Radiation therapy for the management of patients with HTLV-1-associated adult T-cell leukemia/lymphoma

Charles B. Simone, II1,2, John C. Morris3,4, Donn M. Stewart3, Nicole E. Urquhart5, John E. Janik7, Robert J. Kreitman6, Elena Lita2, Kevin Conlon7, Gilian Wharfe5, Thomas A. Waldmann3, and Aradhana Kaushal2

1Hospital of the University of Pennsylvania, Department of Radiation Oncology, Philadelphia, PA, USA; 2National Institutes of Health, National Cancer Institute, Radiation Oncology Branch, Bethesda, MD, USA; 3National Institutes of Health, National Cancer Institute, Metabolism Branch, Bethesda, MD, USA; 4University of Cincinnati, Division of Hematology-Oncology, Cincinnati, OH; 5University of the West Indies, Department of Pathology, Mona, Jamaica; 6National Institutes of Health, National Cancer Institute, Laboratory of Molecular Biology, Clinical Immunotherapy Section, Bethesda, MD, USA; and 7National Institutes of Health, National Cancer Institute, Medical Oncology Branch, Bethesda, MD, USA.

Corresponding Author:
Aradhana Kaushal, M.D.

Address:
Aradhana Kaushal, M.D.
National Institutes of Health, National Cancer Institute
Radiation Oncology Branch
Bldg. 10, CRC Rm. B2-3561
10 Center Drive, MSC 1682
Bethesda, MD 20892-1682
Phone: (301)-496-5457
Fax: (301)-480-5439
Email: kaushala@mail.nih.gov

Running Title: RADIOTHERAPY IN ADULT T-CELL LEUKEMIA/LYMPHOMA
Abstract

HTLV-1-associated adult T-cell leukemia/lymphoma (ATL) typically demonstrates survivals measured in months with chemotherapy. One prior published series (1983-1991) assessed local radiotherapy for ATL. Ten consecutive patients with pathologically-confirmed ATL treated with radiotherapy were reviewed. Subtypes included acute (n=7), smoldering (n=2), and lymphomatous (n=1). Patients received an average of 2.5 systemic therapy regimens prior to radiotherapy. Twenty lesions (cutaneous=10, nodal=8, extranodal=2) were treated to a mean of 35.4Gy/2-3Gy (range, 12-60Gy). At 9.0-month mean follow-up (0.1-42.0 months), all lesions symptomatically and radiographically responded, with in-field complete responses in 40.0% (nodal 37.5% vs. cutaneous 50.0%, p=0.62). No patient experienced in-field progression. Nine patients developed new/progressive out-of-field disease. Median survival was 17.0 months (3-year survival 30.0%). No RTOG acute grade ≥3 or any late toxicity was noted. This report is the first using modern radiotherapy techniques and demonstrates effective local control across ATL subtypes. Radiotherapy should be considered for symptomatic local progression of ATL.

Key Words: Adult T-cell leukemia/lymphoma, HTLV-1, radiation therapy, multimodality therapy, local control.
Introduction

Adult T-cell leukemia/lymphoma (ATL) is a rare peripheral T-lymphoma characterized by blood and bone marrow involvement, hepatosplenomegaly, hypercalcemia, and cutaneous and lytic bone lesions\textsuperscript{1}. ATL is most prevalent in Southwestern Japan, the Caribbean basin, intertropical Africa, the Middle East, and in African-American populations in the Southeastern United States. ATL develops in up to 6\% of individuals infected with human T-cell leukemia/lymphoma virus type 1 (HTLV-1) 20-60 years after infection\textsuperscript{1-6}.

Acute (60\% of cases) and lymphomatous (20\%) ATL typically have aggressive disease courses with shortened median survivals and are characterized by large tumor burdens, multiorgan failure, hypercalcemia, and infectious complications\textsuperscript{2,7}. The median survival of aggressive ATL subtypes ranges from under one month untreated\textsuperscript{8} to 4-6 (acute) and 9-10 (lymphomatous) months with intensive therapy\textsuperscript{1,6,9-11}. Chronic (15\%) and smoldering (5\%) ATL are more indolent, with median survivals of 17-24 and 34-60+ months, respectively\textsuperscript{1,6,9-11}. Transformation into aggressive subtypes is common\textsuperscript{12}. Across subtypes, the 5-year overall survival is 14\%\textsuperscript{13}. The 2- and 4-year survival rates are 16.7\%/5.0\% for acute, 21.3\%/5.7\% for lymphomatous, 52.4\%/26.9\% for chronic, and 77.7\%/62.8\% for smoldering ATL\textsuperscript{9-10,14}.

ATL treatment is based on subclassification, pre-treatment prognostic factors, and response to initial therapy\textsuperscript{7}. Intensive multi-drug chemotherapy regimens are often used for aggressive subtypes. However, disease progression occurs in up to 80\% of patients, and complete responses are infrequent\textsuperscript{15}.

The role for radiotherapy in ATL is not well defined, even for symptom palliation. No large study or randomized trial exists which assesses the role of radiotherapy for ATL. Only one prior case series of ATL patients treated over 20 years ago utilized localized external beam radiotherapy\textsuperscript{16-17}. We report a patient series treated with modern radiotherapy techniques to assess the role of external beam radiotherapy for ATL. We evaluated symptomatic response and local control in these patients.

Methods

This retrospective analysis reviewed 10 consecutive patients with pathologically-confirmed ATL treated with radiotherapy at the National Institutes of Health (NIH) between 1997-2010. The diagnosis was based on pathological confirmation of T-cell lymphoma/leukemia, a clinical picture consistent with ATL, and serological evidence of HTLV-1 infection. This research was approved by the relevant institutional review boards.

Patients were referred for radiotherapy for local disease control, palliation of symptomatic lesions, or sterilization of a single site of disease. Patients underwent weekly evaluations during radiotherapy and one month following the completion of radiotherapy or just prior to their departure from NIH.

Uniform post-treatment surveillance was not possible due to geographical constraints (patients residing in the Caribbean). During subsequent patient visits to NIH for assessment or treatment of disease progression, comprehensive skin assessments and lymph node evaluations were performed. Computerized tomography (CT) was obtained to assess radiotherapy response and for systemic disease assessment. Study follow-up was determined from the: (1) last CT, magnetic resonance imaging, or positron emission
tomography scan following radiotherapy completion for patients with visceral/nodal
disease, (2) last comprehensive skin examination for patients with cutaneous disease, or
(3) patient death.

Treatment response was assessed using Japan Clinical Oncology Group criteria
for ATL modified based on International Consensus Meeting recommendations. Complete
response was defined as disappearance of all clinical/radiographic evidence of
disease within the treatment field and no new in-field lesions, with all lymph nodes
regressed to normal size (≤1.5cm in greatest transverse diameter, or ≤1.0cm in previously
involved nodes that were ≤1.5cm). Partial response was defined as ≥50% reduction in
the sum of the products of the perpendicular diameters of all measurable disease lesions
without new in-field lesions. Absolute percentage of residual abnormal lymphocytes and
bone marrow analysis were not utilized to define response.

Local failure was defined as any identifiable disease on examination or
radiographic assessment remaining within the treatment field measured at 30 days after
radiotherapy or last follow-up. Patients with partial responses or reappearance of tumor
after complete responses were defined to have local failures. Locoregional failure was
any new identifiable disease adjacent to the radiation field, including regional lymph
nodes or satellite cutaneous lesions. Distant failure was development of new distant
cutaneous, nodal, visceral, or systemic disease

Statistical analysis was performed using Excel for Windows (Microsoft Office
2003) [Redmond, WA]. Chi-square statistic and Fisher's exact test for discrete variables
were used to compare proportions, and Student’s t-test was utilized for continuous
variables. Statistical significance was defined as p<0.05.

Results and Discussion

Patients
All 10 patients were of African descent from the Caribbean (Jamaica=9, Haiti=1)
(Table 1). Most were female (n=9) and had a mean age of 48.0 years (range, 30-65yr).
They had acute (n=7), smoldering (n=2), or stage IV lymphomatous (n=1) ATL. Prior to
radiotherapy, in addition to systemic corticosteroids, patients received an average of 2.5
chemotherapy regimens (1-4). Patients received radiotherapy at a mean of 12.3 months
(5-24mo) following their diagnosis.

All 20 disease sites treated were symptomatic prior to irradiation. Patients
received radiotherapy to lymph nodes (n=8) (Figure 1), cutaneous lesions (n=10), whole
brain for leptomeningeal disease (n=1), and a unilateral orbit (n=1).

Radiotherapy
Lesions were treated using photons (n=13, all two-field, 6-15 MV) or electrons
(n=7, single en face field, 6-9 MeV). Bolus (0.5-1.0 cm) was utilized for 75% of lesions.
Patients were treated to a mean dose of 35.4Gy (12-60Gy) in 2Gy (n=12) or 3Gy (n=8)
fractions over a mean of 16 fractions (4-30 fractions).

Radiotherapy response
All patients reported symptomatic improvement following radiotherapy, including
decreased/resolved pain, pruritus, ulcerations, headaches, paresthesias, trismus, brachial
plexopathy, difficulty with ambulation, or B symptoms.
At a mean of 9.0 months (0.1-42.0mo) following radiotherapy, radiographic
and/or clinical response was achieved in all 20 lesions. Partial responses were observed
at 60.0% of sites. Complete responses were achieved in 40.0%, with similar complete response rates for nodal and cutaneous lesions (37.5% vs. 50.0%, p=0.62). Throughout the follow-up period, no in-field progression occurred for any irradiated site (0/20 lesions). Five patients experienced out-of-field progression of disease that was evident prior to radiotherapy. Four patients developed new distant disease. With a partial response indicative of residual local disease, at last evaluation, 8 patients had local and distant disease, 1 had distant-only disease, and 1 had local-only disease. Due to distant disease progression, four patients received multidrug chemotherapy following radiotherapy initiated at a mean of 8.9 months (0.4-14.4mo) after radiotherapy.

Six patients died of progressive disease, with 3 deaths occurring within one month of radiotherapy completion. The 5 patients with acute ATL who died in this cohort did so at a mean of 1.0 month (0.1-2.4mo) following radiotherapy and 10.6 months following diagnosis (5.3-17.9mo). The remaining death occurred in a lymphomatous patient 16.6 months after radiotherapy (31.4mo after diagnosis).

The median survival for the group was 17.0 months (1.4yr). Patients lived a mean of 2.0 years (0.4-4.5yr) from diagnosis to last evaluation/death, with a 2.9-year mean survival (0.7-4.5yr) to date among the 4 patients alive at last evaluation. Both patients with nonaggressive subtypes are alive at a mean of 4.0 years (3.4yr, 4.5yr) from diagnosis and 2.4 years (1.3yr, 3.5yr) following radiotherapy. The 1-, 2-, and 3-year survivals following diagnosis were 70.0%, 40.0%, and 30.0%, respectively.

Toxicity

Acute toxicity was grade 1 in 2 patients (4 lesions) and grade 2 in 2 patients (5 lesions). Acute toxicities were cutaneous/skin (grade 1 in 3 lesions, grade 2 in 3), odynophagia/mucositis (grade 1 in 1, grade 2 in 1), and ocular (grade 2 in 1). No patient suffered any acute grade ≥3 toxicity. No patient experienced any RTOG late toxicity.

Discussion

This is one of the largest studies assessing radiotherapy for the treatment of HTLV-1-associated ATL and is the first to utilize modern radiotherapy techniques. This study demonstrated radiotherapy can achieve excellent local control and symptomatic improvement across a variety of lesion types and ATL subtypes, with both symptomatic improvement and clinical/radiographic disease response in all 20 lesions treated, and no in-field disease progression throughout the follow-up period. This study also found the complete response rate did not differ by lesion type or ATL subtype. However, despite excellent local control, 9 of 10 patients developed new or progressive distant disease.

Radiotherapy was well tolerated. Despite doses up to 60Gy for cutaneous lesions and 50Gy for nodal disease, acute toxicities were mild and resolved spontaneously. No late toxicity was observed.

The 40.0% 2-year and 30.0% 3-year survival in this series is longer than that of other reports, particularly since 70.0% of our patients had acute ATL that is associated with a historical 16.7% 2-year survival.10,14 While this report assessed 10 consecutive patients receiving radiotherapy, the lengthy survival observed may be attributable to fewer referrals of patients with high systemic disease burdens or poor performance statuses.

The only prior reported patient series of localized radiotherapy for ATL was conducted by investigators at Kumamoto University Hospital. In their 5-patient series, total clinical resolution of nodal disease occurred with 30Gy.16 In their subsequent report
of 30 patients treated with radiotherapy from 1983-1991, patients received high energy X-rays, cobalt-60 gamma rays, or electrons to 10.8-40.0 Gy in 1.5-2.0 Gy daily fractions to nodal lesions (n=17 patients), 30.0 Gy in 3 Gy fractions administered three times weekly to focal cutaneous lesions (n=6), or 30.0 Gy in 1.5 Gy fractions with alternating fields treated twice weekly to the total skin (n=7). Cutaneous patients all achieved partial or complete responses and had a 37.7-month mean survival. Nodal patients were less likely to respond (69%) and had a 5.4-month mean survival. Unlike with that cohort, the current study utilized modern radiotherapy treatment planning strategies treating all fields each treatment day, administering daily fractions, utilizing more standard fraction sizes of 2-3 Gy, and employing all linear accelerator-based therapy rather than older Cobalt-60 equipment.

Radiotherapy is well tolerated and can achieve excellent local control and universal symptomatic improvement in ATL patients. Radiotherapy should be considered for palliation for ATL patients with symptomatic local disease progression and may currently be underutilized, particularly among patients with good performance statuses. Distant progression remains common. Radiotherapy should be integrated into multi-modality therapy for ATL patients.

Acknowledgements

Presented, in part, at the American Society for Radiation Oncology 53rd Annual Meeting in Miami, FL from October 2-6, 2011. Supported, in part, by the Intramural Research Program of NIH, National Cancer Institute, Center for Cancer Research.

Author Contributions


Conflict of Interest Disclosures: The authors declare no competing financial interests.
References


<table>
<thead>
<tr>
<th>Patient</th>
<th>ATL Subtype</th>
<th>Prior Systemic Therapy</th>
<th>RT Site</th>
<th>Lesion Type</th>
<th>RT Source</th>
<th>RT Energy</th>
<th>Total Dose</th>
<th>Frac-tion Dose</th>
<th>Initial Local Response</th>
<th>In-field Relapse</th>
<th>Out-of-field Relapse</th>
<th>Additional Therapy After RT</th>
<th>Time from RT to Last Evaluation</th>
<th>Disease at Last Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute</td>
<td>CHOP</td>
<td>Lt neck, bl supraclav</td>
<td>Nodal</td>
<td>Photon</td>
<td>6/15 MV</td>
<td>30 Gy</td>
<td>3 Gy</td>
<td>PR</td>
<td>No</td>
<td>Yes</td>
<td>Fludarabine/cyclophosphamide/LMB-2</td>
<td>2.4 mo</td>
<td>Local + distant</td>
</tr>
<tr>
<td>2</td>
<td>Lymphomatous</td>
<td>Alemtuzumab</td>
<td>Rt groin</td>
<td>Nodal</td>
<td>Electron</td>
<td>6 MeV</td>
<td>24 Gy</td>
<td>2 Gy</td>
<td>CR</td>
<td>No</td>
<td>Yes</td>
<td>CHOP/denileukin difftitox</td>
<td>16.7 mo</td>
<td>Distant</td>
</tr>
<tr>
<td>3</td>
<td>Smoldering</td>
<td>Daclizumab, alemtuzumab</td>
<td>Rt scapula</td>
<td>Cutaneous</td>
<td>Electron</td>
<td>9 MeV</td>
<td>36 Gy</td>
<td>3 Gy</td>
<td>PR</td>
<td>No</td>
<td>Yes</td>
<td>Alemtuzumab, etoposide</td>
<td>42.0 mo</td>
<td>Local + distant</td>
</tr>
<tr>
<td>4</td>
<td>Acute</td>
<td>CHOP, fludarabine/cyclophosphamide/LMB-2, denileukin difftitox</td>
<td>Lt pelvic mass</td>
<td>Nodal</td>
<td>Photon</td>
<td>15 MV</td>
<td>20 Gy</td>
<td>2 Gy</td>
<td>CR</td>
<td>No</td>
<td>Yes</td>
<td>EPOCH/fludarabine, allograft, intrathecal methotrexate, EPOCH/fludarabine</td>
<td>10.0 mo</td>
<td>Local + distant</td>
</tr>
<tr>
<td>5</td>
<td>Acute</td>
<td>EPOCH/alemtuzumab, intrathecal methotrexate, fludarabine/cyclophosphamide/LMB-2</td>
<td>Rt groin</td>
<td>Cutaneous</td>
<td>Photon</td>
<td>6 MV</td>
<td>30 Gy</td>
<td>3 Gy</td>
<td>PR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>1.6 mo</td>
<td>Local + distant</td>
</tr>
<tr>
<td>6</td>
<td>Smoldering</td>
<td>EPOCH/rituximab/siplizumab, 7-hydroxystaurosporine, denileukin difftitox, nelfinavir/alemtuzumab</td>
<td>Lt nares, malar eminence, Submental chin</td>
<td>Cutaneous</td>
<td>Electron</td>
<td>9 MeV</td>
<td>60 Gy</td>
<td>2 Gy</td>
<td>PR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>15.8 mo</td>
<td>Local + distant</td>
</tr>
<tr>
<td>7#</td>
<td>Acute</td>
<td>CHOP, denileukin difftitox</td>
<td>Bl neck</td>
<td>Nodal</td>
<td>Photon</td>
<td>6/15 MV</td>
<td>50 Gy</td>
<td>2 Gy</td>
<td>PR</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0.3 mo</td>
<td>Local</td>
</tr>
<tr>
<td>8</td>
<td>Acute</td>
<td>EPOCH/rituximab,</td>
<td>Lt neck,</td>
<td>Nodal</td>
<td>Photon</td>
<td>6 MV</td>
<td>12 Gy</td>
<td>3 Gy</td>
<td>PR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>0.1 mo</td>
<td>Local +</td>
</tr>
<tr>
<td>Patient</td>
<td>Acute</td>
<td>CHOP, alemtuzumab/deoxycoformycin, intrathecal methotrexate</td>
<td>supraclav</td>
<td>Nodal</td>
<td>Electron</td>
<td>9 MeV</td>
<td>12 Gy</td>
<td>3 Gy</td>
<td>CR</td>
<td>No</td>
<td>distant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>-----------------------------------------------------------</td>
<td>----------</td>
<td>-------</td>
<td>----------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>----</td>
<td>----</td>
<td>--------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Acute</td>
<td>CHOP, alemtuzumab/deoxycoformycin, intrathecal methotrexate</td>
<td>Whole brain</td>
<td>Leptomeningeal</td>
<td>Photon</td>
<td>6 MV</td>
<td>30 Gy</td>
<td>3 Gy</td>
<td>PR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>0.4 mo</td>
<td>Local + distant</td>
</tr>
<tr>
<td>10</td>
<td>Acute</td>
<td>CHOP, EPOCH, yttrium-90 daclizumab</td>
<td>T-spine</td>
<td>Nodal</td>
<td>Photon</td>
<td>15 MV</td>
<td>24 Gy</td>
<td>2 Gy</td>
<td>PR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>0.3 mo</td>
<td>Local + distant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C-spine</td>
<td>Nodal</td>
<td>Photon</td>
<td>6 MV</td>
<td>24 Gy</td>
<td>2 Gy</td>
<td>PR</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ATL = Adult T-cell leukemia/lymphoma; RT = radiation therapy; CR = complete response; PR = partial response; Rt = right; Lt = left; Bl = bilateral; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; EPOCH = etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone; mo = months.

*This patient was male and from Haiti. All remaining nine patients were both female and from Jamaica.

± Patients with new out-of-field disease, as opposed to patients with out-of-field progression of disease that was evident prior to beginning radiation therapy. The times from the completion of radiation therapy to the identification of new out-of-field disease in these patients were as follows: Patient 2 – 9.7 mo, Patient 3 – 13.8 mo, Patient 4 – 0.9 mo, Patient 6 – 1.9 mo [mean 6.6 mo].

*Disease status at the time of patient mortality.
Figure Legend

**Figure 1. Extent of disease among the ATL patient cohort.** CT slices in the sagittal (A) and axial (B) planes of a patient with leptomeningeal disease. (C) CT slice in the axial plane of a patient with extensive cervical neck lymphadenopathy. The patient was treated with a right anterior oblique and left posterior oblique photon beam arrangement to gross adenopathy contoured in red, which radiation isodose lines also depicted (green=102% of the prescribed dose, red=100%, yellow=99%, lavender=98%, cyan=95%, dark blue=50%, pink=20%). (D) Disease extent in another patient with bilateral, left greater than right, cervical and supraclavicular lymphadenopathy depicted in the axial plan and (E) as a three-dimension body reconstruction image with gross tumor contoured in red. (F) Treatment response of the same patient depicted in (D) and (E) demonstrated in the axial plane at 7 weeks following photon radiation therapy to the left neck only. A strong partial response to radiation therapy was obtained in this patient.
Radiation therapy for the management of patients with HTLV-1-associated adult T-cell leukemia/lymphoma

Charles B. Simone II, John C. Morris, Donn M. Stewart, Nicole E. Urquhart, John E. Janik, Robert J. Kreitman, Elena Lita, Kevin Conlon, Gillian Wharfe, Thomas A. Waldmann and Aradhana Kaushal