International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation: Lymphoma

Low-Dose Involved-Field Radiation in the Treatment of Non-Hodgkin Lymphoma: Predictors of Response and Treatment Failure

Andrea L. Russo, MD,* Yu-Hui Chen, MS, MPH,† Neil E. Martin, MD, MPH,‡ Anant Vinjamoori, BA,‡ Sarah K. Luthy, MD,‡ Arnold Freedman, MD,§ Evan M. Michaelson, BA,‡ Barbara Silver, BA,‡ Peter M. Mauch, MD,‡ and Andrea K. Ng, MD, MPH‡

**Harvard Radiation Oncology Program, Boston, Massachusetts; †Biostatistics Core, Dana Farber Cancer Institute, Boston, Massachusetts; and Departments of ‡Radiation Oncology and §Hematologic Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, Massachusetts*

Received Oct 26, 2012, and in revised form Dec 6, 2012. Accepted for publication Dec 31, 2012

Summary

Patients with indolent non-Hodgkin lymphoma (NHL) often have frequent relapses. This study assessed the outcomes of treating NHL with low-dose involved-field radiation therapy of 4 Gy in 2 fractions. The overall response rate was 82%. Those with chronic lymphocytic leukemia (CLL) had an inferior response. Age ≤50 years at diagnosis, CLL, and mantle cell lymphoma predicted a shorter time to further therapy. Low-dose involved-field radiation therapy should be a primary treatment in the palliation of NHL.

Purpose: To investigate clinical and pathologic factors significant in predicting local response and time to further treatment after low-dose involved-field radiation therapy (LD-IFRT) for non-Hodgkin lymphoma (NHL).

Methods and Materials: Records of NHL patients treated at a single institution between April 2004 and September 2011 were retrospectively reviewed. Low-dose involved-field radiation therapy was given as 4 Gy in 2 fractions over 2 consecutive days. Treatment response and disease control were determined by radiographic studies and/or physical examination. A generalized estimating equation model was used to assess the effect of tumor and patient characteristics on disease response. A Cox proportional hazards regression model was used to assess time to further treatment.

Results: We treated a total of 187 sites in 127 patients with LD-IFRT. Histologies included 66% follicular, 9% chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma, 10% marginal zone, 6% mantle cell lymphoma (MCL), and 8% other. Median follow-up time was 23.4 months (range, 0.03-92.2 months). The complete response, partial response, and overall response rates were 57%, 25%, and 82%, respectively. A CLL histology was associated with a lower response rate (odds ratio 0.2, 95% confidence interval 0.1-0.5, $P = .02$). Tumor size, site, age at diagnosis, and prior systemic therapy were not associated with response. The median time to first recurrence was 13.6 months. Those with CLL and age ≤50 years at diagnosis had a shorter time to further treatment for local failures (hazard ratio [HR] 3.63, $P = .01$ and HR 5.50, $P = .02$, respectively). Those with CLL and MCL had a shorter time to further treatment for distant failures (HR 11.1 and 16.3, respectively, $P < .0001$).

Conclusions: High local response rates were achieved with LD-IFRT across most histologies. Chronic lymphocytic leukemia and MCL histologies and age ≤50 years at diagnosis had a shorter time to further treatment after LD-IFRT.

Reprint requests to: Andrea L. Russo, MD, Brigham and Women's Hospital, Department of Radiation Oncology, 75 Francis St, ASB1-L2, Boston, MA 02115. Tel: (617) 732-6310; E-mail: alrusso@partners.org

Presented in part at the 54th Annual Meeting of the American Society for Radiation Oncology, October 28-31, 2012, Boston, MA.

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 86, No. 1, pp. 121–127, 2013
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2012.12.024

Introduction

There were approximately 66,360 new cases of non-Hodgkin lymphoma (NHL) in the United States in 2011 and 19,320 deaths (1). Indolent NHL, which includes follicular (FL), marginal zone (MZ), mantle cell (MCL), and chronic lymphocytic leukemia (CLL) lymphomas constitutes approximately 40% of all NHL (2). Although early-stage FL is potentially cured with definitive radiation therapy (RT), advanced-stage disease, which is diagnosed in more than two-thirds of patients at initial presentation (3), is presently not considered curable in the majority of patients. Patients with advanced-stage disease, however, often have a long median survival in excess of 10 years (2, 4) and tend to have frequent and late relapses, requiring treatment with various systemic agents, or occasionally are observed until symptoms develop (5). Similarly, those with nonfollicular NHLs are often treated initially with chemo-immunotherapy (6), but often will relapse after having an initial response. Given the long natural history of indolent NHLs, many individuals will require multiple types of treatment at many points during the disease course, and some may ultimately require stem cell transplantation (7).

Low-dose involved-field RT (LD-IFRT) given in 2 daily fractions can offer durable local control and ideally delay the need for more potentially toxic systemic therapy. Others have previously reported on outcomes of patients with advanced indolent NHL treated with LD-IFRT and have shown response rates of 81-92% (8-14). These studies have found various inconsistent predictors of poor response, including older age at treatment, prior use of chemotherapy, and tumor size. We sought to evaluate our institution's experience of the effectiveness of LD-IFRT in a large series of patients and to assess clinical and pathologic factors significant in predicting response to treatment.

Methods and Materials

Patient population and treatment

A retrospective review of medical records of patients with NHL treated between April 2004 and September 2011 was conducted. This study was approved by the Dana-Farber Cancer Institute institutional review board. Patients over the age of 18 years with advanced or recurrent NHL treated with LD-IFRT were included in the analysis. Patient, disease, and treatment characteristics including sex, age, date of diagnosis, stage at diagnosis, prior systemic or localized treatments, site of LD-IFRT, tumor size (cm) measured by largest dimension, indication for treatment, and treatment outcome including response to LD-IFRT, in-field and out-of-field progression, further treatments after LD-IFRT, time to further treatment, and status at last follow-up were reported. Tumor size >4 cm or ≤4 cm was used to assess response to treatment because >4 cm has previously been shown to be predictive of lack of response (8). A total of 187 sites in 127 patients were evaluated.

Low-dose involved-field RT was given as 4 Gy in 2 fractions of 2 Gy per fraction over 2 consecutive days. The radiation treatment field was IFRT as per prior published guidelines, with inclusion of the involved nodal region in the treatment field (15). No other therapy was given concurrently with LD-IFRT. Before LD-IFRT patients were evaluated with physical examination and computed tomography scanning. Treatment response and disease control were determined by computed tomography scan and/or physical examination. Treatment response was analyzed by treatment site, not by individual patient, because several patients had multiple different sites requiring treatment at various time points. Complete response (CR) was defined as complete clinical or radiologic disappearance of disease. Complete response undocumented (Cru) was defined as >75% reduction in tumor size with residual mass. Partial response (PR) was defined as >50% reduction in tumor size with residual mass. Stable disease (SD) was defined as no change in tumor size. Progressive disease (PD) was defined as a 20% increase in tumor size. Overall response includes CR, Cru, and PR.

Statistical methods

Of the 127 patients included in this analysis, 38 patients had multiple recurrence sites. The analysis unit used was recurrence site for both disease response and time to further treatment for failures. To assess the effect of tumor and patient characteristics on disease response, a generalized estimating equations model (16) with the exchangeable association structure was used to account for the correlation among disease sites within each patient. Times to further treatment for local failure and distant failure were defined as the time from the date of LD-IFRT to the date of further treatment administered for local failure and distant failure, respectively. Because the risk of failures changed owing to the administration of systemic treatment during the follow-up period, a Cox proportional hazards regression model with systemic treatment as a time-dependent covariate was used to evaluate the associations between patient/tumor characteristics and time to further treatment for failures. For this analysis, the marginal approach developed by Lee et al (17) was used to account for the dependence among disease sites within each patient. The patient/tumor characteristics of interest include tumor size (<4 cm vs ≥4 cm), site of RT (head and neck, supradiaphragmatic, infradiaphragmatic, pelvic, or cutaneous), histology (CLL, follicular, mucosa-associated lymphoid tissue/MZ, MCL, or other), age at diagnosis (≤50 vs 51-70 vs >70 years), and prior systemic therapy. Kaplan-Meier curve estimates were generated to demonstrate time to further treatment for local and distant failures at 2 years.

Results

Patient characteristics

Patient and disease characteristics are listed in Table 1; treatment site characteristics are listed in Table 2. The median age at diagnosis was 54 years (range, 25-95 years). Fifty-four percent were male. Seventy percent of patients had 1 disease site, 19% had 2 sites, 7% had 3 sites, 3% had 4 sites, and 1% had 7 sites treated. The median follow-up time was 23.4 months (range, 0.03-92.2 months). The median follow-up time among survivors was 25.4 months. The median interval from diagnosis to the start of LD-IFRT was 57.3 months (range, 0.3-284.5 months). Before receiving LD-IFRT, 52% of patients received systemic therapy, 27% received conventional-dose RT, and 7% underwent stem-cell transplant; 28% of patients received no prior treatment. The