Original Study

Annual Facility Treatment Volume and Patient Survival for Mycosis Fungoides and Sézary Syndrome

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Abstract

Mycosis fungoides and Sézary syndrome (MF/SS) management is complex, with heterogeneous treatments. We analyzed a national registry of > 2200 MF/SS patients divided into cohorts by the annual treatment volume quintile of their treatment facility. A greater facility annual treatment volume was associated with improved survival for patients with MF/SS.

Background: Management of mycosis fungoides and Sézary syndrome (MF/SS) is complex, and randomized evidence to guide treatment is lacking. The institutional treatment volumes for MF/SS might vary widely nationally and influence patient survival. **Patients and Methods:** Using the National Cancer Database, we identified patients with a diagnosis of MF/SS from 2004 to 2011 in the United States who had received treatment at a reporting facility. The patients were grouped into quintiles according to their treatment facility's average annual treatment volume (ATV). The characteristics associated with ATV were identified and compared using χ^2 tests. Overall survival (OS) was compared among the ATV quintiles using the Kaplan-Meier method with log-rank tests and multivariable Cox regression with hazard ratios (HRs). OS was also analyzed using the annual patient volume as a continuous variable. **Results:** A total of 2205 patients treated at 374 facilities were included for analysis. The ATV quintile cutoffs were 1, 3, 6, and 9 patients. With a median follow-up period of 59 months, the 5-year estimated OS survival increased with ATV from 56.7% in the lowest quintile ($\leq$ 1 patient annually) to 83.8% in the highest quintile ($>$ 9 patients annually; $P < .001$). On multivariable analysis, greater ATV was associated with improved survival when analyzed as a continuous variable (HR, 0.96 per patient per year; 95% confidence interval, 0.94-0.98; $P < .001$) and when comparing the highest quintile to the lowest quintile (HR, 0.46; 95% confidence interval, 0.39-0.55). **Conclusion:** The present national database analysis demonstrated that higher facility ATV is associated with improved OS for patients with MF/SS. Further study is needed to determine the underlying reasons for improved survival with higher facility ATV.

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Introduction

Mycosis fungoides (MF) represents approximately three quarters of cutaneous T-cell lymphoma cases. Its incidence, approximately 0.4/100,000 persons in the United States, has been increasing during the past several decades.[1] The diagnosis and management of MF and its leukemic variant, Sézary syndrome (SS), remains challenging. A reference standard for diagnosis is lacking, because the initial presentation of MF can be nonspecific and can mimic multiple benign inflammatory dermatoses.[2] Also, management decisions are challenging, given the paucity of randomized trials of MF. Numerous skin-directed and systemic treatment options are available, many of which require specialized equipment, institutional expertise, and/or cross-disciplinary coordination.[3-6] Furthermore, MF is generally a chronic disease, and optimal management requires an individualized approach that adapts to a patient's clinical course over time.

Although the prognosis of patients with early-stage MF is favorable, later-stage MF and SS have been associated with significant detriment to patients' disease-specific and overall survival

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(OS).[7-9] Given the complexity of MF treatment, low prevalence, and lack of nationally accepted treatment guidelines, MF patient outcomes might vary according to differences in institutional experience nationally. In the present study, we evaluated the association between institutional treatment volume and patient survival for MF.

Patients and Methods

Data Source and Study Population

The analysis was conducted using the National Cancer Database (NCDB) registry.[10] The NCDB is a hospital-based database that currently captures approximately 70% of all newly diagnosed malignancies in the United States annually from facilities accredited by the Commission on Cancer (CoC). The data used in the present study were derived from a de-identified NCDB file. The American College of Surgeons and the CoC have not verified and are neither responsible for the analytical or statistical method used nor the conclusions drawn from these data in the present study.

The inclusion criteria were patients aged ≥ 18 years, MF or SS pathologically or clinically diagnosed from 2004 to 2011, and no previous cancer diagnosis. The sample was limited to patients who had completed part or all of their first course of treatment at the reporting facility, who had known clinical staging information available (American Joint Committee on Cancer, 6th to 7th edition: stages I-IV), and with no missing demographic and clinical characteristic data. Patients aged < 40 years were missing facility characteristic data in the NCDB user file and, thus, were excluded from the final cohort. Patients without recorded follow-up data or who had died within 3 months of the diagnosis were excluded to account for patients who likely had not completed their first treatment course.

Statistical Analysis

To estimate the facility treatment volume, we assigned an average annual treatment volume (ATV) to each facility appearing in the NCDB. The ATV was calculated by dividing the total number of cases reported by each facility by the number of years of accreditation from 2004 to 2011. Because the number of CoC-accredited cancer programs changes from one diagnosis year to the next, not all medical facilities available in the NCDB were accredited for all the diagnosis years included during the study period. The patients were grouped into quintiles by their treatment facility's ATV (Q1, 0 to < 20th percentile; Q2, 20th to < 40th percentile; Q3, 40th to < 60th percentile; Q4, 60th to < 80th percentile; and Q5, 80th to 100th percentile). ATV thresholds defining each quintile were rounded to the nearest whole number.

The patient characteristics included the treatment facility's ATV (by quintile and as a continuous variable), age at diagnosis (continuous), gender (male vs. female), stage (I vs. II vs. III vs. IV), race (white vs. black vs. other), insurance (private vs. nonprivate), income (≥ $46K vs. < $46K), residence in metropolitan area (yes vs. no), Charlson-Deyo comorbidity score (CDS; 0 vs. 1 vs. 2), distance to treatment facility (< 20 miles vs. ≥ 20 miles), and location where MF was diagnosed (at treatment facility vs. elsewhere). The facility characteristics included affiliation (academic vs. nonacademic) and region (Northeast vs. Southwest vs. Midwest vs. West). The NCDB captures the first course of treatment in broad categories but does not include information regarding specific treatment modalities that would be applicable to MF, other than chemotherapy and radiotherapy. Additionally, the NCDB lacks specifics regarding the subsite of radiotherapy and chemotherapy type, which includes traditional cytotoxic agents, targeted agents, retinoids, topical agents, and others. A detailed description of all variables captured can be found in the NCDB Participant-User File data dictionary.[11]

The demographic, clinical, and facility characteristics were compared between the ATV quintile groups using χ^2 and K-sample equality-of-median tests, as appropriate. OS was evaluated using the time from diagnosis until death. The Kaplan-Meier method with the log-rank test was used to compare OS among the ATV quintiles. Univariable Cox regression was performed for each variable captured to calculate the hazard ratios (HRs) and their 95% confidence intervals (CIs). Variables significantly associated with survival on univariable analysis ($P < .10$) were included in the multivariable Cox proportional hazards model. The model was adjusted for intragroup correlations within each ATV quintile. Sensitivity analyses were performed using forward and backward stepwise selection with an entry threshold probability of $P < .05$ and removal threshold probability of $P < .10$. We tested for interaction between ATV and stage. Schoenfeld residuals were calculated for each model to ensure the proportional hazards assumption had not been violated. Cox regression analysis was performed using ATV quintiles and ATV as a continuous variable. Subgroup survival analysis was conducted by disease stage.

All tests were 2-sided, and $P < .05$ was considered statistically significant. All analyses were performed using Stata SE, version 13 (StataCorp, College Station, TX).

Results

Patient and Facility Characteristics

A total of 2205 patients were included in our analysis (Figure 1). The patients had been treated at 374 unique facilities. The range of annual facility volume was 1 to 21 cases/y (Figure 2). Fewer than 20 facilities (< 5.3%) treated 50% of the patients annually, and 275 facilities (73.5%) treated ≤ 1 patient annually. The quintile cutoffs, rounded to the nearest whole number, were 1, 3, 6, and 9 patients annually. Therefore, quintile 1 (Q1) included 369 patients (16.7%), Q2 included 587 (26.6%), Q3, 445 (20.2%), Q4, 439 (19.9%), and Q5 included 365 patients (16.6%). As the initial treatment, 424 patients (19.2%) had received chemotherapy, 211 (9.6%) had received radiotherapy, 190 (8.6%) had received hormonal therapy (including steroids), 51 (2.3%) had received immunotherapy, 402 (18.2%) had received "other" treatment (including phototherapy and extracorporeal photopheresis), 510 (23.1%) had received combination therapy, and 417 (18.9%) had received treatment not otherwise specified. Treatment varied by disease stage (Supplemental Table 1; available in the online version). The patient and facility characteristics stratified by ATV quintile are listed in Table 1.

The higher volume facilities were more likely to be academic institutions ($P < .001$). Also, the patients treated at higher volume facilities tended to have a lower CDS ($P < .001$), be younger ($P = .01$), live farther from the treatment facility ($P < .001$), and have a lower stage ($P < .001$), except that Q5 had a greater proportion of