Rituximab and dose dense chemotherapy in primary breast lymphoma

Treatment of primary breast lymphoma (PBL) remains unsatisfactory. We assess a clinical study to evaluate efficacy and toxicity of a dose dense regimen (CEOP-14) and rituximab in 32 previously untreated female patients with PBL in early stage. There was no difference in complete response rate (87%), event free-survival (75%) and overall survival (63%) compared with historical patients.

Haematologica 2007; 92:1147-1148

Primary breast lymphoma (PBL) with no evidence of presentation elsewhere, account for 0.5 to 1 % of all malignant lymphomas. More than 80% of PBL are B-cell lymphoma and are in most cases CD20$^+$. Generally, reports included small numbers of patients and treatment has been retrospectively analyzed.[1-7] There is still no standard universal management. Most studies agree that combined therapy: anthracycline-based chemotherapy and radiotherapy (involved field) is the best therapeutic schedule in patients with PBL.[6,8] In a previous controlled study we demonstrated that CHOP (cyclophopshamide, doxorubicin, vincristine and prednisone) chemotherapy followed by radiotherapy involving the breast or chest wall using a tangential technique and including the breast and its lymphatic axial and supraclavicular lymphatics is superior to radiotherapy or chemotherapy alone.[9] However, systemic relapse remains high and overall survival at 10 years is 76%. Dose dense chemotherapy and rituximab are considered the treatment of choice in patients with nodal diffuse large cell lymphoma. We began a single arm, prospective study to evaluate if rituximab and a dose dense chemotherapy regimen can improve outcome measured for event-free survival (EFS) and overall survival (OS).

Between June 1999 to December 2002, 2,788 cases were diagnosed as malignant lymphoma in our Institution. Patients who fulfilled the following criteria were considered candidates for inclusion in the study: diagnosis of PBL, diffuse large cell histology, CD 20$^+$, early stage IE or IIE, performance status according to the ECOG are ≤2; previously untreated, age >18 years to <65 years , negative for immunodeficiency virus test, and normal hepatic, renal, pulmonary and cardiac function (measured with left ejection ventricular function, normal >50%). In all cases complete inmunophenotype was performed: CD 45, CD20, CD 10, CD 30, and CD 3. Molecular and cytogenetic studies are not available routinely in our Institution. All patients completed the staging procedures that including physical examination, complete blood count, serum chemistry, computed tomography of thorax, abdomen and pelvis, aspirate and bone marrow biopsy, immunodeficiency virus test and lumbar puncture.

Treatment. In this single-arm, prospective study, consecutive patients were allocated to receive: cyclophosphamide 1500 mg/m^2, iv, day 1, epirubicin 120 mg/m^2, iv, day 1, vincristine 1.2 mg/m^2, iv, day 1, prednisone 100 mg/m^2, po, daily, days 1 to 5, rituximab 375 mg/m^2, iv, day 1. Granulocyte colony-stimulating factor (G-CSF), 5 ug/kg/day, began on day 2 and was administered to avoid severe granulocytopenia. The planned chemotherapy was 6 cycles, and each cycle was administered every 14 days, if patients had >1.5/10^9 and platelets >150×10^9. If granulocytopenia or thrombocytopenia grade 1 or 2 were observed, cycle was delayed until hematological recovery.

Table 1. Main characteristics.

	No	*(%)*
Number	32	100
Age (mean) year	45.9	
< 40 years	16	50
> 40 years	16	50
Tumor size:		
< 5 cm	15	46
> 5 cm	17	53
Stage		
IE	24	74
IPI clinical risk		
Low	26	81
Low-intermediate	6	18
DHL level		
Normal	31	96
ECOG		
0	23	71
1	8	25
2	1	3

Table 2. Toxicity.

Grade	*I*	*II*	*III*	*IV*	
No (%)					
Total (%)					
Cycles	189 (100)				
Granulocytopenia	36 (19)	11 (6)	10 (6)	15 (7)	0
Thrombocytopenia	5 (3)	5 (3)	0	0	0
Infection-related Granulocytopenia	8 (4)				
Febrile neutropenia	11 (6)				
Death-related treatment	0				
Neurotoxicity	18 (9)	11 (6)	5 (3)	0	0
Cardiac toxicity	0				

If at 28 days this was not observed the patient was excluded from the study. No dose reduction was considered. Four weeks after the last cycle of chemotherapy, the patient received radiotherapy at dose and schedule previously reported.[9]

Restaging was similar to a previous study.[9] Patients gave their informed consent to participate in the study which was approved by the Ethical Committee of our Institution. The study did not received any financial support and was conducted under the clinical and ethical guides or the Instituto Mexicano del Seguro Social with the own resources. EFS was considered from the beginning of the treatment to the date of failure(relapse, progression, toxic

death or death from any cause). OS was considered from diagnosis to death from any cause. Prognostic factors which can influence response rate, EFS and OS: age, performance status, stage, tumor size, lactic dehidrogenase (LDH) level, and International Prognostic Index (IPI). These factors were uniformly presented in our patients so statistical analyses were not performed. β2 microglobulin were only available in 11 patients. Thirty-two women were included in the study. Median follow-up was 64.5 months (range 43 to 71 months). Table 1 shows main patient characteristics. Median age was 56.7 years (range 31 to 65 years old). All patients were analyzed according to intention to treat. A complete response was observed in 28 cases (87%), four patients showed disease progression during chemotherapy and did not respond to salvage chemotherapy. Twenty-eight patients completed the program, four patients received only 5 cycles for progression. Twelve patients relapsed: lung (5), lung, bone marrow and nodal disease (4), lung, bone and bone marrow (3). Relapse at the central nervous system (CNS) was not observed. Actuarial curves at 3-years showed that EFS was 75%. Eight patients died from tumor progression and 4 responded to salvage chemotherapy. Therefore, actuarial curves at 3 years showed OS to be 63%. Treatment has been well tolerated. Table 2 shows the hematologic and non-hematologic toxicity.

Treatment of PBL lymphoma must still be defined. This is still probably because it is a rare presentation of malignant lymphoma and only a small number of patients can be diagnosed even in tertiary centers. Until now, no multicentric studies has been carried out in PBL. The combination of chemotherapy and radiotherapy appears to be the best treatment option in these patients (1,2,5,6), but , at least 26% of those with early stages and good prognostic factors die from tumor progression.[9] It is, therefore, evident that other therapeutic options must be explored. The use of rituximab has recently been introduced in the treatment of diffuse large B-cell lymphoma and improved EFS and OS have been observed. We, therefore, combined a dose dense chemotherapy and rituximab to evaluate the possibility of improving outcome in PBL. Although treatment was well tolerated, outcome was not improved. Dose intensity of cyclophosphamide, epirubicin and rituximab was >90%. Radiotherapy was also administered according to programmed dosage and schedule. Prognostic factors such as age, IPI, stage, levels of LDH and tumor size have been considered to predict outcome in PBL.[3,6,7] But our patients presented low clinical risk, uniform age performance status and tumor size, with normal levels of LDH in most cases. They were, therefore, considered to have a good prognosis. However, EFS and OS did not differ from studies with combined therapy.[8,9] PBL has been thought to have a higher risk of relapse at the central nervous system which have been associated with prognostic factors such as high clinical risk, high levels of LDH, involvement of >1 extranodal.[10] and probably for this reason we did not observed these However, our patients did not present these adverse prognostic factors and such complications were not be observed. Definitive conclusions cannot be made in such a small series of patients. But given that aggressive chemotherapy and rituximab did not improve outcome, innovative therapies that include reinforcement or intensification of dose should be considered to improve OS in this very special patient group with limited disease and good prognosis factors.

Agustin Avilés, Claudia Castañeda,° Natividad Neri,° Sergio Cleto,° M. Jesús Nambo°*

**Oncology Research Unit; °Department of Hematology, Oncology Hospital, National Medical Center, IMSS, México, D.F.*

Key words: rituximab, chemotherapy, primary breast lymphoma.

Correspondence: Agustin Avilés MD, Plaza Luis Cabrera 5-502, Colonia Roma, 06700, México, D.F. Mexico. Phone: international +52.55.56276959. E-mail: agustin.aviles@imss.gob.mx

References

1. Barista I, Baltali E, Tekuzman G, Kars A, Ruacan S, Özisik Y, et al. Primary breast lymphoma. Acta Oncol 2000;39:135-9.
2. Lyons JA, Myles J, Pohlman B, Macklis RM, Crowe J, Crownover RL. Treatment and prognosis of primary breast lymphoma. Am J Clin Oncol 2000;23:334-6.
3. Ribrag V, Bibeau F, Weshi AE, Frayfer J, Fadel C, Cebotaru C, et al. Primary breast lymphoma. A report of 20 cases. Br J Haematol 2001;115:253-6.
4. Cabras MG, Amichetti M, Nagliati M, Orrú P, Mamusa AM, Angelucci E. Primary non-Hodgkin's lymphoma of the breast. Haematologica 2004;89:1527-8.
5. Kuper-Hommel MJJ, Snijder S, Janssen-Heijnen MLG, Vrints LW, Kluin-Nelemans JC, Coebergh JWW, et al. Treatment and survival of 38 female breast lymphoma. Ann Hematol 2003;82:397-404.
6. Wong WM, Schild SE, Halyard MY, Schomberg PJ. Primary non-Hodgkin's of the breast. The Mayo Clinic experience. J Surg Oncol 2002;80:19-25.
7. Duncan UE, Reddy VVB, Jhala NC, Chhieng AC, Jhala DN. Non-Hodgkin's lymphoma of the breast. Ann Diag Pathol 2006;10:144-8.
8. Liu MT, Hsieh CY, Wang AY, Pi CP, Chang TH, Huang CA. Primary breast lymphoma. A pooled analysis of prognostic factors and survival in 93 cases. Ann Saud Med 200525:288-93.
9. Avilés A, Delgado S, Nambo MJ, Neri N, Murillo E, Cleto S.: Primary breast lymphoma. Results of a controlled clinical trial. Oncology 2005;69:256-60.
10. McMillan A, Central nervous system .Directed preventive therapy in adults with lymphoma. Br J Haematol 2005; 131:13-21.