Original Study

Characterizing Autoimmune Disease-associated Diffuse Large B-cell Lymphoma in a SEER–Medicare Cohort

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Abstract

We used the Surveillance, Epidemiology, and End Results (SEER)–Medicare-linked database to characterize the patterns of presentation, treatment, and survival in older diffuse large B-cell lymphoma (DLBCL) patients with concomitant autoimmune disease. DLBCL patients with autoimmune disease were more likely to be female but otherwise did not differ significantly from other DLBCL patients in demographic data, treatment, or clinical outcomes.

Background: Severe immune dysregulation such as seen in autoimmune (AI) disease is known to act as a significant risk factor for diffuse large B-cell lymphoma (DLBCL). However, little is known about the demographics or clinical outcomes of DLBCL that arises in the setting of AI disease. **Patients and Methods:** We used the Surveillance, Epidemiology, and End Results (SEER) database for patients with a diagnosis from 1999 to 2009 linked to their Medicare claims data through 2011 to characterize the presentation, treatment, and survival patterns in DLBCL patients, including those with rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren syndrome, and other B-cell–mediated AI diseases. We examined the baseline clinical characteristics for patients with B-cell–mediated AI disease, plotted the overall survival and lymphoma-related survival (LRS) for these groups, and compared the median survival times. **Results:** Patients with DLBCL and AI disease were more commonly female. However, patients with DLBCL and rheumatoid arthritis, SLE, Sjögren syndrome, or other B-cell AI diseases did not differ from other DLBCL patients in any other baseline presenting features and received similar first-line treatment. A trend toward decreased LRS was seen in patients with SLE and DLBCL compared with all other groups, but this difference was not statistically significant in this cohort. **Conclusion:** In the present retrospective claims-based cohort of older patients with DLBCL, concomitant AI disease was uncommon and was more likely to occur in female DLBCL patients, which likely reflects the greater incidence of AI disease in women. The possibility of lower LRS for SLE patients should be explored in future studies.

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Introduction

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy worldwide.[1] Its most frequently diagnosed subtype, diffuse large B-cell lymphoma (DLBCL), accounts for ~25% to 30% NHL cases in Western countries.[2,3] Importantly, although DLBCLs appear histologically similar, they demonstrate a wide degree of genetic and clinical heterogeneity. DLBCL can be curable; however, nearly 50% of patients will eventually relapse, with subsequent dismal prognosis.[4,5] Thus, substantial research efforts have been focused on identifying the biologic and clinical features that underlie these stark differences in outcomes with the hope that targeted therapeutic approaches could abrogate such disparities.

Severe immune dysregulation such as that seen with human immunodeficiency virus infection, immunosuppression after solid organ transplantation, and autoimmune (AI) disease is known to act as a major risk factor for NHL. The InterLymph Subtypes Project pooled cases and controls to provide well-powered comparisons of risk factors for specific NHL subtypes, including DLBCL. Multivariate analysis of 4667 DLBCL cases and 22,639

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controls showed that B-cell–activating AI diseases in general (odds ratio, 2.4; 95% confidence interval, 1.8-3.1), and systemic lupus erythematosus (SLE) and Sjögren syndrome (SS) in particular, were the most strongly associated with increased DLBCL risk after controlling for all other risk factors.[6] These findings mirror those of large cohort studies of patients with AI disease. SS has long been known to carry the greatest risk of NHL (relative risk, 4-40 times that of the general population), most of which are mucosa-associated lymphoid tissue lymphomas.[7] However, DLBCL cases comprised about 15% of SS-associated lymphoma in a 584-patient cohort.[8] Similarly, a 2005 cohort study involving 9547 SLE patients found that aggressive subtypes predominated among the NHL diagnoses, with DLBCL constituting more than one half of the cases for which subtype was specified.[9] The significant heterogeneity in the studies of NHL risk in patients with rheumatoid arthritis (RA) preempted the InterLymph group from performing focused analyses of NHL subtype risk in that population.[10] However, a large Swedish study that included > 74,000 RA patients found that patients with greater indexes of inflammatory activity exhibited an increased risk of NHL in general and DLBCL in particular (48% of cases).[11]

Given that the processes of inflammation and chronic self-antigen stimulation that define AI diseases represent specific pathways that could promote lymphoma development, it is possible that AI-associated lymphomas are a distinct subset within DLBCL exhibiting characteristic clinical and biologic behavior. However, little is known about the demographic data or clinical outcomes of DLBCL that arises in the setting of AI disease. We examined the Surveillance, Epidemiology, and End Results (SEER)–Medicare-linked database to determine the frequency of common B-cell AI diseases among older patients with DLBCL and to characterize the patterns of presentation, treatment, and survival for DLBCL patients with concomitant AI disease.

Patients and Methods

Data Source

We used the National Cancer Institute (NCI) SEER database for patients with a diagnosis from 1999 to 2009 linked to their Medicare claims data through 2011 to characterize the presentation, treatment, and survival patterns in patients with DLBCL, including those with RA, SLE, SS, and other B-cell–mediated AI diseases as defined by the InterLymph criteria (AI hemolytic anemia, Hashimoto's thyroiditis/hypothyroidism, myasthenia gravis, and pernicious anemia[12]). The SEER program reports data on cancer incidence and survival collected from US registries, covering about 28% of the population as of 2016.[13] The collected data include patient demographics, tumor pathology, disease stage, primary tumor site, first-line treatment, and dates of diagnosis and death.

Linking SEER with the Medicare claims data allows for the identification of concomitant health conditions and specific treatments received by elderly cancer patients. Among individuals > 65 years, 97% are Medicare-eligible, and 93% of those listed in SEER are linked to the Medicare enrollment file.[14] Because this database does not include patient identifiers, our study did not require approval from an institutional review board. However, a data use agreement was signed before initiation of the study.

Eligibility Criteria

Patients were considered eligible for analysis if they had received a diagnosis of DLBCL from January 1, 2002 to December 31, 2009, had linked Medicaid claims data available ≤ 2011, and were aged ≥ 66 years at diagnosis. The minimum required age was 66 years to ensure that patients had been enrolled in Medicare for ≥ 12 months before the diagnosis. Cases were identified using the World Health Organization International Classification of Diseases for Oncology, 3rd edition, histology codes 9680 and 9684.[15] The following International Classification of Diseases, 9th revision, Clinical Modification codes were used to identify the presence of concomitant AI disease: SLE, 710.0; RA, 714.0 to 714.3; AI hemolytic anemia, 283.0; myasthenia gravis, 358.00 and 358.01; pernicious anemia, 281.0; and SS: 710.2. The exclusion criteria are shown in Figure 1.

Patient Characteristics

Patients were stratified into groups by AI disease (none coded, SLE, SS, RA, or other B-cell–activating AI disease) as identified in Medicare claims. Self-reported race was categorized as white, African-American, or other; using SEER data, the "other" category includes individuals of Asian, Native American, Pacific Islander, or Alaskan Native ancestry.[16] The SEER–Medicare database uses census tract information (eg, percentage of residents living in poverty and percentage with only a high school education) from the 2000 US Census as a surrogate for socioeconomic status, as described in other SEER–Medicare studies.[17-19] Other demographic variables analyzed in the present study included sex, marital status, and type of geographic area (less urban or rural, urban, or metropolitan).

In terms of disease status, patients were classified with regard to the following: Ann Arbor stage (I/II, III/IV, or unknown), primary disease site (nodal vs. extranodal), presence of B symptoms, performance status, NCI comorbidity index score (0, 1, or ≥ 2), and year of diagnosis. Performance status was classified as poor if a patient had claims for any of the following: hospice, home health agency, skilled nursing facility, oxygen, or wheelchair or related supplies. Such claims-based measures of performance status have been used in other cancer studies.[20-23] The NCI comorbidity index scores were calculated using the Deyo adaptation of the Charlson comorbidity index to identify the 15 noncancer comorbidities included in the Charlson comorbidity index from the Medicare claims.[24,25]

Treatment and Mortality Classification

We determined the initial management strategies using the Medicare claims made within 6 months of diagnosis; if no treatment was documented within that period, management was categorized as "observation." The SEER–Medicare data set does not include information regarding the receipt of oral medications without an intravenous equivalent. Thus, patients with claims for cyclophosphamide, doxorubicin, and vincristine were categorized as having received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), and those with claims for cyclophosphamide and vincristine were classified as having received CVP (cyclophosphamide, vincristine, prednisolone). Patients with those same claims who also received rituximab were classified as having received R-CHOP and R-CVP, respectively.