose of up to 24 Gy can be considered.

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