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Improved survival with rituximab-based chemoimmunotherapy in older patients with extranodal diffuse large B-cell lymphoma

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ABSTRACT

Using the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, we investigated the relative benefits of adding rituximab to CHOP chemotherapy in diffuse large B-cell lymphoma (DLBCL) of extranodal origin, and found similar advantage for nodal and extranodal lymphomas. Hazard ratio for overall survival was 0.64 for nodal, and 0.70 for extranodal DLBCL. Hazard ratios for lymphoma-related death were 0.62 and 0.57, respectively. The advantage was largest for DLBCL of the spleen, liver and lung. Conversely, it was not evident for thyroid or testicular lymphomas. Compared with nodal DLBCL, spleen was the only site with significantly better prognosis after R-CHOP.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma subtype with approximately 22,000 new cases each year in the United States (US) [1]. Its prognosis has substantially improved with the addition of rituximab to standard chemotherapy [2–4]. In a third of cases DLBCL arises from extranodal sites, and these lymphomas differ in clinical characteristics [5]. Previous studies of prognosis in primary extranodal DLBCL showed varying results, and whether the benefits of rituximab-based chemoimmunotherapy are the same for nodal and extranodal disease is controversial.

Advanced nodal lymphoma may also involve extranodal sites by direct invasion or diffuse spread. Rituximab appears to improved outcomes in advanced DLBCL with extranodal extension, but some studies found no such benefit in primary extranodal DLBCL [6,7]. Worse outcomes in early-stage DLBCL with extranodal involvement were suggested, while the opposite was reported in advanced stage [6,8]. Finally, specific extranodal sites of involvement were prognostic in patients with DLBCL in some studies, but not in others, and this issue has not been analyzed in the context of treatment effects [5,9–11].

We conducted a retrospective analysis of DLBCL cases from the Surveillance Epidemiology and End Results (SEER)–Medicare database. Our primary objective was to assess the relative benefits of adding rituximab to chemotherapy for primary nodal and extranodal DLBCL. The secondary objective was to identify specific extranodal sites associated with better or worse outcomes after rituximab-based chemotherapy.

2. Methods

2.1. Data source and variables

The study was approved by the Institutional Review Board and conducted in accordance with the Helsinki Declaration. We extracted data on all DLBCL cases diagnosed between 1996 and 2009 from the SEER–Medicare database curated by the National Cancer Institute (NCI). SEER collects cancer registry data (demographic, clinicopathologic and survival variables) from 18 geographic areas currently covering 26% of the US population. Medicare provides medical insurance to all Americans who are ≥65 years old or disabled, and the linked database captures inpatient and outpatient medical services rendered to patients [12]. This database has been validated for identification and analysis of intravenous chemotherapy in lymphomas [4,13,14]. The available SEER-Medicare submission contained Medicare claims until December 31, 2010 and survival data until December 31, 2011.

We identified DLBCL cases using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology codes (9680, 9684), excluding transformed indolent B-cell lymphomas, primary intravascular, effusion, mediastinal or central nervous system DLBCL (Fig. 1). Extranodal sites were categorized using the ICD-O-3 topography codes. Waldeyer's ring and spleen were included as separate

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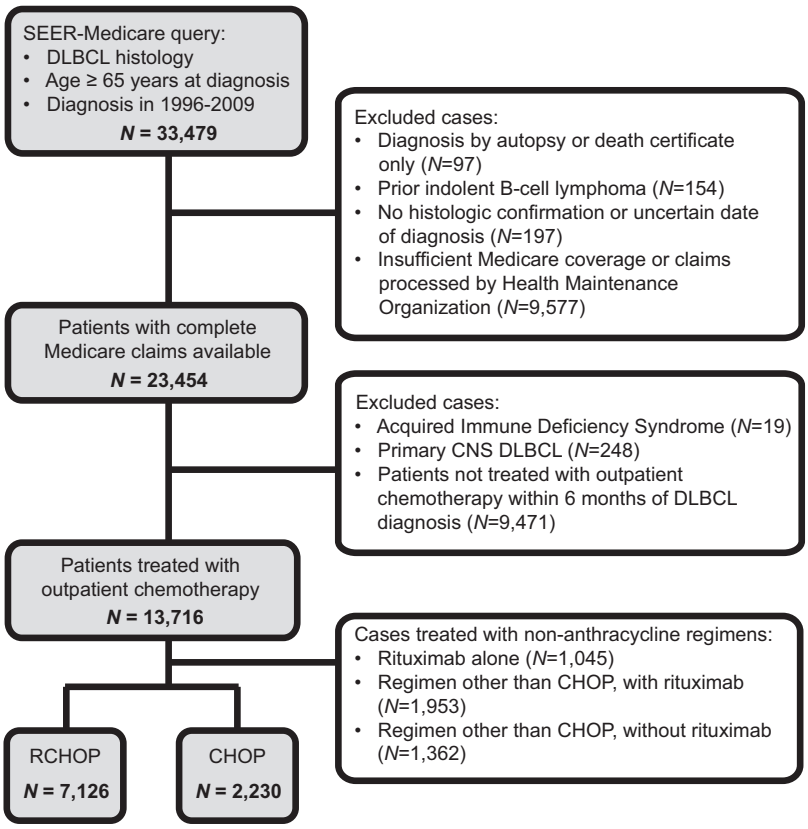

Fig. 1. CONSORT diagram for cohort selection.

sites because of potential prognostic significance [11]. The SEER manual contains specific modules for ascertainment of the primary site of DLBCL, enabling consistent distinction of the primary extranodal involvement from secondary dissemination of nodal lymphoma [15]. All lymphomas originating from liver, lung or bone marrow were recoded as stage IV in concordance with the Ann Arbor staging system. We excluded about 29% of cases (primarily Health Maintenance Organization enrollees) who did not have complete Medicare claims available in the period from 12 months before to 6 months after the DLBCL diagnosis. Additionally, 40% of patients did not receive outpatient chemotherapy—a group characterized by extremely short survival (median 3 months) suggestive of palliative approaches or early inpatient mortality (Fig. S1, online supporting information).

Specific intravenous chemotherapy agents were identified using Healthcare Common Procedure Coding System codes. Patients were assumed to receive CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or an equivalent regimen if all intravenous drugs were given within 60 days of treatment initiation, although specific doses, detailed schedules and relative intensity could not be discerned from the data. Oral prednisone was not recorded. Rituximab could be delivered within 180 days of treatment initiation, accommodating post-CHOP maintenance strategies [16]. Patients treated with non-anthracycline regimens had a markedly shorter survival indicating prohibitive comorbidities (Fig. S2, online supporting information). We used claims from the 12-month period before treatment to construct correlates of the unavailable components of the International Prognostic Index (IPI)—lactate dehydrogenase levels and performance status. These included number of comorbid conditions (using the NCI modification of the Charlson Comorbidity Index), poor functional status indicator (based on utilization of home care, durable medical equipment and other medical services) and anemia (using claims for related medical services, blood transfusions and erythropoietin administration) [13,17]. These variables strongly correlated with survival outcomes (Fig. S3, online supporting information). The receipt of radiotherapy (within 1 year of DLBCL diagnosis) was ascertained from the Medicare claims, but not included in the regression models, because we could not discern treatments given as part of initial course, at progression or as a palliative modality.

2.2. Endpoints

We used overall survival (OS) and cumulative incidence of lymphoma-related death (LRD) as the endpoints for comparative analysis. LRD was differentiated from other causes of death using death certificates and analyzed by competing risk methodology. Accounting for competing risks is of particular importance for older patients, in whom non-cancer mortality is substantial [18]. LRD was defined by standard SEER algorithms, additionally including all events attributed to a "lymphoma" or "leukemia" on death certificates. Death certificates were only available until December 31, 2009. Later events were censored for LRD analysis.

2.3. Statistical analysis

Basic group characteristic were compared using chi-square or rank-sum tests. Kaplan–Meier OS curves were compared using log-rank test, and the cumulative incidence curves using Gray's test. Missing values of race, stage and B symptoms were accounted for by multiple imputation using chained equations, with 40 imputed datasets [19]. OS and LRD were studied in multivariate proportional hazard Cox and Fine-Gray models, respectively. The proportional hazard assumption was evaluated using time-interaction tests, but the inclusion of time-varying terms had no impact on the coefficients of interest. All analyses were performed using two-sided tests, 95% confidence intervals (CI), and alpha level 0.05, using Stata version 13.1 (StataCorp LP, College Station, TX).

3. Results

3.1. Patient characteristics

Our analytical cohort included 9356 patients treated with either CHOP or R-CHOP regimens (Table 1). The proportion receiving R-CHOP increased from 1% in 1998 to 96% by 2004 (Fig. S4, online supporting information). Consequently, the median follow-up for patients receiving CHOP and R-CHOP was 11.7 years and 5.2 years, respectively. The median age was 75 years (range: 65–99 years), equal in both groups ($P = 0.53$). The R-CHOP cohort had an unfavorable distribution of stage, comorbidities, B symptoms and anemia. Extranodal primary site was present in 35%, with most common involvement of the gastrointestinal tract, head and neck (including Waldeyer's ring and paranasal sinuses) and skin/connective tissue (Table 2). Over 50% of DLBCLs of liver or lung origin had an incorrect assignment of Ann Arbor stage I or II instead of IV, which was corrected.