# Survival in Advanced Diffuse Large B-Cell Lymphoma in Pre- and Post-rituximab Eras in the United States

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**Abstract.** *Background: Rituximab was approved by the United States Food and Drug Administration (FDA) as a first-line agent for treatment of advanced diffuse large B-cell lymphoma (DLBCL) in February 2006. We conducted this population-based study to determine if the results from the clinical trials have translated into survival benefit in the general population. Patients and Methods: We selected patients with advanced diffuse large B-cell lymphoma from the Surveillance, Epidemiology, and End Results (SEER) 18 database, and calculated relative survival rates for patients diagnosed from 2002-2005 (pre-rituximab) and 2006-2009 (post-rituximab). We used the Z-test in the SEER*Stat to compare relative survival rates of patients categorized by race (White, Black, or Others), gender (male, female), and age groups (<60, 60+ years). Results: One-year relative survival in Whites and Others improved significantly in the post-rituximab era compared to the pre-rituximab era (64.80±0.6% vs. 61.3±0.6%; p=0.0002 and 64.5±1.9% vs. 54.9±2.2%; p=0.0011, respectively). The 3-year relative survival improved significantly in Whites and Others in the post-rituximab era compared to the pre-rituximab era (53.7±0.7% vs. 50.3±0.7%; p=0.0001 and 52.0±2.3% vs. 40.8±2.3%; p=0.0002, respectively). However, no significant improvements were observed in 1-year and 3-year relative survival in Blacks, and in young males during the post-rituximab era compared to the pre-rituximab era. Conclusion: The relative survival rates among young males and 'Black' patients with advanced diffuse large B-cell lymphoma have not improved during the post-rituximab era.*

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Diffuse large B-cell lymphoma (DLBCL) is the most common form of Non-Hodgkin's lymphoma, comprising approximately 30% of cases (1). Chemotherapy is the standard treatment for advanced-stage DLBCL. The results of the Groupe d'Étude des Lymphomes de l'Adulte study (2) were practice-changing. In that study, 399 elderly patients, aged 60-80 years, were randomized to receive eight cycles of rituximab–cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) or CHOP. The complete response was significantly higher for patients receiving R-CHOP compared to those receiving CHOP (76% *vs.* 63%, $p$=0.005). Similarly, event-free and overall survival rates were significantly higher in the R-CHOP group. A recent update of the study showed a significantly higher 10-year overall survival rate of 43.5% in the R-CHOP group compared to 27.6% in the CHOP group (3). Another study in a younger patient population confirmed the beneficial effects of adding rituximab to CHOP-like chemotherapy (4). Based on the findings of these studies, the FDA granted approval for the use of rituximab in combination with CHOP or other anthracycline-based regimens in February 2006 (5).

Recently, there has been a considerable interest in addressing disparities in cancer burden and survival of patients belonging to different ethnic groups. The Institute of Medicine study committee recommended that the National Institute of Health research priority "should include, first, the development and refinement of valid measures of exposure relevant to understanding and evaluating health disparities." (6).

We conducted the current study to determine if the results of randomized controlled trials have translated into improvement of survival of patients with newly-diagnosed advanced DLBCL in a large population-based cohort. In addition, we examined the survival rates by age, gender and ethnicity in the pre- and post-rituximab eras.

## Patients and Methods

*Description of data and sample.* The Surveillance, Epidemiology, and End Results (SEER) 18 database (Nov 2012 submission), a population-based cancer database sponsored by the National Cancer

Table I. *Relative survival (RS) of advanced diffuse large B-cell lymphoma patients by age, gender and race.*

| Age | Gender | Race | Pre-rituximab (2002-2005) (N) | Post-rituximab (2006-2009) (N) | 1-Year RS (%)* | | *p*-Value | 3-Year RS (%)* | | *p*-Value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Pre-rituximab | Post-rituximab | | Pre-rituximab | Post-rituximab | |
| All | M+F | All | 7,407 | 8,220 | 60.8±0.6 | 64.7±0.5 | 0.0001 | 49.5±0.6 | 53.2±0.6 | 0.0001 |
| | | W | 6,173 | 6,821 | 61.3±0.6 | 64.8±0.6 | 0.0002 | 50.3±0.7 | 53.7±0.7 | 0.0001 |
| | | B | 698 | 717 | 60.1±1.9 | 62.5±1.9 | >0.05 | 47.6±2.0 | 48.1±2.1 | >0.05 |
| | | O | 511 | 642 | 54.9±2.2 | 64.5±1.9 | 0.0011 | 40.8±2.3 | 52.0±2.3 | 0.0002 |
| <60 Years | M+F | All | 2,878 | 3,086 | 72.9±0.8 | 75.9±0.8 | 0.0122 | 60.1±0.9 | 64.3±0.9 | 0.0020 |
| | M | All | 1,823 | 2,016 | 70.4±1.1 | 73.2±1.0 | >0.05 | 58.4±1.2 | 61.4±1.2 | >0.05 |
| | F | All | 1,055 | 1,070 | 77.1±1.3 | 80.9±1.2 | 0.0365 | 62.9±1.5 | 69.9±1.5 | 0.0012 |
| ≥60 Years | M+F | All | 4,529 | 5,134 | 53.1±0.8 | 57.9±0.7 | 0.0001 | 42.6±0.8 | 46.3±0.8 | 0.0001 |
| | M | All | 2,217 | 2,582 | 52.4±1.1 | 58.0±1.0 | 0.0003 | 40.7±1.2 | 46.1±1.2 | 0.0001 |
| | F | All | 2,312 | 2,552 | 53.7±1.1 | 57.7±1.0 | 0.0064 | 44.4±1.1 | 46.5±1.2 | 0.0419 |

FF: Female; M: male; B: black; O: other; W: white. *Data ±standard error.

Institute, covers 27.8% of the United States population (7). The SEER program collects data on primary tumor site, stage, age, gender, histology and survival from several population-based cancer registries. The SEER program's standard for case ascertainment is 98% (8). The geographical areas covered in the SEER 18 database include San Francisco-Oakland, Connecticut, Detroit (metropolitan), Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Atlanta (metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia, Greater California, Kentucky, Louisiana, New Jersey and Greater Georgia.

*Study participants*. The participants encompassed patients with newly diagnosed advanced DLBCL utilizing Localized/Regional/ Distant stage (9) between 2002 and 2009. Patients with advanced DLBCL as the only primary cancer were included. We excluded cases that were diagnosed at autopsy, from death certificate only, or alive without survival date. We categorized patients into various cohorts based on race (White, Black or Others), gender (male or female), age group (<60 or 60+) and time period (pre-rituximab era 2002-2005 or post-rituximab era 2006-2009). American Indian/AK Native, Asian/Pacific Islander are included in "Others" race category.

*Statistical analysis*. We used the Z-test in the SEER*Stat to compare the relative survival rates in various cohorts. Relative survival (RS) measures a net cancer survival in the absence of other causes of death. RS is defined as the ratio of the proportion of observed survivors in a cohort of patients with cancer to the proportion of expected survivors in a comparable general population who do not have the same type of cancer. The Cansurv Software of the National Cancer Institute (10), specifically, Cox proportional hazard function, was used to investigate the influence of age, sex, and race, as well as marital status (married, single or separated/divorced/widowed), on the relative survival.

## Results

A total of 15,627 patients with advanced-stage DLBCL as the only primary cancer were identified. Patients' characteristics are summarized in Table I. Patients were predominantly white of non-Hispanic, non-Spanish/non-Latino origin, males, belonging to the older age category and married. The median age at diagnosis was 65 years. As expected, the 1- and 3-year relative survival rates of patients increased significantly from pre- to post-rituximab era.

The survival rates of younger patients improved from 72.9±0.8 to 75.9±0.8 at one year and from 60.1±0.9 to 64.3±0.9 at three years in the post-rituximab era. Similarly, survival of older patients improved from 53.1±0.8% to 57.9±0.7% at 1 year and from 42.6±0.8% to 46.3±0.8% at three years. On further analysis, improvement in survival rates among young patients was limited to females (Table I). The respective RS rates of young males were 70.4±1.1% and 73.2±1.0%, $p>0.05$ at one year, and 58.4±1.2% and 61.4±1.2%, $p>0.05$ at three years in pre- and post-rituximab eras. Among older patients, survival benefit was seen in both males and females.

One-year relative survival in Whites and Others improved significantly in the post-rituximab era compared to pre-rituximab era (64.80±0.6% *vs*. 61.3±0.6%; $p=0.0002$ and 64.5±1.9% *vs*. 54.9±2.2%; $p=0.0011$, respectively). The 3-year RS improved significantly in 'Whites' and 'Others' in the post-rituximab era compared to the pre-rituximab era (53.7±0.7% *vs*. 50.3±0.7%; $p=0.0001$ and 52.0±2.3% *vs*. 40.8±2.3%; $p=0.0002$, respectively). However, no significant improvements were observed in 1-year and 3-year relative survival in Blacks during the post-rituximab era compared to the pre-rituximab era. Interestingly, in the pre-rituximab era, relative survival of Blacks was comparable to that of Whites. Factors such as young age, female sex, non-Hispanic origin, White race, marriage status and the post-rituximab era were associated with significantly better survival rates (Table II).

## Discussion

Use of rituximab has been a major advance in the management of DLBCL. Rituximab-based chemotherapy has not only improved the overall response rate and complete

Table II. *Factors associated with relative survival in patients with diffuse large B cell lymphoma.*

| Parameter | All | | Pre-rituximab | | Post-rituximab | |
|---|---|---|---|---|---|---|
| | HR | *p*-Value | HR | *p*-Value | HR | *p*-Value |
| Age (≥60 *vs*. <60 years) | 1.968 | <0.0001 | 1.3642 | <0.0001 | 1.5068 | <0.0001 |
| Gender (F *vs*. M) | 0.8421 | <0.0001 | 0.9789 | <0.0001 | 0.8796 | <0.0001 |
| Origin (Hispanic *vs*. non-Hispanic ) | 1.2074 | <0.0001 | 1.0722 | <0.0001 | 1.0024 | 0.7444 |
| Race | | | | | | |
| White | Reference | | | | | |
| Black | 1.2462 | <0.0001 | 1.0114 | 0.4163 | 1.1006 | <0.0001 |
| Others | 1.1844 | <0.001 | 1.0727 | <0.0001 | 0.9489 | 0.3234 |
| Marital status | | | | | | |
| Married | Reference | | | | | |
| Single | 1.3995 | <0.0001 | 1.1864 | <0.0001 | 1.2435 | <0.0001 |
| S/D/W | 1.461 | <0.0001 | 1.1429 | <0.0001 | 1.2486 | <0.0001 |
| Era (post- *vs*. pre-rituximab) | 0.8718 | <0.0001 | | | | |

S: Single; D: divorced; W: widow. HR: Hazard ratio.

remission rate, but it has also improved the overall survival rate of patients with DLBCL (2). Our study showed significant improvements in the survival rates of patients with advanced DLBCL except for Blacks and young male patients.

Ethnic differences in cancer outcomes are well-known (11, 12), and may be either due to differences in treatment efficacy or differences in access to care. A review by Shavers *et al*. did not show significant ethnic differences in the effectiveness of treatment of cancer (13). Their study did not review outcomes in lymphoma. Wang *et al*. analyzed patients with non-Hodgkin's lymphoma from the SEER-Medicare database and found that African–American patients were less likely to receive lymphoma therapy and had inferior survival compared to Caucasians (14). However, the differences in the risk of mortality were not significant after controlling for socioeconomic status and treatment. A recent retrospective study analyzed 701 patients with DLBCL (15). Black race was associated with worse survival among patients treated with CHOP. Treatment with R-CHOP was associated with improved survival irrespective of race. More research is required to evaluate other potential explanations, including differences in biology that may explain racial disparities in survival of patients with DLBCL.

Lack of improvement in survival of young male patients in the post-rituximab era is worrisome. Sex differences in outcomes of patients with cancer are known (16). A previous study showed improved survival among female patients with DLBCL receiving induction rituximab therapy (17). Differences in drug metabolism may be one of the factors responsible for age- and sex-related differences in survival of patients with DLBCL. Decreased clearance of rituximab among elderly females with DLBCL compared to elderly males and increased clearance of rituximab with increasing weight have also been reported (18).

The strengths of our study include a large sample size, as well as a long-term follow-up of patients. There are several limitations of this study, related to some extent to the information available in the SEER database (19). The SEER program does not have any information on the chemotherapy used in patients with cancer. Furthermore, individual-level data on socioeconomic status are not available. Therefore, the conclusions of this study are based on the assumption of a changing pattern of treatment of DLBCL since the approval of rituximab.

Overall, we found that survival rates of patients with advanced DLBCL in the United States have improved in the post-rituximab era. More studies are required to explore the factors that may be responsible for lack of improvement in survival of young male and Black patients with advanced DLBCL.

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