Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.202293354-357

Poor Prognosis of Diffuse Large B-Cell Lymphoma of the Breast: The Role of Dose-Dense Chemotherapy

Agustin Aviles[a*], Luis Silva[b], Sergio Cleto[b]

[a]*Oncology Research Unit, Oncoloy Hospital National Medical Center, IMSS, Mexico*

[b]*Hematology Department, Oncoloy Hospital National Medical Center, IMSS, Mexico*

ARTICLE INFO

Received:
30 April 2022
Revised:
5 June 2022
Accepted:
7 June 2022

Keywords:
Primary breast lymphoma, diffuse large B-cell lymphoma, dose-dense chemotherapy

ABSTRACT

Background: The aim of the study was to determine if the use of an intensive regimen (dose-dense) of chemotherapy may improve the response rate and outcome in patients with primary breast lymphoma (PBL), which is considered as lymphoma presentation with a poor prognosis.

Methods: Patients with pathologically confirmed diagnosis of diffuse large B-cell lymphoma with clinical presentation in the breast (PBL), > 18 years old, stage I and II, negative for immunodeficient syndrome, hepatitis A and B, previously untreated, and having non-germinal center cells were included in an open label clinical trial. Phase II patients received a dose dense regimen of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone).

Results: Between July 2006 and December 2016, seventy-eight patients were enrolled in the study. Complete response was achieved in 76 (94.4%) patients. Five patients relapsed, so progression free survival at 5 years was 94.0% (95% confidence interval (CI: 87% to 98%%): three patients achieved a second response and are alive; the overall survival at 5-years was 95.3 (96% CI: 89% to 102%). Relapse at central nervous system has not been observed. Severe granulocytopenia was observed in 42.8 (93.0%) cycles, but no death associated with treatment was observed.

Conclusion: The use of a dose-dense regimen of chemotherapy improved the outcome in these patients; although severe acute toxicities were frequent, they were well-controlled. Relapse in central nervous system was not observed. Thus, we considered that dose-dense chemotherapy should be employed for this group of patients.

INTRODUCTION

Primary breast lymphoma (PBL) is a rare lymphoma, arising in the breast without evidence of systemic disease. The most common histology is diffuse large B-cell lymphoma. This represents 0.5% of malignant breast tumors and 2% of all extranodal lymphomas. Until now, no clear treatment has been defined, probably due to the small number of cases[1]. Even in early stages I and II, prognosis is associated with poor prognosis and frequent relapse in the central nervous system. Multiple studies have been reported, but no definitive schedule has been established to improve the outcomes.[2-10] The role of radiotherapy has not been determined.

Dense-dose schedules have been employed in some cancers[11], with the hypothesis that these regimens can eliminate more resisting tumoral cells. Thus, this study aims to assess the efficacy and toxicities in patients with PBL and poor prognosis factors.

***Address for correspondence:**
Agustin Aviles,
Avenida Cuauhtemoc 330, Colonia Doctores, 06620, Ciudad de Mexico, MEXICO
Tel: +52 55 5627 6900
E-mail: mirandaolder73@gmail.com

METHODS

Between July 2006 and December 2016, we studied patients with pathological diagnosis of diffuse large B-cell lymphoma, which was confined to the breast, in early stages I or II, previously untreated, age >18 years old without previous treatment, with pathological diagnoses including a battery of monoclonal and polyclonal antibodies: CD45, CD20, CD19, CD5, CD10, bcl-2, bcl-6, and MUM1, performance status <2, negative for immunodeficiency human syndrome, hepatitis B and C and associated with poor prognosis with elevated LDH and non-GCB genotype. Patients with stage III and IV, or a history of CNS disease were excluded. Staging included complete physical examination, measuring the two dimensions of tumor, complete blood counts, and serum chemistry. We also considered serum determinations LDH, and B2M, Immunodeficiency, hepatitis B and C virus, bilateral mammography and ultrasound, computed tomography of neck, thorax, abdomen and pelvis. International Project Index (IPI) was employed to determine clinical risks.

Chemotherapy

- Cyclophosphamide, 1500mg/m^{2,}, IV, day 1
- Doxorubicin 75mg/m^{2,}, IV, day 1
- Vincristine 2mg, standard dose, IV, day 1
- Prednisone 60mg/m^2, oral, days 1 to 5, in each cycle.

They were programed to receive 6 cycles, every 14 days, if hemoglobin>12 g/dL, granulocytes>1x 10^9, platelets>100x10^9. If, these values are abnormal, the cycle was delayed, until hematological recovery. Four weeks after chemotherapy, the patient received radiotherapy at a dose and schedule previously reported[10]. To diminish the risks of severe neutropenia, granulocyte-colony stimulating factors, 5mg/kg, daily, was administered from day 2 to 12 of each cycle. Response criteria was according to the International criteria.[12]

Statistical analysis

Progression free survival (PFS) was considered from the beginning of the treatment to the date of failure, relapse, progression, toxic death or death from any cause; Overall survival (OS) was considered from diagnosis to death from any cause. Prognostic factors were age, stage, performance status, International Project Index (IPI) score, tumor size, genotype, use of hormonal therapy, smoking, marital status and previous pregnancies. In regards to PFS and OS, we used the Kaplan-Meir methods and comparison between groups, we used the log-rank test: Univariate analysis was carried out using Cox proportional hazards model; variables with a P<0.01 in univariate analysis were included in the multivariable analysis and the results were reported with a hazards ratio.

Eighty patients were considered, but two were excluded because they were at stage IV, so 78 patients were included in the study.

RESULTS.

Table 1 shows the clinical and laboratory characteristics. As expected in patients with true PGL, they were younger, their performance status and IPI were low, and only one patient had a tumor size>10cm.

All patients were considered for treatment. The overall response rate was 97.4% and the complete response also was 97.4%. In both cases, the 95% confidence interval was 91.6 % to 106.4%. Relapse was observed in five patients, who were treated with salvage chemotherapy without stem cell transplant and three patients achieved a second longer response. With a median follow-up of 9.8 (range 5.8 to 14.7) years, the actuarial curves at 5 years showed that PFS was 93.45 %, and OS was 94.6%.

The most frequent adverse event was neutropenia: 428 (93.0%) cycles. The delay in treatment was observed in 107 (22.8 %), and hematological recovery was observed at a median of 6.8 (5 to 13) days. No death related to treatment was observed. At a longer follow-up, cardiac toxicity, second neoplasm and acute leukemia have not been observed.

DISCUSSION

The present study aimed to determine whether a dose-dense anthracycline-based regimen can improve the CR and outcome. The findings showed that six cycles of CHOP were beneficial in these patients, although they had adverse prognostic factors, such as non-GCB genotype, tumor size>5cm, elevated levels of LDH and beta-2-microglobulin, with more that 90% of patients alive, disease-free at more than 5 years. On the other hand, the central nervous system relapses are frequent in this neoplasm, but in the present study, we did not observe this adverse event.

Multiple studies have been performed, but no definitive results have been observed. The CHOP regimen is the standard therapy for diffuse large B-cell lymphoma. The addition of rituximab to CHOP remains controversial and some studies have reported improved outcomes while most did not observe any benefit.[13-15] Luo *et al*. employed multiple regimens of combined chemotherapy, but the number of patients in each group was very small to achieve definitive conclusions.[16]

Table 1. Clinical and laboratory characteristics

Variables	N(%)	P-Value
Number	78 (100)	
Age (years) median	59.9	
Range	36 – 73	
Sex		
Female	78 (100)	
Smoking		
Yes	31(39.7)	
No	47 (60.2)	0.865
Married		
Yes	65 (83.3)	
No	13 (16.6)	0.120
Previous pregnancy		
Yes	69 (88.4)	
No	9(11.5)	0.02
Hormonal therapy		
Yes	58 (74.3)	
>3 years	24 (41.3)	
<3 years	34 (58.6)	0.866
No	20 (25.6)	0.035
Stage I	44 (56.4)	
II_1	34 (43.5)	0.756
Tumor size (cm)		
0-5	39 (50.0)	
5.1 – 10	38(48.7)	0.824
>10	1(1.2)	
Performance status		
0,1	67(85.7)	
2	11(14.1)	0.045
IPI		
0	36(46.1)	
1	35 (44.8)	0.775
2	7 (8.9)	
Genotype		
No-GCB	36(78(100)	
LDH High	78 (100)	
B2M high	78 (100)	

IPI: International Project Index, GCB: germinal center B-cells; LDH. Lactic dehydrogenase, B2M: beta 2microglobulin.

CONCLUSION

The present study was biased regarding the evidence: the number of patients was small, and the study was performed in a single center. Our hospital is a tertiary reference cancer center, to which about 20,000 new cases of cancer refer, including a median of 455 new patients with malignant lymphoma. It is evident that these results should be validated in other studies, but the small number of patients prevented us from performing controlled clinical trials. The results showed that the use of a dose dense regimen of chemotherapy improves complete response rate and the outcome.

ETHICAL CONSIDERATIONS

The study was conducted according the Declaration of Helsinki, and was approved by the Ethical and Scientific Committee of our Hospital (2006-HO-07). All patients signed informed consent to participate in the study.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

FUNDING

This work did not receive any financial support and was performed with the resources of the Instituto Mexicano del Seguro Social.

REFERENCES

1. Thomas A, Link RK, Altekruse S, Romiti A, Schoeder MS. Primary breast lymphoma in the United States. *J Nat Cancer Inst* 2012; 109;294djw. doi: 10.193/jnci/djw294.
2. Yhim HY, Kang HJ, Chus YH, Kim SJ, KIM WS, Kim JS, et al. Clinical outcomes and prognostic factors in patients with breast diffuse large B-cell lymphoma. *BMC Cancer* 2010;10:321. doi: 108186/1471-2407-10.321.
3. Jia Y, Sun G, Liu Z, Whang W, Zhou X. Primary breast diffuse large B-cell lymphoma. A population based study from 1975 to 2014. *Oncotarget* 2018; 9:3956.3907. doi: 10.18632/oncotarget.23285.
4. Hu S, Song Y, Sun X, Su L, Zhang W, Jia J, et al. Primary breast diffuse large B-cell lymphoma in the rituximab era: Therapeutic strategies and patterns of failure [published correction appears in Cancer Sci. 2019 Apr;110(4):1503]. *Cancer Sci*. 2018;109(12):3943-3952. doi:10.1111/cas.13828.
5. Ryan G, Martinelli C, Kuper-Hommel M, Tsang R, Pruneri G, Yuen K, et al. Primary diffuse large B-cell lymphoma of the breast. Prognosis factors and outcome of the study the Internartional Extranodal Lymphoma Study Group. *Ann Oncol* 2008; 19:233-241. doi: 10.1093/annoncol/mdm471.
6. Zhang T, Zhao H, Cui Z, Xu H, Liu X, Li Y, et al.: A multicentric retrospective study of primary breast diffuse large B-cell lymphoma and high-grade B-cell lymphoma treatment strategies and survival. *Hematol* 2020:25:203-210. doi 10.1080/1607-8454.2020/1769419.
7. Liu PP, Wang KF, Jin JT, Bi XW, Sun P, Wang Y, et al. Role of radiotherapy in primary breast lymphoma diffuse large B-cell lymphoma in the rituximab era. *Cancer Med* 2018:7;1895-1889. doi: 10.1002/cam4.1457.
8. Validare P, Capovilla M, Asscano B, Kroud Y, Goudefroy R, Planchet C, et al.: Primary breast non-Hodgkin lymphoma . Single center styydt of initial characteristics, natural history and prognostic factors. *Am J Hematol* 2009;84:133-139. doi: 10/1002/ajh.21353.
9. Hossein PJ, Maragulia JC, Salzberg MP, Press O, Habermann T, Vose JM et al.: A multicenter study of primary breast diffuse large B-cell lymphoma in the rituximab era. *Br J Haematol* 2014;105;359-363. doi: 10.1111/bjh.12753.
10. Aviles A, Delgado S, Nambo MJ, Neri N, Murillo E, Cleto S.: Primary breast lymphoma. Results of a controlled clinical trial. *Oncology* 2005;256-260. doi: 10.1159/00008833.
11. Aviles A, Nambo MJ, Neri N: Primary gastric diffuse large B-cell lymphoma. The role of dose-dense chemotherapy. *J Oncol Pharm Practice* 2019;25:1682-1686. doi:10.1177/1078115821.880454.
12. Cheson BD, Pfister B, Juweid ME, Gascoyne RD, Specht L, Horning S, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007:576-586. doi: 10.1200/jco2006.29.2803.
13. Bataillard EI, Cheah CY, Maurer MJ, Khurana A, Eyre T, El-Galaly. Impact of R-CHOP intensity in survival outcome in diffuse large B-cell lymphoma. *Blood Adv* 2021; 5:2426-2436. doi 10.1182/bloodadvances.20211004655.
14. Aviles A, Castañeda C, Neri N, Nambo MJ. Rituximab and dose-dense chemotherapy in lymphoma primary of the breast. *Haematologica* 2007;92:1147-1148. doi 10.3324/hematol.1089.
15. Yhim HY, Yoon DH, Kim SJ, Yang DH, Eom HS, Kim KH, et al. First line treatment for primary breast diffuse large B-cell lymphoma using immunotherapy and central nervous system prophylaxis. *Cancers* 2020; 12:2192. doi 10/339/cancers1208219216.
16. Luo H, Yi P, Wang W, Li K, Meng L, Li J, et al. Clinicopathological Features, Treatment, and Prognosis in Primary Diffuse Large B Cell Lymphoma of the Breast: A Retrospective Study of 46 Patients. *Med Sci Monit*. 2019 Nov 17;25:8671-8682. doi: 10.12659/MSM.917550.

How to Cite This Article

Aviles A, Silva L, Cleto S. Poor Prognosis of Diffuse Large B-Cell Lymphoma of the Breast: The Role of Dose-Dense Chemotherapy. Arch Breast Cancer. 2022; 9(3): 354-7.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/585