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Letter

IMPACT OF DOSE INTENSITY IN OLDER PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. The gold standard treatment is combined immunochemotherapy with the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) for 6 cycles. This strategy achieves long-term disease control in nearly 90% of patients with localized disease and up to 60% of cases with advanced stages[1]. However, the incidence of DLBCL progressively increases with age, and 50% of patients are over 60 years old at diagnosis[2]. Advanced age correlates with increased comorbidity and frailty, which limit treatment options. Previous retrospective studies have shown that maintaining immunochemotherapy doses above 70%, ideally above 90%, improves patients overall survival[3,4]. However, only 40% of patients over 60 years can achieve doses higher than 85%[5].

Given the scarce data in our country, we aimed to evaluate overall survival (OS) and progression-free survival (PFS) in patients over 65 years with DLBCL of our center. We also aimed to evaluate OS and PFS in patients who received chemotherapy with or without dose reduction and to assess treatments, adjustments, and toxicities.

Analytical, retrospective cohort study of consecutive patients diagnosed with DLBCL over 65 years old and treated at the *Hospital Italiano de Buenos Aires*. We include patients diagnosed according to the WHO 2017 criteria by a hematopathologist between January 2014 and December 2018. Patients without follow-up at the center were excluded. A systematic search was conducted through the hospital's epidemiology department using the Electronic Medical Record to identify patients. The data were anonymized and entered into an electronic database.

Full-dose chemotherapy group included R-CHOP, R-DA-EPOCH, MR-CHOP, Hyper-CVAD, and R-ESHAP regimens. Reduced-dose chemotherapy group included R-mini-CHOP, R-CEOP, R-CVP, R-Bendamustine, and patients who had to undergo dose reduction of more than 30% after initiating intensive regimens.

Descriptive statistics were used for clinical and pathological characteristics. Quantitative variables are expressed as median and interquartile range, while qualitative variables are presented as total number and percentage. Survival function (Log-Rank test) using the Freedman method was performed as the main hypothesis test, with an alpha of 0.05 and an estimated hazard ratio of 0.8. The Kaplan-Meier method was used to estimate time to event. A p-value less than 0.05 was considered statistically significant. Estimators are reported with their 95% confidence intervals. Statistical analysis was performed using Stata 13 software.

This study was approved by the Research Protocol Ethics Committee (CEPI) of the hospital and conducted in compliance with the Helsinki Declaration.

A total of 290 patients were analyzed, 131 did not meet inclusion criteria or had exclusion criteria. Finally, 159 patients were included. The median age was 75 years (IQR 70-81, range 65-

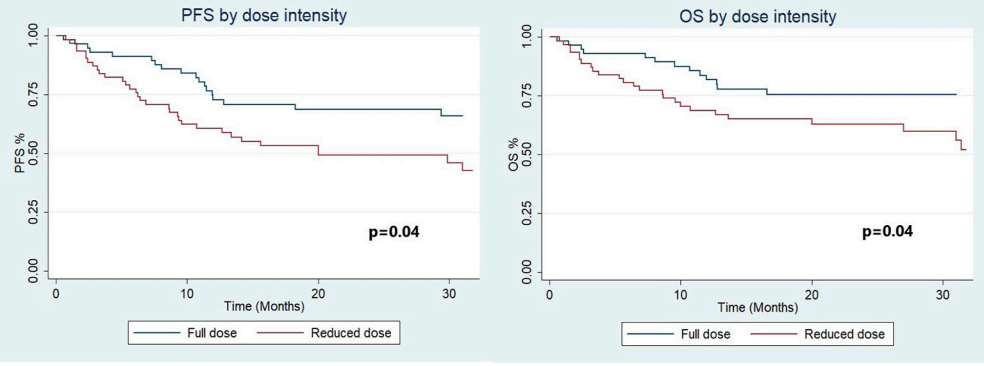
97), and 83 patients (52.2%) were female. Regarding clinical characteristics, advanced stages predominated with 108 patients (68%), and the International Prognostic Index (IPI) was high or intermediate/high in 75 cases (47.2%). Thirty-eight patients (23.9%) had B symptoms, and 35 (22%) had bulky disease at diagnosis. A total of 121 patients (78%) received chemotherapy, with 58 (48%) receiving full-dose regimens and 63 (52%) receiving reduced-dose regimens (55 patients with dose reduction from the beginning, 8 patients initially started with full-dose regimens but had to undergo dose reduction). The most common protocols were R-CHOP in 52 (38.1%), R-mini-CHOP in 32 (20.6%), R-CVP and R-DA-EPOCH in 6 (3.9%). Eighteen patients (11.3%) received radiotherapy, with only 4 (3.2%) receiving it as only treatment. Thirty-four patients (21.4%) did not receive disease-specific treatment and were managed with palliative care.

Regarding treatments, the median number of cycles was 6 (IQR 5-6), with 89 patients (84%) out of 106 evaluated with correctly cycling chemotherapy. Twenty-three patients (14.5%) discontinued treatment, 7 (33.3%) due to toxicity and 5 (23.8%) due to lack of response. One hundred and fourteen patients (91.2%) experienced some degree of hematological toxicity. The most common toxicity was neutropenia in 95 patients (76%), with grade III-IV neutropenia being predominant in 76 patients (61%). Anemia was grade I-II in 72 patients (57.6%) and grade III-IV in 27 patients (22%). Finally, thrombocytopenia was the least severe adverse effect, with 35 patients (28%) not experiencing it, 57 patients (46%) having grade I-II, and only 16 patients (13%) having grade III-IV. In terms of end-of-treatment response, 67 patients (53.6%) achieved complete response, and 11 patients (8.8%) achieved partial response.

The median follow-up for the entire cohort was 13 months (IQR 3-31). The one-year PFS and OS was 52% (95% CI 44%-60%) and 55% (95% CI 47%-63%), respectively. The three-year PFS and OS was 39% (95% CI 30%-48%), and 44% (95% CI 35%-53%). When considering only patients who received chemotherapy, one-year PFS for the full-dose group was 71% (95% CI 57-81), compared to 59% (95% CI 45-70) for the reduced-dose group (p = 0.04). The one-year OS was 77% (95% CI 63-86) for the full-dose group, compared to 66% (95% CI 52-76) for the reduced-dose group (p = 0.04), with both groups being comparable in terms of age, IPI, and stage at diagnosis. In patients who underwent treatment and were evaluated for frailty (68 patients, 56%), a higher proportion of frail patients was observed in the reduced-dose group (58%) compared to the full-dose one (35%), p = 0.00 (Fig. 1).

Despite the well-demonstrated benefit of the R-CHOP regimen in first-line treatment of DLBCL in eligible patients, our study shows the variability and lack of uniformity in the treatment practices for patients over 65 years old. One-fifth of the total population could not receive disease-specific treatment, and among those who started chemotherapy, almost half had to receive reduced doses or radiotherapy. The PFS and OS of the entire cohort are comparable to previous series, with three-year OS rates of 44% and PFS rates of 39%. A phase II study by Storti et al. evaluating treatment with R-bendamustine in elderly patients showed a two-year PFS of 38% and an OS of 51%[6]. Merli et al. also conducted a

Figure 1 |



phase II study evaluating the Obinutuzumab mini-CHOP regimen, which yielded slightly better results with two-year PFS and OS rates of 49% and 68%, respectively[7].

Our study demonstrates a statistically significant difference in PFS and OS in favor of the full-dose group. Although previous studies have shown no difference in OS between patients over 80/85 years old with or without dose reduction, these results could not be confirmed in younger elderly patients, suggesting that, at least for patients between 65 and 80 years old, the goal should still be full-dose chemotherapy[2,8-10].

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