

ORIGINAL ARTICLE

Survival in adolescents and young adults with B-cell non-Hodgkin's lymphoma in a referral hospital in Peru

Supervivencia en adolescentes y adultos jóvenes con linfoma no Hodgkin de células B en un hospital de referencia en Perú

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ABSTRACT

Objective: Compare the survival rates between pediatric and adult regimens for adolescents and young adults with B-cell non-Hodgkin lymphoma in Peru.

Materials and methods: This retrospective study included patients aged 10-39 years with B-cell non-Hodgkin lymphoma (2010-2016). Characteristics were analyzed using Fisher's exact test, and survival differences were compared.

Results: Thirty-one adolescents and young adult patients (6 with pediatric regimens, and 25 with adult regimens) were included. The 3-year overall survival rate was 100% for the pediatric group and 64% for the adult group ($p=0.13$). The only patient in the pediatric regimen who relapsed, achieved a second complete remission with Rituximab plus ifosfamide, carboplatin, etoposide and autologous stem cell transplantation, while all patients of the adult regimen group died of progressive disease. **Conclusions:** our findings suggest that adolescents and young adults with the diagnosis of B-cell Non-Hodgkin's lymphoma have better survival rates in comparison to those who are treated with adult regimens. Multicenter studies with a larger number of patients are required to confirm these results.

Keywords

Survival; Lymphoma, B-Cell; Lymphoma, non-Hodgkin; Adolescent, Young adult; Cancer (source: MeSH NLM).

RESUMEN

Objetivo: Comparar las tasas de supervivencia entre los regímenes pediátrico y adulto para adolescentes y adultos jóvenes con linfoma no Hodgkin de células B en Perú. **Materiales y métodos:** Este estudio retrospectivo incluyó pacientes de 10 a 39 años con linfoma no Hodgkin de células B (2010-2016). Las características se analizaron mediante la prueba exacta de Fisher y se compararon las diferencias de supervivencia. **Resultados:** Se incluyeron 31 pacientes adolescentes y adultos jóvenes (6 con regímenes pediátricos, 25 con regímenes para adultos). La tasa de supervivencia global a los 3 años fue del 100% para el grupo pediátrico y del

64% para el grupo de adultos ($p=0,13$). El único paciente del régimen pediátrico que recayó logró una segunda remisión completa con rituximab más ifosfamida, carboplatino, etopósido y trasplante autólogo de progenitores hematopoyéticos, mientras que todos los pacientes del grupo del régimen de adultos fallecieron por progresión de enfermedad. **Conclusiones:** nuestros resultados sugieren que adolescentes y adultos jóvenes con diagnóstico de linfoma no Hodgkin de células B tienen tasas de supervivencia comparados con aquellos que son tratados con regímenes para adultos. Sin embargo, se necesitan estudios con un mayor número de pacientes.

Palabras clave

Supervivencia; Linfoma de células B; Linfoma no Hodgkin; Adolescente, Adulto joven; Cáncer (fuente: DeCS BIREME).

INTRODUCTION

Adolescents and young adults (AYAs) cancers account for approximately 8% of all Non-Hodgkin's lymphoma (NHL) ⁽¹⁾. Most of the NHLs in AYAs are mature B-cell lymphomas, and the histological subtypes are divided in accordance with age. Burkitt's lymphoma is the most common NHL in children aged <15 years (38%), while diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBL) are most common after 15 years of age (55-70%) ^(1,2).

B-cell lymphoma treatment in AYAs depends on whether a pediatric or adult approach is taken. This is the case with BL, DLBCL, and PMBL, which are treated with the same approach in most pediatric trials but not in the adult ones ⁽³⁾. The Berlin-Frankfurt-Munster (BFM) and the French-American-British/Lymphomes Malins de Burkitt 96 (FAB/LMB96) groups are the most used in pediatric protocols. These regimens achieve event-free survival (EFS) rates of 82% and 87%, respectively ^(4,5). In adult patients, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is the standard first line treatment for DLBCL, which has a 6-year EFS of 60-80% ⁽⁶⁾. In BL and PMBL, the standard regimen is DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), and the EFS is 85% and 93%, respectively ^(7,8).

AYAs with NHL generally have a lower survival rate than children, suggesting the presence of a different disease ⁽²⁾. Additionally, although treatment differences between pediatric and adult regimens regarding survival outcomes between B-cell lymphomas in AYAs have been reported separately, little is known about which of these regimens is the best for the AYA population. This study therefore aims at comparing the survival rates between pediatric

and adult regimens for AYA patients with B-cell lymphoma in Peru. We hypothesized that the pediatric approach is associated with better survival rates than the adult approach. The main endpoint of this study is, therefore, overall survival (OS) between groups, which was defined as the percentage of AYAs patients belonging to the treatment group who are still alive for a certain period of time after being diagnosed or starting treatment.

MATERIALS AND METHODS

Study design and setting

We conducted a retrospective study, with a cohort of patients with an anatomopathological diagnosis of B-cell NHL were identified and reviewed retrospectively through a search of clinical records at the Department of Oncology and Radiotherapy, Hospital Nacional Edgardo Rebagliati Martins, Peru.

Subjects

Patients were diagnosed between January 2010 and December 2016 and their cases were followed up until June 2018. The anatomopathological diagnosis of B-cell NHL followed the histopathological criteria defined in the World Health Organization Classification ⁽⁹⁾. Additional inclusion criteria were as follows: ⁽¹⁾ patients aged 10-39 years, ⁽²⁾ anatomopathological diagnosis of B-cell NHL performed by the Department of Pathology at Hospital Nacional Edgardo Rebagliati Martins (or reviewed and confirmed by our pathologist if biopsy was performed outside of our hospital), and ⁽³⁾ patients who completed at least 3 cycles of chemotherapy. We excluded patients with prior treatment in other healthcare centers, lost or destroyed medical records, and incomplete or insufficient data for pathological characterization.

We collected, from medical records, data about the following sociodemographic and clinical covariates: gender, age, place of residence, Eastern Cooperative Oncology Group performance status (ECOG-PS), B symptoms, histology subtype, clinical stage, extranodal disease, and clinical stage, for B-cell NHL, we used the Ann Arbor staging system for adult's patients and Murphy/St Jude for pediatric patients⁽¹⁰⁾.

Data collection

Using a standardized case report form, an oncology resident collected all data related to this study.

Data analysis

We used Fisher's exact test to compare categorical variables. OS and EFS were estimated using Kaplan-Meier curves and the log-rank test, with a significance level of 5%. All statistical procedures were conducted using Stata/SE version 16.1 (StataCorp, College Station, TX) for Windows 10 Pro 64-bit.

Ethical approval

The study was approved by the Ethics Committee of the Hospital Nacional Edgardo Rebagliati Martins (Letter No. 2034-GNHERM-GRPR-ESSALUD-2018) for the use of patient data. The information was drawn exclusively from medical records and no contact was ever made with the patients. Additionally, no information that could identify the patient was collected; hence, informed consent was not requested. We ensured that the data were securely and anonymously stored.

RESULTS

Among patients who were diagnosed with B-cell lymphomas, only 31 met the inclusion criteria. Six patients were treated with pediatric regimens (LMB96 with/without rituximab and BFM95), and 25 patients with adult regimens like R-CHOP (rituximab, prednisone, vincristine, cyclophosphamide, and doxorubicin), and methotrexate at high doses) or R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), and methotrexate at high doses) (Figure 1).

The median age of the pediatric and adult regimen groups was 13.3 and 33.8 years, respectively (p=0.001). The stage of disease, extranodal disease, B symptoms, and histology subtype were similar between the groups. The proportion of patients with ECOG-PS of ≤1 was significantly higher in the pediatric regimen group than in the adult regimen group (100% vs 64%, p=0.03). Regarding the relapse rate, there is no statistically significant difference (17%, n=1, in the pediatric regimen group, and 32%, n=8, in the adult regimen group; p=0.43). Among relapsed cases, the only patient in the pediatric regimen who relapsed, achieved a second complete remission with R-ICE (rituximab, ifosfamide, carboplatin, and etoposide phosphate) and autologous stem cell transplantation. Meanwhile, all patients from the adult regimen who relapsed died of progressive disease (Table 1).

For the whole cohort, the 3-year EFS was 67% and the OS was 70%. The 3-year EFS was 83% in the pediatric treatment group and 64% in the adult treatment group

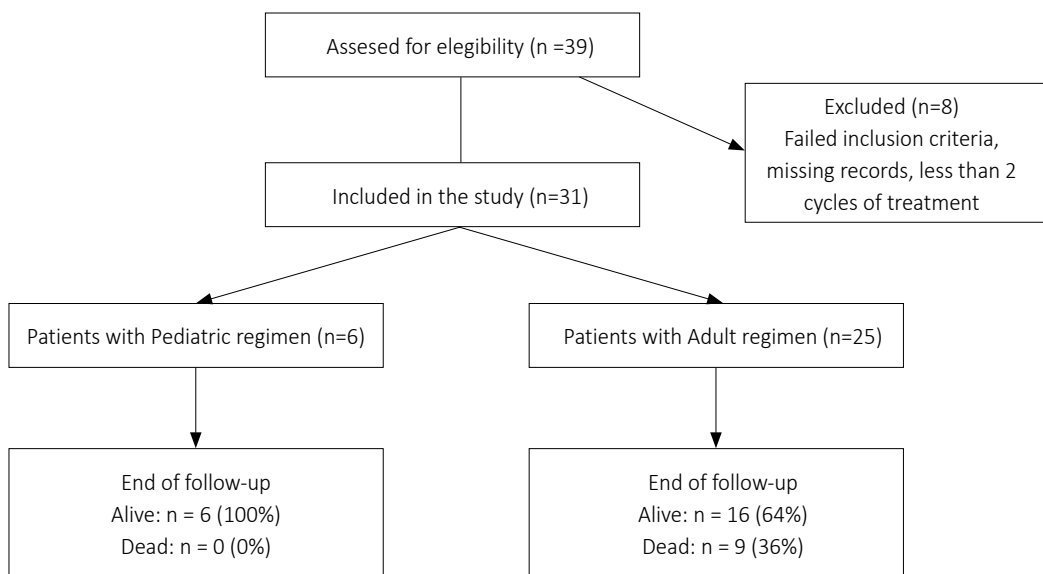


Figure 1. Flow-chart of participation in the study.

Table 1. Characteristics of the total study cohort and according to the regimens.

| | Pediatric regimens N=6 | Adult regimens N=25 | p-value |
|--|---------------------------|------------------------|----------|
| Gender (male/female) | 3/3 (50%/50%) | 14/11 (56%/44%) | 0.79* |
| Age, years (median, range) | 12.5 (10-15) | 33.8 (24-39) | 0.0002** |
| Place of residence (Lima/outside Lima) | 2/4 (33%/67%) | 16/9 (64%/36%) | 0.208* |
| Stage (I-II/III-IV) | 2/4 (33%/67%) | 9/16 (36%/64%) | 0.902* |
| Extranodal disease (≤ 1 , ≥ 2) | 6/0 (100%/0%) | 19/6 (76%/24%) | 0.309* |
| B symptoms (yes/no) | 4/2 (67%/33%) | 16/9 (64%/36%) | 0.902* |
| Histology (DBGCL/Burkitt's/other) | 5/1/0 (83%/17%/0%) | 22/1/2 (88%/4%/8%) | 0.598* |
| ECOG-PS (≤ 1 , ≥ 2) | 6/0 (100%/0%) | 16/9 (64%/36%) | 0.101* |
| Follow-up, years (median, range) | 2.6 (1.7-3.3) | 3.6 (0.5-6.9) | 0.201** |
| Relapse rate | 1 (17%) | 8 (32%) | 0.423* |
| Death rate | 0 (0%) | 9 (36%) | 0.101* |

* By Fisher's exact test

**By Mann-Whitney U test

ECOG-PS: Eastern Cooperative Oncology Group performance status.

($p=0.35$). The 3-year OS was 100% in the pediatric treatment group and 64% in the adult treatment group ($p=0.13$) (Figure 2).

DISCUSSION

Our alternative hypothesis was to prove that the pediatric approach is associated with a better survival than the adult approach. In our preliminary report, we suggested a trend of better survival rates in AYA patients with B-cell NHL when using the pediatric approach. This result could be supported by previous findings showing that the outcome after treatment for children with NHL is superior to that observed in adults^(11,12).

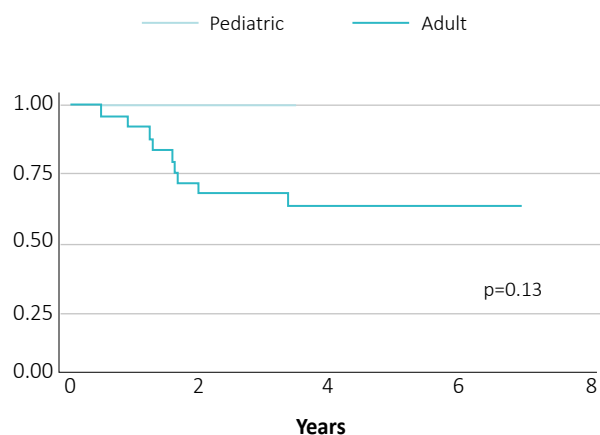


Figure 2. Overall survival by regimen of treatment.

Our result of better survival rates with the pediatric approach could be due to the fact that our patients who were treated with the pediatric approach were younger (10-15 years old) and our patients who were treated with the adult approach were older (24-39 years old). For instance, although the research question of comparing regimens was not directly assessed between AYAs with B-cell lymphoma, a large German trial showed a significant difference between age groups, wherein the younger patients (<15 years old) had better 5-year EFS than the older AYA group (15-18 years old) (85% vs 79%) and both groups were treated with the same pediatric BFM protocol⁽⁴⁾. The rationale could be that a biological factor such as age is an important prognostic factor for survival.

Another theory that could explain our results is that pediatric approaches are intensive regimens characterized by higher doses and broader drug combinations, compared to adult approaches. Even though pediatric treatments do not usually employ protocols that include rituximab use, as adult approaches do⁽¹³⁾. For instance, our results are supported by some retrospective studies showing that AYA lymphoblastic leukemia had a better outcome when treated with pediatric protocols^(14,15).

Most pediatric B-cell NHL protocols worldwide treat BL and DLBCL on the same risk-stratified regimens with excellent outcomes. The BFM, for example, consists of 5 days of therapy pulses per course, based on dexamethasone, ifosfamide, cyclophosphamide, methotrexate, cytarabine, doxorubicin, etoposide, and intrathecal chemotherapy. The number of courses is



defined according to the spread of the disease. This treatment achieved a 5-year EFS of 82% for patients with BL, 85% for patients with DLBCL, and 57% for patients with PMLBL⁽⁴⁾. Meanwhile, the FAB/LMB96 consists of pulses of chemotherapy, which start with cyclophosphamide, vincristine, prednisone, and doxorubicin and continue with methotrexate at high doses, cytarabine, etoposide, and intrathecal chemotherapy, according to the risk classification. The 3-year EFS was 88% for the entire cohort^(2,5).

Another explanation for our findings is that compared with patients treated with the pediatric approach, those treated with the adult approach had a higher rate of adverse clinical features, such as an ECOG-PS of >1 (36% vs 0%) and extranodal compromise (24% vs. 0%), and a higher relapse rate (32% vs. 17%).

Importantly, previous studies on AYA B-cell lymphomas have made comparisons between the AYA population and adult population, and interestingly, there was a trend to use adult regimens in all of them. Also, it is remarkable that none of these studies compared pediatric protocols with adult protocols. For instance, Coso et al. demonstrated that AYAs aged 15-30 years who had B-cell lymphomas did not show differences in OS or EFS, compared with the adult population (31-65 years old), after receiving adult treatment (CHP [cyclophosphamide, doxorubicin, and prednisone], R-CHOP, or BEAM [carmustine, etoposide, cytarabine, and melphalan])⁽¹⁶⁾. In addition, Suzuki et al. found similar OS and PFS in an observational study in AYAs aged 40-60 years, the majority of whom received the CHOP or R-CHOP regimen⁽¹⁷⁾. The results of these two previous studies were quite similar to our results on the adult regimen.

On the other hand, Beck et al., who evaluated a cohort of patients aged 13-30 years with DLBCL, observed a lower 5-year EFS (52%) and OS (58%) than our results (EFS of 64% and OS of 64%). However, nearly 97% of patients were treated with adult protocols as described in their study⁽¹¹⁾.

In conclusion, this study revealed that AYA patients who were diagnosed with B-cell NHL treated with pediatric regimens had a trend toward higher survival rates than those treated with adult regimens, although the difference was not statistically significant.

Within the limitations of the study, it is the small sample size that could decrease its power and an observational design that could limit the availability of complete data. Additionally, patients in each age group received only one form of treatment (pediatric or adult, respectively) which prevented the comparison of their effectiveness within each of them. There were also no

patients between 16 and 23 years old. It is necessary to annotate that, since this study was carried out in a single center in Peru, generalization cannot be guaranteed. Another important limitation was that the follow-up was only carried out until 2018, and it could not be continued due to the unavailability of the researchers. However, the main strength was that our hospital is a highly specialized cancer referral center concentrating on the majority of NHL cases in the AYA population.

Finally, AYA is a population that deserves to be studied not only in its clinical-biological aspects but also to determine which are the best treatments, since it is, undoubtedly, a special group with a behavior different from that of the pediatric population and, according to our results, this study could be the basis for future experimental studies with a larger population and thus help determine the best approach in patients whose ages are within the AYA group.

This study was presented as an abstract in the Poster Discussion Plenary Session at the 6th International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin's Lymphoma, held on September 26-29, 2018, in Rotterdam, The Netherlands.

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