Original Study

Radiation Therapy Is an Effective Modality in the Treatment of Mantle Cell Lymphoma, Even in Heavily Pretreated Patients

Waqar Haque,[1] K. Ranh Voong,[2] Ferial Shihadeh,[2] Isidora Arzu,[2] Chelsea Pinnix,[2] Ali Mazloom,[2] L. Jeffrey Medeiros,[3] Jorge Romaguera,[4] Alma Rodriguez,[4] Michael Wang,[4] Pamela Allen,[2] Bouthaina Dabaja[2]

Abstract

Radiotherapy (RT) is an effective modality in heavily pretreated and chemorefractory patients with mantle cell lymphoma. Low dose radiation offered palliation in 95% of patients, 92% of treated sites showed complete response to RT.

Introduction: Mantle cell lymphoma has an aggressive clinical course and continuous relapse pattern with a median survival of 3 to 7 years. Multiple courses of chemotherapy are the basis of treatment. Radiotherapy is underutilized in this disease. We undertook this study to assess the role of radiation therapy. **Materials and Methods:** A total of 41 consecutive patients with mantle cell lymphoma diagnosed from December, 1999 to January, 2010 who received radiation therapy were reviewed retrospectively. The main endpoint was in-field lymphoma response at each irradiated disease site. **Results:** There were 39 evaluable patients (68 symptomatic sites). Sites treated included: nodal stations (n = 31), soft tissue (n = 13), mucosal sites (n = 11), central nervous system (n = 10), gastrointestinal tract (n = 2), and bone (n = 1). Median maximum tumor size at presentation was 3.5 cm (range, 1.3 cm-9.6 cm). The median dose of radiation was 30.6 Gy (range 18-40 Gy). Median follow-up post radiation per site was 12.3 months (range, 0.6-80.9 months). Response to treatment was complete in 47 sites (69.1%), partial in 16 sites (23.5%), and 5 sites (7.4%) had stable disease. In 9 (13.2%) sites local relapse occurred (median 7 months; range 2-21). The mean size of lymphoma at time of RT correlated with relapse, with tumors with local relapse larger than those without a local relapse ($P = .005$). **Conclusions:** Our data add to accumulating evidence that mantle cell lymphoma is a radio-sensitive disease with excellent responses to relatively low radiation doses, even in patients with chemo-refractory disease.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 14, No. 6, 474-9
Keywords: Chemotherapy, In-field response, Refractory disease, Relapse, Site-specific treatment

Introduction

Mantle cell lymphoma (MCL) was initially described by Lennert in 1973 as centrocytic lymphoma and subsequently by others in the United States, as reviewed by Swerdlow and Williams.[1] In 1992, a consensus statement from Banks et al.[2] summarized the morphologic, immunophenotypic, and molecular features, and the name "mantle cell lymphoma" was accepted. MCL has been similarly defined in the current World Health Organization lymphoma classification.[3-5] MCL is a mature B-cell lymphoma that comprises nearly 6% of all non-Hodgkin's lymphomas. It is characterized by an aggressive clinical course, with patients typically presenting with disseminated disease. Most patients have occasional circulating tumor cells, but approximately 10% to 20% will have leukemic disease at presentation.[6-8] Historically, the median overall survival (OS) for patients with MCL has been 3 to 4 years, although more recent series have reported a median OS of 5 to 7 years.[9-14]

The recommended treatment of MCL include systemic chemotherapy and stem cell transplantation owing to the systemic nature of the disease, with radiation therapy (RT) rarely used for management.[12,15-17] This has led to the underusage of RT for the management of MCL.

[1]Department of Radiation Oncology, University of Texas Medical Branch, Galveston, TX
[2]Department of Radiation Oncology
[3]Department of Hematopathology
[4]Department of Lymphoma and Myeloma
University of Texas MD Anderson Cancer Center, Houston, TX

Submitted: Mar 7, 2014; Revised: Jul 2, 2014; Accepted: Jul 8, 2014; Epub: Jul 15, 2014

Address for correspondence: Bouthaina Dabaja, MD, Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030
E-mail contact: bdabaja@mdanderson.org

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2014.07.003

However, some reports have described the efficacy of RT for the management of MCL. M'kacher et al.[18] showed in vitro that MCL cell lines are sensitive to RT, suggesting that the addition of RT to chemotherapy for MCL would lead to improved clinical outcomes. Two studies have demonstrated improved OS and durable local control with the use of RT as upfront therapy in patients with limited-stage MCL.[19,20] Another report from Rosenbluth and Yahalom[16] has demonstrated significant palliative benefit using RT in patients with MCL.

In the present work, we report the results of a single institution review of the records of patients with MCL treated with involved-site RT (ISRT). Our purpose was to assess the potential role of ISRT in patients with MCL, including patients with chemo-refractory MCL.

Materials and Methods

The institutional review board approved the present analysis. To determine the outcomes of patients with MCL treated with RT at the University of Texas MD Anderson Cancer Center, we reviewed the records of all patients diagnosed with MCL from December 1999 to January 2010. We limited our analysis to patients who had received RT specifically for MCL and had remained alive for the duration of RT.

A total of 41 consecutive patients with MCL diagnosed from December 1999 to January 2010 were treated with RT at our institution. Each patient's records and images were retrospectively reviewed to determine the patient characteristics, tumor characteristics, and patient outcome. The main endpoint was the in-field lymphoma response at each irradiated disease site. The response to RT was determined by visual inspection, physical examination and palpation, and/or radiographic studies, including computed tomography or positron emission tomography. The local response (LR) was categorized as a complete response (CR) or partial response (PR). A CR was defined as the complete disappearance of clinical evidence of disease, and a PR was defined as at least a 50% decrease in the tumor diameter, as specified in the International Working Group response criteria.[21] If the treated lymphoma had no response or had progressed, it was recorded as being stable disease or progressive disease, respectively.

The data for age at treatment, stage, previous systemic therapy, outcome, radiation dose, and toxicity were retrospectively tabulated for all patients. Survival was defined as the interval from the date of RT completion to the date of death or last follow-up examination (in months).

We performed Kaplan-Meier analyses to provide estimates of OS for all patients, for patients categorized by gender, and for patients categorized by age. For all analyses, our threshold for statistical significance was $P = .05$. Data analysis was performed using the Statistical Analysis Systems software, version 9.3 (SAS Institute, Cary, NC). Toxicities were categorized using the Common Terminology Criteria for Adverse Events, version 4.0.

Results

Patient Characteristics

Of the 41 patients, 39 were evaluable (68 symptomatic sites); 2 patients were excluded from the analysis because they had died before RT completion. The patient characteristics are summarized in Table 1. The median patient age at RT was 71 years (range, 48-81 years). Of the 39 patients 16 (41%) were women and 23 (59%) were men. Thirty-three (84.6%) patients had stage IV disease, 1 (3%) stage III, 2 (5%) stage II, and 3 patients (7.7%) had stage I disease. The hyper-CVAD chemotherapy regimen (hyper-fractionated, course A, cyclophosphamide, vincristine, doxorubicin [Adriamycin], dexamethasone; course B, methotrexate, cytarabine) was administered to 37 patients (95%), with a median of 6 cycles (range, 1-8). Twenty-nine patients (74%) received $\geq$ 3 systemic regimens (median 4, range 1-11). Forty-eight sites (71%) had been treated with $\geq$ 3 cycles (median 3, range 0-11) of chemotherapy before RT. Seventeen patients (43.5%) were treated with $\geq$ 2 radiation courses (median 1; range, 1-5). The sites treated included nodal stations in 31, soft tissue sites in 13, mucosal sites in 1, central nervous system in 10, gastrointestinal tract in 2, and bone in 1. The median maximum tumor size at presentation was 3.5 cm (range, 1.3-9.6 cm); 4 patients were treated for consolidation after complete remission with chemotherapy, and 1 patient was treated to the surgical bed. The median radiation dose was 30.6 Gy (range, 18-40 Gy). The median follow-up interval after RT per site was 12.3 months (range, 0.63-80.93 months).

Clinical Outcomes

The clinical outcomes are summarized in Table 2. The overall LR rate was 94.1% in the treated sites, with a CR in 47 (69.1%) and a PR in 17 (25%). Four sites (5.8%) had stable disease. Of the treated patients, 21 had some pain, discomfort, or functional deficit before treatment, and 20 of 21 (95%) had symptom relief after RT (Figure 1). The median OS for all patients after treatment was 72.9 months, and the 1-year OS after treatment was 84.6% (Figure 2A). The median OS for men was significantly greater than the median OS for women (80.3 months vs. 33.1 months, $P = .001$; Figure 2B). The median OS for those < 60 years old was significantly longer than that of those > 60 years old (113.8 months vs. 57.6 months, respectively; $P = .0006$; Figure 2C).

Nine sites (13.2%) exhibited local relapse in the previously irradiated area, occurring a median of 7 months (range, 2-21

Table 1 Baseline Patient Characteristics

Characteristic	Value
Patients	100 (39)
Male gender	59 (23)
Age (Years)	
Median	71
Range	48-81
Stage	
I	7.7 (3)
II	5 (2)
III	3 (1)
IV	84.6 (33)
Follow-up (mo)	
Median	12.3
Range	1-81

Data presented as % (n), unless otherwise noted.