Abstract

Diffuse large B cell lymphoma (DLBCL) is the most common type of Non-Hodgkin Lymphoma (NHL). The treatment of the older NHL patients has always been a struggle, however, the treatment statistics began showing favorable results similar to that of the younger DLBCL patients thanks to newer treatment protocols. 87 DLBCL patients, who were diagnosed and treated in the Dokuz Eylul University Department of Hematology between the years 2000 and 2016, were included in this study. Median age was 72 (65-89), 13 (14.9%) patients were older than 80 years old. Median follow-up time was 19 months and 45 patients (51.7%) died during the follow-up period. Median OS was 55 months and median PFS was calculated as 27 months. 63 patients (72.4%) received standard R-CHOP therapy. Additionally, the complete response (CR) was seen in 46 (52.9 %) patients. The median survival time for the patients who had a complete response was 136 months (p<0.001), however overall survival (OS) were not statistically different between older (>80) and younger patients (p=0.236). According to our findings, we think that being able to complete the standard R-CHOP therapy is vital for the survival rate of the elderly DLBCL patients.

Keywords: Lymphoid Cells Neoplasms, B-Cell Neoplasms, Lymphomas, Non Hodgkin Lymphoma

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hastaların genel sağkalım süreleri arasında anlamlı istatistiksel fark izlenmedi (p=0.236). Bu veriler
şığında yaşlı DBBHL’li hastalarda standart R-CHOP tedavisinin tamamlanmasının sağkalım süresine
önelmli etkisi bulunduğunu söyleyebiliriz.

Introduction

Diffuse large B cell lymphoma DLBCL is the most common NHL type and accounts for 30-40 % of all
NHL cases [1]. In the US, its incidence is 7/100.000 [2] whereas in Europe it is 4.9/100.000 [3]. In
Turkey, based on 2014 data, the incidence of DLBCL is 6/100.000 [4]. The diagnosis rate for DLBCL is
higher in Caucasians, than Africans and Asians [5]. The median age for DLBCL is 64 and it is slightly
more common in men than women (male/female=1.5)[2].

According to recent studies, approximately 70% of all newly diagnosed neoplasms will be observed in
geriatric patients by 2020 [6]. Nearly 53% of all the newly diagnosed NHL patients are over 65 years old
[7]. Because of their comorbid diseases and their frail conditions, elderly patients have always been
considered as poor responders to treatment in comparison to younger patients, however recent studies
with newer treatment agents had shown that, the older DLBCL patients may also respond well to
treatment, such as younger patients. According to early studies which were conducted in elderly DLBCL
patients when the CHOP regimen alone was the standard of care, the CR was 40% to 50% and 3-year
overall survival was around 30%, which was considered unsatisfactory, whereas in studies conducted in
the rituximab era, the CR was reported as 60% to 80% and the 3-year overall survival rates were found to
be around 70% [8].

In light of these information, it is especially important to consider the right treatment option for elderly
DLBCL patients. In this study, we analyzed the progress of our own elderly DLBCL patients who had
been followed between the years of 2000 and 2016 in our center.

Material and Methods

Total 87 patients were included in this study who were diagnosed and followed between the years of
2000 and 2016 in Dokuz Eylul University Hospital, Department of Hematology. Consents of the patients
and approval of the University’s Ethics Board were obtained before the start of the study. Patients who
had previously been diagnosed with another form of malignancy were excluded from the study. In this
retrospective study, university archives were used to analyze patient information such as; age, time of
diagnosis, stage, treatment regimens, treatment results, side effects, and comorbid diseases. Additionally,
in order to assess the pathological subtype of DLBCL, immunohistochemical staining was applied to
some of our patient’s biopsy materials by the department of pathology with the informed consent of
patients and/or their relatives.

Statistical Analyses

Assessment of the acquired data was made with SPSS v17. The suitability of the numeric variants was
assessed using the Kolmogorov Smirnov Test. The chi-square test was used to test the relationship
between two categorical variables. The Kaplan Meier analyze was used in order to show the impact of
prognostic factors on survival rates. For multivariate data analysis, the Cox regression method was used.
Probability values less than 0.05 were considered statistically significant.

Immunohistochemical Method

Immunohistochemical stains were applied to some patient’s biopsy materials whose subtypes were
unknown. To achieve that, formalin-fixed, paraffin embedded 4 µm sections from patient samples
collected. On lysine lames; CD10 (VENTANA anti CD-10 SP67 1:100 dilution), Bcl-6 (Cell Marque
1:200 dilution) and MUM-1 (VENTANA, 1:100 dilution) stains were applied. Afterward, these lames
were analyzed under the microscope.

Results

The median age of patients was 72 (65-89). 47 patients (54%) were male and 40 (46%) female. 74
(85.1%) of our patients were younger than 80 years old and 13 (%14.9) of them were older than 80.
Median follow-up time was 19 months (1-180). In total, 45 patients (51.7%) died during the follow-up.
Comorbid diseases such as type 2 diabetes, hypertension and congestive heart failure were seen in 62 of
our patients (71.3%) whereas 25 (28.7%) patient had no previously diagnosed comorbidities (Table 1).
Patient Demographics and Clinical Data (Table 1)

| Age (Mean, Range) | 72 (65-89) |
|-------------------|------------|
| Age (n, %)        |            |
| <80               | 74 (85.1%) |
| ≥80               | 13 (14.9%) |
| Gender (n, %)     |            |
| Male              | 47 (54%)   |
| Female            | 40 (46%)   |
| Comorbidity (n, %)|            |
| Yes               | 62 (71.3%) |
| No                | 25 (28.7%) |

The 51 patients, whose subtypes could have been identified by immunochemical staining; 14 (27.5%) were classified as GCB (Germinal Center Type B Cell) subtype and 37 (72.5%) as non GCB. Patients were also categorized using Ann-Arbor staging; 11 (12.6%) patients were stage I, 31 (35.6%) stage II, 22 (25.3%) stage III and 23 (26.4) stage IV respectively. We also calculated patients IPI (international prognostic index) scores. Patients with IPI score 2 and 3 were by a majority with 30 (34.5%) patients each, there were 15 (17.2%) patients with an IPI score of 4 and 12 (13.8%) patients with an IPI score of 1, there were no patients with an IPI score of 5 (Table 2).

Most of the patients (72.4%) were treated with regular dosage of R-CHOP, 2 patients (2.3%) with reduced dose R-CHOP, 4 patients (4.6%) with R-CEOP, 3 patients (4.6%) with R-CVP, 10 patients (11.5%) with CHOP, 1 patient (1.1%) with mini CEOP and 3 patients (3.4%) were treated with R-steroid respectively. Anthracycline based chemotherapy was given to 75 patients (86.2%) in total whereas rituximab was used in 76 (87.4%) of all patients. Additionally, high risk patients had received their proper intrathecal methotrexate as a part of CNS prophylaxis strategy according to their NCCN central nervous system risk score. Radiotherapy was used in 24 (27.6%) patient (Table 3).

Tumor Related Characteristics (Table 2)

| Immunohistochemical (IH) Subtypes (n, %) |            |
|-----------------------------------------|------------|
| Germinal                                | 14 (27.5%) |
| Non-Germinal                            | 37 (72.5%) |
| Staging (Ann-Arbor) (n, %)              |            |
| I                                       | 11 (12.6%) |
| II                                      | 31 (35.6%) |
| III                                     | 22 (25.3%) |
| IV                                      | 23 (26.4%) |
| IPI Score (n, %)                        |            |
| 1                                       | 12 (13.8%) |
| 2                                       | 30 (34.5%) |
| 3                                       | 30 (34.5%) |
| 4                                       | 15 (17.2%) |
60 patients (69%) were able to complete their designated therapy and within those patients, 46 (52.9%) had complete response. When comparing IH subtypes and treatment results, we saw that 9 (64.3%) patients with GCB subtype had complete response (CR) whereas in patients with non GCB subtypes, 14 (37.8%) of them had CR, however statistically we found no significant difference between the IH subtypes (p=0.174). CR was seen in 6 patients (46.2%) who were older than 80 and in 40 patients (46%) who were under the age of 80; there was no statistically significant difference between the treatment results and age (p=0.585).

The most common side effect in this study was neutropenia, which occurred in 65 (74.7%) of our patients, other side effects were heart failure, neuropathy, pneumonia, sepsis, renal failure, thrombosis and reactivation of tuberculosis.

Median progression free survival time (PFS) was 27 months. Median overall survival time (OS) in our study was 55 months. 3-year, 5-year and 10-year OS was calculated as 54%, 44% and 33% respectively. For patients older than 80 years old, OS was 31 months, while in younger patients it was 57 months, however no significant statistical difference was found between the two groups (p=0.236) (figure 1).
OS in patients with GCB subtype was 27 months and in patients with non GCB subtype the OS was 21 months, between these two subtypes we have found no statistically important difference (p=0.218) (figure 2). In patients who could have completed standard dose R-CHOP therapy, 3 years OS was 48% for GCB group and 42% for non GCB.
Figure 2: Overall Survival and Immunohistochemical Subtypes

Even though we couldn’t see a statistical difference between the stage and overall survival (p=0.999), we did find a statistical difference between IPI scores and survival rates. In patients whose IPI score was 1 median survival time was 97 months and the ones who had an IPI score was 4 it was seen 14 months (p=0.008). When the general survival rate was evaluated in our elderly patient group, the IPI score was detected as an independent predictive feature even if it was adapted by using gender and comorbidity in Cox regression analysis (p=0.003). The median survival time was 69 months for patients who had no previous comorbid disease and 35 months in patients who had previously diagnosed with a chronic comorbid disease, statistically, there was no significant difference (p=0.366). 3-year OS was calculated as 70% in patients without comorbidities and 45% for the ones who had an accompanying chronic disease (figure 3).
The median survival rate for rituximab received patients were 58 months and 3-year OS was 57%, whereas for patients who did not receive rituximab, the median survival rate was 27 months and 3-year OS was found as 36% (p=0.379). Additionally, 5-year OS and 10-year OS for patients who had received rituximab therapy was 47% and 37% respectively.

The median survival of patients who had a complete treatment response was 136 months which was statistically important compared to other patients who had a partial response or non-responders (p<0.001) (figure 4). Relapse was seen in 22 patients (25.3%). Median relapse time was 16.5 months (3-132). The OS in patients with an early relapse (<1 year) was 14 months whereas it was 69 months for the late relapsers (>1 year) which was statistically significant (p=0.025). The PFS in patients with an early relapse (<1 year) was 8 months whereas it was 27 months for the late relapsers (>1 year) which was also statistically significant (p<0.001).
Discussion: DLBCL is the most common type of NHL and its prevalence grows by age [1]. The treatment options have always been a struggle in elderly patients because of the reasons like frailty and comorbid diseases [9]. According to previous other studies, being unable to receive appropriate treatment, which is the standard treatment regimen R-CHOP, usually have negative effects on elderly patients [10]. DLBCL is an aggressive hematologic malignancy and patients diagnosed with DLBCL has an average lifespan of less than a year without treatment. However, as recent studies show, with newer and improved therapy options the survival rates are much better than before in older DLBCL patients [11].

In our study, we analyzed DLBCL patients who were older than 65 years old retrospectively. Our population was between the age of 65 and 89 (mean:72) and men women ratio was 1.17, which was similar to literature [2]. Additionally, we have studied immunohistochemical subgroups based on Hans Algorithm [12]. In various other studies, it has been shown that non GCB subtypes are more common in older DLBCL patients. In 51 patients whose subgroup we could identified; we found out most of them (72.5%) were patients with non GCB subtype, which was similar to literature [13]. Based on literature, 60% of patients diagnosed with DLBCL who are older than 70 have an accompanying chronic disease [14]. In our study group 62 patients (71.3%) had other comorbidities, and the most common comorbid disease was diabetes mellitus type 2 (17.2%), that were followed by, hypertension (14.9%) and heart failure (14.9%) respectively. In our study group, patients mostly received standard dose R-CHOP therapy (72.4%). Among literature, neutropenic fever is the most common side effect seen in DLBCL patients, in elderly patients its frequency is nearly 40% [15]. Consistent with other studies, neutropenic fever was the most common side effect (42.5%) in our study.

In this study, treatment completion rate in general was 69% and, 52.9% of the patients had complete treatment response. Furthermore, CR was higher (76.1%) in patients who had received R-CHOP therapy which was similar to other larger randomized studies such as RICOVER-60 [11]. Additionally, we saw 64.3% complete response rate in patients with GCB subtypes whereas 37.8% patients with non GCB had CR. According to other studies in the past, patients with GCB subtypes were found to be better responders to treatments compared to patients with non GCB subtype, however, according to the recent studies that were conducted after the rituximab era, the two subtypes have begun showing similar treatment results. In a 10-year prospective study made in Finland with 194 DLBCL patients showed that adding rituximab to therapy leads to better survival rates in patients with non GCB subtypes [16]. As much as it seems that there was a favorable outcome in our study for patients with GCB subtype, no statistically important difference was discovered (p=0.205). This may be explained by the lack of
patients and the fact that we included patients from both pre-rituximab and post-rituximab era within our study population. There are many studies in literature which analyzed the relationship between age and treatment results. In a large retrospective study conducted by Thieblemont et al., after the rituximab era in 2008, revealed that even though younger patients showed more favorable results, there were no statistically important difference between younger patients and the patients who were older than 80 [17]. We also found similar results within our study group; patients older than 80 had 46.2% CR whereas younger patients had 46% CR (p=0.572).

In our study, median survival time in general was calculated as 55 months. We also found out that, for patients younger than 80 years old overall median survival time was 57 months whereas for older patients it was 31 months, however, there were no statistically important difference between the two groups (p=0.236). In several large studies among DLBCL patients; in German DLBCL group by Pfreundschuh et al., patients between the age of 60-80 who received rituximab, the 3-year OS was found as 78% [11]. In another large scale study, conducted by the GELA group (Coiffier et al.), the 10-year OS was shown as 44% for the patients who received rituximab treatment [18]. Within our study group’s rituximab received patients; the 3-year OS was calculated as 54% and 10-year OS was 37%. For patients older than 80 years old, the 3-year OS was 38% and for the ones younger than 80 it was 58%. Perhaps the difference between the literature and our study can be explained by the different current lifespans of those countries (France, Germany etc.) and ours. According to the 2015 WHO data, life expectancy in Turkey is 75.8, 82.5 in France and 81.1 in Germany. Additionally, in our study population we had patients older than 80 years old and that was also different from those large studies in which maximum age was 80.

Even though we could not have identified all of our patient’s subgroups, we have found out that median survival time was 27 months for GCB types and 21 months for patients with non GCB subtypes which wasn’t a significant statistical difference (p=0.218). In a large study of DLBCL patients between the age 23-88 made by Seki et al., 3-year OS was found as 68% in patients with GCB subtype and 67% for non GCB, within patients who received R-CHOP [19]. In our study, we have found out the 3-year OS of patients who received R-CHOP with GCB subtype as 48% and 42% for the non GCB subtype which was consistent with post-rituximab era literature. When we analyzed the effect of disease stage on patients, we have found out no statistical difference, median survival time of patients with stage 1 was found as 72 months and stage 4 was calculated as 69 months (p=0.999). However, like other previous studies [20] we have found a significant statistical difference regarding the IPI scores of our patients. The median survival time was 97 months for the patients with IPI score 1 and 14 months for patients with an IPI score 4 (p=0.008). In literature, there are studies that had shown the negative effects of comorbidities on elder DLBCL patients [14]. In our study, the median survival time for patients without any comorbid diseases was found as 69 months whereas it was 35 months for patients with an accompanying chronic disease, however as much as survival times of the patients without comorbidities seemed favorable there wasn’t a statistically important difference (p=0.366).

Before the age of rituximab, anthracycline based CHOP therapy was considered the standard therapy for patients with DLBCL, the cure rates at those times were around 60-50% for younger patients and 25-30% for older patients [21-25]. In the GELA group study made by Coiffier et al.,10-year OS for the patients who had only received CHOP therapy was 28% and they showed that adding rituximab to therapy had risen the 10-year OS to 44% [18]. Among our study group, the median survival time of rituximab received patients were calculated as 57 months compared to 27 months for the ones who didn’t receive rituximab treatment. While we saw a tendency in favor of the rituximab group, it wasn’t statistically significant (p=0.513). Despite old age and frailty, we saw 60 (69%) of our patients could have completed their designated therapies and 63 (72.4%) of them received full standard dose R-CHOP therapy. Within those patients, we saw a complete treatment response in 46 (52.9%) patients, among those 46 patients, median survival time was calculated as 136 months and which was statistically significant (p<0.001). The median relapse time in our study was calculated as 16.5 months and relapse rate was 25.3%, in other studies conducted among similar aged patients (60-80) relapse rates were found generally higher (up to 51%) [8]. This difference might be explained by the fact that our study group was relatively smaller. However, similar to literature, we did find a statistically important difference between the early relapers (<1 year) and the late relapers (OS p=0.025, PFS p<0.001).

Finally, we think that in elderly DLBCL patients, being able to complete rituximab based standard therapy regimen is directly affecting the survival rates. Additionally, having comorbidities and higher IPI scores are very important on the survival of DLBCL patients. To sum up, based on our results, we can safely say that treating elderly DLBCL patients with standard RCHOP therapy is very important and shows favorable similar to younger patients.
REFERENCES

1. Swerdlow, S.H., et al., The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, 2016. 127(20): p. 2375-90.
2. Morton, L.M., et al., Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood, 2006. 107(1): p. 265-76.
3. Sant, M., et al., Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood, 2010. 116(19): p. 3724-34.
4. Turkey, R.o., Ministry of Health 2014 Statistics
5. Shirley, M.H., et al., Incidence of haematological malignancies by ethnic group in England, 2001-7. Br J Haematol, 2013. 163(4): p. 465-77.
6. Balducci, L., Geriatric oncologic challenges for the new century. Eur J Cancer, 2000. 36(14): p. 1741-54.
7. Morrison, V.A., et al., Approach to therapy of diffuse large B-cell lymphoma in the elderly: the International Society of Geriatric Oncology (SIOG) expert position commentary. Ann Oncol, 2015. 26(6): p. 1058-68.
8. Sarkozy, C. and B. Coiffier, Diffuse large B-cell lymphoma in the elderly: a review of potential difficulties. Clin Cancer Res, 2013. 19(7): p. 1660-9.
9. Dixon, D.O., et al., Effect of age on therapeutic outcome in advanced diffuse histiocytic lymphoma, the Southwest Oncology Group experience. J Clin Oncol, 1986. 4(3): p. 295-305.
10. Bastion, Y., et al., Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment, and survival--a Groupe d'Etude des Lymphomes de l'Adulthe study on 453 patients older than 69 years. J Clin Oncol, 1997. 15(8): p. 2945-53.
11. Freudenschuh, M., et al., Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol, 2008. 9(2): p. 105-16.
12. Hans, C.P., et al., Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood, 2004. 103(1): p. 275-82.
13. Mareschal, S., et al., The proportion of activated B-cell like subtype among de novo diffuse large B-cell lymphoma increases with age. Haematologica, 2011. 96(12): p. 1888-90.
14. Janssen-Heijnen, M.L., et al., A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. Br J Haematol, 2005. 129(5): p. 597-606.
15. Pettengell, R., et al., Impact of febrile neutropenia on R-CHOP chemotherapy delivery and hospitalizations among patients with diffuse large B-cell lymphoma. Support Care Cancer, 2012. 20(3): p. 647-52.
16. Nyman, H., et al., Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. Blood, 2007. 109(11): p. 4930-5.
17. Thieblemont, C., et al., Non-Hodgkin's lymphoma in very elderly patients over 80 years. A descriptive analysis of clinical presentation and outcome. Ann Oncol, 2008. 19(4): p. 774-9.
18. Coiffier, B., et al., Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood, 2010. 116(12): p. 2040-5.

19. Seki, R., et al., Prognostic impact of immunohistochemical biomarkers in diffuse large B-cell lymphoma in the rituximab era. Cancer Sci, 2009. 100(10): p. 1842-7.

20. Ziepert, M., et al., Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol, 2010. 28(14): p. 2373-80.

21. McKelvey, E.M., et al., Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer, 1976. 38(4): p. 1484-93.

22. O'Reilly, S.E., et al., Malignant lymphomas in the elderly. Clin Geriatr Med, 1997. 13(2): p. 251-63.

23. Connors, J.M. and S.E. O'Reilly, Treatment considerations in the elderly patient with lymphoma. Hematol Oncol Clin North Am, 1997. 11(5): p. 949-61.