DOI: 10.46765/2675-374X.2023V4N2P186

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IS AN EFFECTIVE TREATMENT OPTION IN EARLY RELAPSED AND PRIMARY REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA IN THE BRITISH HOSPITAL TRANSPLANT UNIT

Ana Carolina Oliver, Eloisa Riva, Victoria Irigoin, Sebastián Galeano, Silvia Pierri, Laura Bello, Virginia Carcalain, Regis Gai, Pablo Muxi.

Affiliations for all: Unidad de Trasplante de Progenitores Hematopoyéticos, Hospital Británico. Montevideo. Uruguay

Corresponding author: Ana Carolina Oliver - carolinaoliver80@gmail.com - ORCID: 0000-0002-7782-2024

Received: 06 Dec 2022 • Revised: 16 May 2023 • Accepted: 18 May 2023.

ABSTRACT

Introduction: Around 10-15% of diffuse large B-cell lymphomas (DLBCL) patients fail to achieve complete response (CR) after R-CHOP, and are considered primary refractory. There is limited transplant data in this population. **Objetive:** to evaluate the outcomes of primary refractory DLBCL patients transplanted at our center. **Results:** we evaluated 34 R/R patients treated with R-CHOP as first line. After second line, 30.4% of primary refractory/early relapse achieved CR, and 88.2% did so after ASCT. Median follow-up: 56.1 months, median OS was not reached; the estimated 5-year OS was 61.7%. Median OS of late relapse (Group 1) was not reached, and was 52 months for primary refractory/early relapse (Group 2) (p=0.023). The 5-year OS was 87.5% in Group 1 vs 49% in Group 2 (p=0.023). **Conclusions:** Primary refractory and early relapsed DLBCL undergoing second-line therapy and ASCT have worse OS compared to late relapse. However, 49% of primary refractory patients who proceeded to ASCT had prolonged survival, which supports the role of ASCT in this population.

Keywords: Hematopoietic stem cell transplantation. Autologous transplantation. B cell lymphomas. Diffuse large cell lymphoma. Primary Refractory.

INTRODUCTION

Around 10-15% of patients with diffuse large B-cell lymphomas (DLBCL) do not achieve complete response (CR) after first line chemoimmunotherapy with R-CHOP, and are considered primary refractory.[1]

In addition, a subgroup of those achieving initial CR will relapse 3-6 months after the end of treatment. In this situation, the standard of care for fit patients is Rituximab associated with second-line chemotherapy followed by consolidation with autologous stem cell transplantation (ASCT) in chemosensitive patients. Overall, 40-50% of these patients can be cured with this approach.[2-5]

This strategy is based on the results of the PARMA study, which enrolled 215 patients with relapsed Non-Hodgkin Lymphoma (NHL); 109 responded after two cycles of salvage therapy with DHAP (dexamethasone, cisplatin, and cytarabine) and were randomized to either conventional therapy (four additional cycles of DHAP) or ASCT. The 5-year OS was

53% for the patients undergoing transplantation vs 32% for those receiving conventional therapy.[2]

Primary refractory patients are scarcely represented in the medical literature.

In the pre-rituximab era, the Memorial Sloan Kettering Cancer Center group presented a series of 85 patients primary refractory to CHOP, who received second-line ICE protocol and consolidation with ASCT. The 3-year event free survival (EFS) was 25% and the 3-year overall survival (OS) was 22%.[6]

In the rituximab era, the British Columbia Cancer Agency (BCCA) published their series of 45 patients younger than 70 years with primary refractory DLBCL who were fit for ASCT; 12 were chemosensitive to two lines: 27% in the intention to treat analysis. The 5 years OS was 8%.[7]

The study of Vardhana *et al* from Memorial Sloan Kettering Cancer Center (MSKCC) is the largest series published in this field. They presented 82 patients with less than a partial response after R-CHOP who received second line chemotherapy. The 3-year OS was 38% and the PFS was 29% for the global cohort. In the 33 patients that proceeded to ASCT, 3-year OS was 65% and 3-year PFS was 60%.[8]

There is limited data on primary refractory DLBCL in the rituximab era. We evaluated the outcomes of primary refractory DLBCL transplants at our center, analyzing CR and OS rates. We compared these outcomes with those of patients transplanted for DLBCL relapsing beyond 6 months after the end of therapy.

METHODS

This is a retrospective single-center cohort study that evaluates the outcomes of second-line therapy and OS in primary refractory DLBCL and compares them with the outcomes of patients transplanted in late relapse.

Population:

All patients with DLBCL transplanted at the British Hospital´s hematopoietic stem-cell Transplant Unit from 2000 to 2020 were included.

Inclusion criteria were adult patients (>18 years) with relapsed and/or refractory histologically confirmed DLBCL or transformed low-grade lymphoma undergoing ASCT as second line consolidation. Exclusion criteria: rituximab-free first-line therapy, ASCT at first CR after R-CHOP, patients on the same protocol as first and second line, and CNS primary DLBCL.

Early relapse was defined as the relapse occurring within 6 months after completion of the first line treatment. Primary refractoriness was defined as not achieving CR at a maximum of 6 cycles of R-CHOP. Late relapse was defined as a relapse occurring beyond 6 months from the end of frontline therapy.

For this analysis, Group 1 included patients with late relapses, whereas Group 2 included primary refractory and early relapsed patients.

Response criteria were defined according to the Report of the International Workshop to standardize response criteria for non-Hodgkin's lymphomas and, since PET-CT became available, by the Lugano Response Criteria for Non-Hodgkin Lymphoma.[9,10]

Second-line therapies and the timing for ASCT were defined by the treating physician. The protocols used are shown in table 1.

Transplantation procedures:

After 5 days of stimulation with granulocyte colony-stimulating factor (G-CSF) with 10 mg/kg/d, repeated leukaphereses were performed to obtain a minimum of 2 x 10^6/kg recipient´s body weight of CD34+ cells. Peripheral blood stem cells (PBSC) were frozen using a controlled-rate method and stored in liquid nitrogen at -196 °C. The standard conditioning regimen was BEAM (Carmustine, Etoposide, Cytarabine and Melphalan). In 5 patients, due to a shortage in Carmustine, NEAM (Mitoxantrone, Etoposide, Cytarabine and Melphalan) protocol was used. Harvested stem cells were infused 24 hours after the end of chemotherapy, and patients received G-CSF 5 mg/kg/d subcutaneously from day +5 until leukocyte recovery after ASCT.

Response evaluation was performed around day 100 post-transplant and included routine analysis and imaging (PET-CT or CT) as judged by the treating physician.

Statistical Analysis:

OS was defined from the date of transplant until death from any cause, and patients who did not die during the study period were censored at the date of last follow-up. EFS was defined from the date of transplant until treatment failure, relapse or death, whichever came first, and patients who did not experience any of these events were censored at the date of last follow-up.

The data was analyzed using descriptive statistical methods, and statistical significance for differences between groups was calculated using t- test for non-categorical variables and chi-square or Fisher's exact test for categorical variables. Survival was determined with the Kaplan Meier curve. Significance was established with logrank test at $P < 0.05$.

Ethics:

All the procedures were in accordance with the Helsinki Declaration of 1975, revised in 2008 and with the acceptance of the Hospital Britanico's Ethics Committee.

RESULTS:

Between 2000 and 2020, 66 ASCT were performed in 66 patients with DLBCL at our institution. Of them, 34 fulfilled the inclusion criteria and are our study cohort. (Figure 1).

Patients´ characteristics:

Median age was 56 years (29-71) and 26.4% were older than 60 years; 50% were males.

Ann Arbor stage at diagnosis was I-II in 29.4%, and III-IV in 70.6%. B symptoms were present in 53%. R-IPI was intermediate or high in 76.4%. Patients' characteristics are shown in Table 1. The evaluation of response after R-CHOP was done with PET-CT in 22 patients (64.7%). A biopsy to confirm refractory/relapse disease was decided by the treating hematologist and it was done in 17 (50%) of the study cohort.

Salvage therapy:

Eleven patients had late relapses (Group 1), while 23 patients were primary refractory or early relapsed (Group 2). Table 2 shows the characteristics of group 1 and 2. These groups are balanced regarding age and response to second line therapy.

DHAP was the most used second-line therapy (44.1%), followed by ICE (29.4%) and GDP (11.8%). Rituximab was used in 10 patients, 7 from Group 1, and 3 from Group 2, p=0.003. Responses to second line therapy before ASCT were 29.4% CR (10), 55.9% PR (19) and 14.7% progression (5). This response was evaluated by CT in 25 patients (73.5%) and by PET-CT in 9 (26.5%).

Outcomes after transplant:

Response rates: at day-100 after ASCT, 88.2% achieved CR (76.7% assessed by PET and 23.3% by CT) and 11.8% progressed (50% assessed by PET and 50% by CT). (Figure 2)

Overall survival: with a median follow-up of 56.1 months (1.8-177.4), the median OS was not reached in the whole cohort; the estimated 5-year OS was 61.7%. (Figure 3) Median follow-up in the primary refractory and early relapse group (Group 2) was 42.5 months (1.8-141.2) compared to 97 months (38.5-177.4) for the late relapse group (Group 1). (Figure 4).

The median OS of Group 1 was not reached, and it was 52 months for group 2, log rank p=0.023. The 3-year OS was 100% in Group 1 vs 60% in Group 2, and the 5-year OS was 87.5% versus 49%, p=0,023.

No difference in OS between transplanted patients in CR or PR after second line therapy was observed (p = 0.44); 26.5% were evaluated by PET/CT before ASCT. There was no statistically significant difference in OS among patients within Group 2 (primary refractory, progressive disease or early relapse). The 5-year event free survival (EFS) was 87.5% in Group 1 and 51.4% in Group 2, p=0.075. (Figure 5).

DISCUSSION

Overall, DLBCL can be cured in 50-70% of the cases.[11]

The standard treatment in fit patients who achieve less than CR after frontline R-CHOP therapy is a second line of therapy followed by ASCT. The same approach is recommended for those who relapse, early or late after the end of frontline treatment. Primary refractory patients have been defined in various ways, in some studies they are those who achieve PR or less with R-CHOP, in others only those who achieve less than PR with R-CHOP.[8,12] These patients have been underrepresented in studies that evaluate the role of ASCT in DLBCL.

One of the main factors that impact the outcomes of refractory/relapsed DLBCL is response to second line treatment. The complete response rate to second line chemotherapy in our series was 27.3% and 34.8% in patients with late relapse and primary refractory disease, respectively. Noteworthy, only 29.4% received Rituximab associated with second line treatment. This is due to regulatory issues in our country, where Rituximab is approved for second-line use in patients with late relapses only.

In our series, 1/3 of the patients had their response evaluated with PET at this stage while the others were evaluated with CT.

Novel imaging techniques like PET/CT provide additional sensitivity and specificity compared to CT. However, non malignant pathologies may yield false positives. The evaluation of response to therapy has been varied in recent studies, some including only CT and others with PET/CT. The CORAL study showed a CR rate of 24% for R-ICE and 28% for R-DHAP, in a cohort where 53% were late relapses, with a median time to relapse of 89 months overall. The response was evaluated by CT.[4] Responses to second line in a French retrospective study with 104 patients were CR 23%, with 77% patients receiving Rituximab in salvage regimens.[13] The NCIC-CTG LY.12 study showed a CR of 13.8% for GDP and 14.6% for

DHAP in a population with 71% primary refractory or relapsed within 1 year. In this study, the response was also evaluated by CT.[5]

Compared to these results, our patients achieved slightly higher rates of response to second line treatment. In the CORAL study more than half of the patients had late relapses whereas in the NCIC-CTG LY.12 the most frequent were primary refractory or early relapses. In addition, the evaluation of response in these trials did not include the use of PET/CT, which may interfere with the interpretation of differences, as 1/3 in our study were evaluated with this technique.

In our series, at the time of ASCT, 29.4% were in CR, mostly assessed by CT (73.5%) After ASCT, CR rates increased to 88.2%, supporting the role of high-dose chemotherapy in this context. However, 4 (11.8%) patients progressed after ASCT (50% assessed by PET). Of them, 2 were in PR and 2 in progression at ASCT according to PET in 3 and CT in 1. It is important to notice that 3 of the 5 patients transplanted in progression achieved a CR after transplant. Of them, 2 are alive and in CR and 1 relapsed 21 months after transplant and died 28 months after ASCT due to progressive disease. This is a real world series, and even though transplant is indicated in chemosensitive DLBCL, 5 of our patients were transplanted in progression (3 confirmed by PET). Although the numbers are small some of them achieved long-term survival after ASCT.

The results of our series show an estimated median OS at 5 years of 61.7%. There are few published studies with a large number of patients in this setting, particularly in the real world.

A study published in 2017 from MSKCC reported the outcomes of 33 patients after second line and ASCT: 27% were in CR, and the estimated 3-year OS and PFS were 65% and 60% respectively.[8]

The Danish registry identified 90 refractory or relapsed patients who proceeded to ASCT. The 5-year OS from the time of infusion was 46% (95% CI: 37%–59%), and the median survival was 1,172 days. In this cohort, there was no difference in OS in the refractory or relapsed population.[14]

The CIBMTR report is the largest addressing this topic, including primary refractory DLBCL patients who received an ASCT between 2003 and 2018. Primary refractory disease was defined as either stable disease (SD) or progressive disease (PD) after rituximab and anthracycline-containing frontline chemoimmunotherapy. One hundred and sixty-nine adult patients with primary refractory DLBCL were included. The majority had PD (N=124; 73%) and the remaining had SD (N=45; 27%) after completion of frontline chemoimmunotherapy. All patients showed chemosensitivity to salvage therapy before ASCT. PFS or OS did not differ significantly at any time points between the two groups. Regarding the status of remission before ASCT, the 4-year PFS was 39% for the CR group versus 43% for the PR group (p=0.69). At 4 years, OS is comparable at 50% in the CR vs 49% in the PR groups, respectively (P=0.8).[12]

A Japanese study published in 2021 included 69 primary refractory patients after R-CHOP: 41 PR or early relapsed and 28 progressors under the first line. Of these, 17 proceeded to ASCT (13 partial responders and 4 primary progressors). The 3-year PFS and OS rates of the 17 patients treated with HDC-ASCT were 41% and 47%, respectively. Patients in the primary progressor group had a significantly poorer prognosis than those in the partial responders' group (3-year OS: 15% vs. 48%, respectively; $p < 0.001$).[15]

Nowadays, the use of bispecific antibodies and CART in DLBCL R/R are under development with promising results, but these strategies are yet unavailable in our country.[16,17]

It is noteworthy that ASCT after salvage chemotherapy provides the possibility of cure to a proportion of around 50% of RR DLBCL eligible patients, so it continues to be a useful and accessible strategy achieving good results. This study may have unintentional biases derived from its retrospective nature and the limited number of patients. In particular, there is a probable selection of fit, chemosensitive patients which makes broader generalizations difficult.

However, to the best of our knowledge, this is the first report from Latin America focusing on the outcomes of DLBCL patients transplanted for relapsed or refractory disease and it is one of the few international series approaching this issue.

CONCLUSIONS

Primary refractory and early relapsed patients with DLBCL undergoing second-line therapy and ASCT have worse OS compared to transplanted patients after late relapse. Chemoresistance is one of the most important factors affecting OS in DLBCL. However, 49% of primary refractory patients who proceeded to ASCT in this retrospective study had prolonged survival, which supports the role of ASCT in this population.

TABLE 1. Patients' characteristics.

N=34	Frequency (%)	
Median age (range)	56 (29-71)	
>60 years old	9 (26.4)	
Sex Female Male	 17 (50) 17 (50)	
Stage I-II III-IV	 10 (29.4) 24 (70.6)	
B symptoms	18 (53)	
HIV	1 (2.9)	
RIPI Low Intermediate High No data	 4 (11.8) 14 (41.4) 12 (35) 4 (11.8)	
Response after 1st line CR* PR+ Progressive	 16 (47) 13 (38.3) 5 (14.7)	 ByPET 10 (29.4) By PET 9 (26.5) By PET 3 (8.8)
Second-line therapy DHAP§ ICE** GDP++ MA § § Codox-M-IVAC*** ESHAP+++ R-CHOP § § §	 15 (44.1) 10 (29.4) 4 (11.8) 2 (5.9) 1 (2.9) 1 (2.9) 1 (2.9)	 +R: 5 (14.7) +R: 4 (11.8)
Pre ASCT response CR ≤ CR	 10 (29.4) 24 (70.6)	 By PET 9 (26.5)
Post ASCT response CR Progression	 30 (88.2) 4 (11.8)	
Indication for ASCT: Partial Response Progression Early relapse (<6 months) Late relapse (> 6 months)	 13 (38.2) 5 (14.7) 5 (14.7) 11 (32.4)	

*CR: Complete Response; +PR: Partial Response; §DHAP: Dexamethasone, Cisplatin, Cytarabine; **ICE: Ifosfamide, Carboplatin, Etoposide; ++GDP: Gemcitabine, Cisplatin, Dexamethasone; § §MA: Methotrexate, Cytarabine; ***Codox-M-IVAC: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, Methotrexate, Ifosfamide, Cytarabine, etoposide; +++ESHAP: Etoposide, Cytarabine, Methylprednisolone, Cisplatin; §§§R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Prednisone.

TABLE 2. Characteristics of Groups 1 and 2

	Late relapse (Group 1) n (%)	Primary refractory and early relapse (Group 2) n (%)	p
N: 34	11	23	
Median age (rage)	50 (29-65)	57 (32-71)	0.093
Second line therapy DHAP* ICE+ GDP§ MA** Codox-M-IVAC++ ESHAP§§ R-CHOP***	 4 (36.4); +R 2 (18.2) 5 (45.5); +R 4 (36.4) 1 (9.1) 0 0 0 1 (9.1)	 11 (47.8); +R 3 (13) 5 (21.7) 3 (13) 2 (8.7) 1 (4.3) 1 (4.3) 0	NS
Rituximab in second line	7	3	0.003
Response at ASCT+++ CR§§§ ≤ CR	 3 (27.3) 8 (72.7)	 7 (30.4) 16 (69.6)	 0.84

*DHAP: Dexamethasone, Cisplatin, Cytarabine; +ICE: Ifosfamide, Carboplatin, Etoposide; §GDP: Gemcitabine, Cisplatin, Dexamethasone; **MA: Methotrexate, Cytarabine; ++Codox-M-IVAC: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, Methotrexate, Ifosfamide, Cytarabine, etoposide; §§ESHAP: Etoposide, Cytarabine, Methylprednisolone, Cisplatin; ***R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Prednisone; +++ ASCT: Autologous Stem Cell Transplantation; §§§CR: Complete response.

FIGURE 1. Flowchart of DLBCL transplanted patients

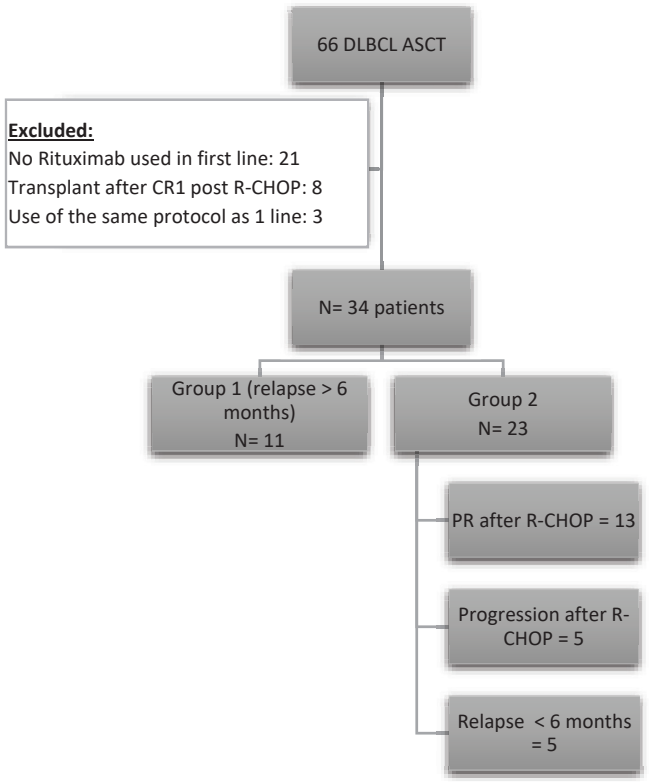


FIGURE 2. **Response before and after Autologous Stem Cell Transplantation.**

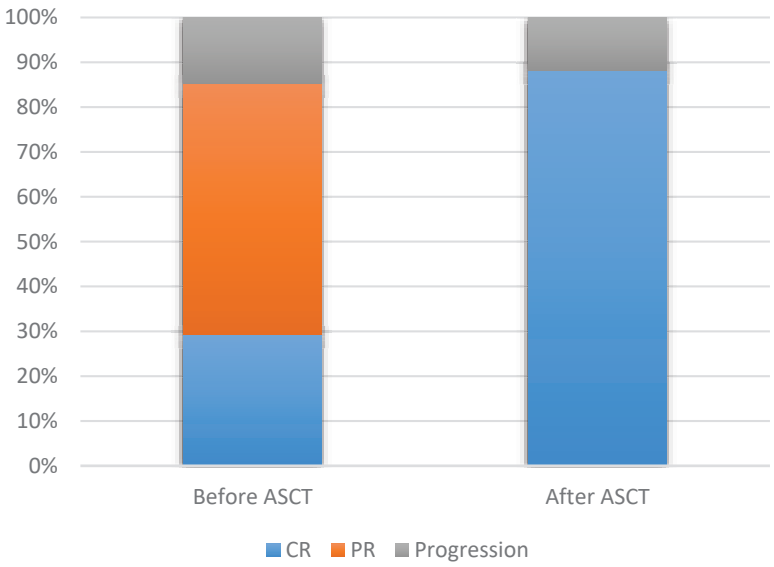


FIGURE 3. **Overall Survival in the entire cohort.**

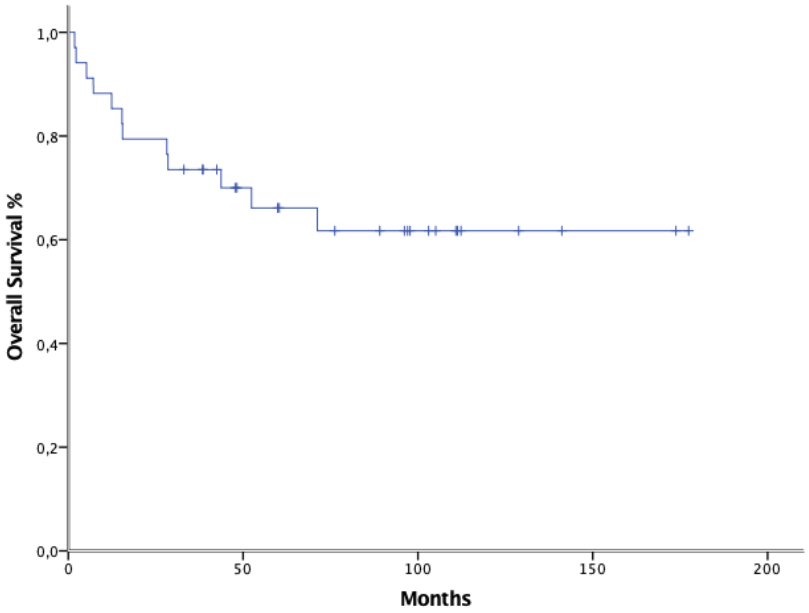


FIGURE 4. **Overall Survival according to time to relapse or primary refractory to R-CHOP.**

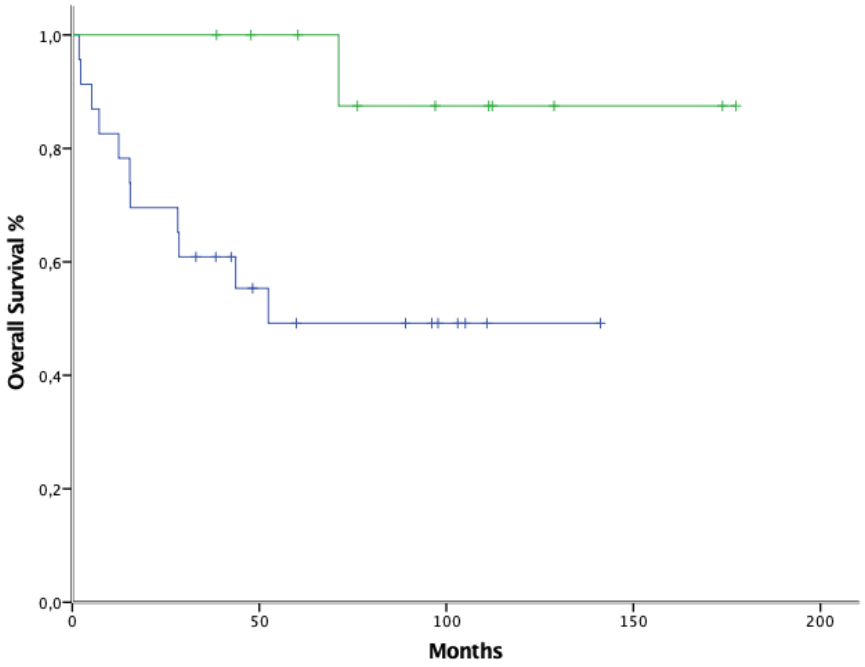
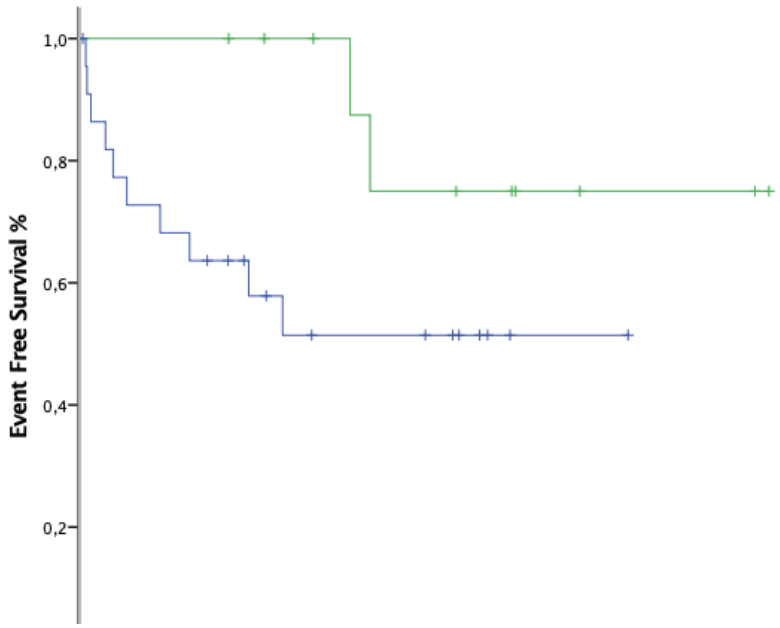


FIGURE 5. **Event Free Survival according to time to relapse or primary refractory to R-CHOP.**



REFERENCES

1. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. Chop Plus Rituximab Vs. CHOP alone in elderly patients with Diffuse LArge B-Celll Lymphoma. N Engl J Med. 2002;346:235-242.
2. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous Bone Marrow Transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive Non-Hodgkin's Lymphoma. N Engl J Med. 1995;333:1540-1545.
3. Vose JM, Zhang MJ, Rowlings PA, Lazarus HM, Bolwell BJ, Freytes CO, et al. Autologous Transplantation for Diffuse Aggressive Non-Hodgkin's Lymphoma in Patients Never Achieving Remission: A Report from the Autologous Blood and Marrow Transplant Registry. JCO 2001;19(2):406-413.
4. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. JCO 2010;28(27):4184-4190.
5. Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti V, Kouroukis CT, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. JCO 2014;32(31):3490-3496.
6. Kewalramani T, Zelenetz AD, Hedrick EE, Donnelly GB, Hunte S, Priovolos AC, et al. High-Dose Chemoradiotherapy and Autologous Stem Cell Transplantation for Patients with Primary Refractory Aggressive Non-Hodgkin Lymphoma: An Intention-to-Treat Analysis. Blood 2000;96(7):2399-2404.
7. Hitz F, Connors JM, Gascoyne RD, Hoskins P, Moccia A, Savage KJ, et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. Ann Hematol 2015;94(11):1839-1843.
8. Vardhana SA, Sauter CS, Matasar MJ, Zelenetz AD, Galasso N, Woo KM, et al. Outcomes of primary refractory diffuse large B-cell lymphoma (DLBCL) treated with salvage chemotherapy and intention to transplant in the rituximab era. Br J Haematol 2017;176(4):591-599.
9. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. JCO 1999;17(4):1244-1244.
10. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. JCO 2014;32(27):3059-3067.
11. Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, 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):1-8.
12. Bal S, Costa LJ, Sauter C, Litovich C, Litovich C, Hamadani M. Outcomes of Autologous Hematopoietic Cell Transplantation in Diffuse Large B Cell Lymphoma Refractory to Firstline Chemoimmunotherapy. Biology of Blood and Marrow Transplantation. Transplant Cell Ther 2021;27(1):55.e1-55.e7.
13. Filliatre-clement L, Maucort-Boulch D, Bourbon E, Karlin L, Safar V, Bachy E, et al. Refractory diffuse large B-cell lymphoma after first-line immuno-CT: Treatment options and outcomes. Hematol Oncol 2018;36(3):533-542.
14. Arboe B, Olsen MH, Gørløv JS, Duun-Henriksen AK, Dalton SO, Johansen C, et al. Treatment intensity and survival in patients with relapsed or refractory diffuse large B-cell lymphoma in Denmark: A real-life populationbased study. Clin Epidemiol 2019;11:207-216.
15. Suzuki T, Maruyama D, Miyagi-Maeshima A, Nomoto J, Tajima K, Ito Y, et al. Clinicopathological analysis of primary refractory diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone chemoimmunotherapy. Cancer Med 2021;10(15):5101-5109.
16. Shah NN, Ahn KW, Litovich C, He Y, Sauter C, Fenske TS, et al. Is autologous transplant in relapsed DLBCL patients achieving only a PET+ PR appropriate in the CAR T-cell era? Blood 2021;137(10):1416-1423.
17. Lekakis LJ, Moskowitz CH. The Role of Autologous Stem Cell Transplantation in the Treatment of Diffuse Large B-cell Lymphoma in the Era of CAR-T. Hemasphere 2019;3(6):e295.