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RESEARCH ARTICLE

SURVIVAL AND TREATMENT OF OVARIAN LYMPHOMA, WHETHER PRIMARY OR SECONDARY ,WITH A FOCUS ON DLBCL, DIFFUSE LARGE B-CELL LYMPHOMA TYPE: A LITERATURE REVIEW BASED ON THE YUN ET AL STUDY

***Donatello, D.**

MD, Graduated at the University of Bologna, Radiologist, Independent Researcher, Italy.

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****Corresponding author: Donatello, D.***

ABSTRACT

Object: To describe the treatment and survival of OL (ovarian lymphoma) both primary and secondary. **Method:** Review of the literature (the study by Yun et al). **Discussion:** The review points out how the R-CHOP protocol appears to be superior to CHOP alone in terms of response and relapse rate in the case of secondary lymphoma ovarian involvement in DLBCL type. The HyperCVAD regimen is effective in other histotyps.The estimated five-year survival rates for primary and secondary ovarian involvement by DLBCL-type lymphoma are 70.0% and 59.3%, respectively. **Conclusion:** The study deducts that patients with primary ovarian NHL appear to have similar outcome with patients with other NHL. They, thus recommend a treatment with curative intent by a combination of chemotherapy regimens appropriate for their specific histology.On the other hand other studies are necessary.

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INTRODUCTION

In modern literature there are few sources that deal with the survival and treatment of ovarian lymphoma, whether primary or secondary. The study relating to survival of ovarian localized lymphoma is discussed below. In a past study by Jina Yun et al. (1), a sample of patients affected by ovarian lymphoma, both with primary and secondary involvement, was described, highlighting the clinical figures and survival of these patients. From a total of 4250 cases of non-Hodgkin lymphoma, observed from 1993 to 2009, only 32 patients included in this total present ovarian involvement. Based on the definition of ovarian involvement, the 32 patients were divided into 2 groups, one with primary involvement (n = 14) and the other with secondary involvement. Because all secondary involvement results from disseminated systemic non-Hodgkin lymphoma, all patients with secondary ovarian lymphoma are in an advanced state of disease, and their clinical outcomes were correspondingly poorer than the primary lymphoma group.

Therefore the International Prognostic Index (IPI) is high in patients suffering from secondary ovarian lymphoma. (Table 1). Table 1 (DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; LBL, lymphoblastic lymphoma; MZL, marginal zone B-cell lymphoma; PTCL, peripheral T-cell lymphoma; LDH, lactate dehydrogenase; ECOG, Eastern Oncology Cooperative Group; CR, complete response; PR, partial response; SD, sTable disease; PD, progressive disease.)

DISCUSSION

Patient characteristics: Symptoms presented initially are the same as other types of ovarian cancer, including abdominal pain (31.3%), abdominal distension (19%), or a lower abdominal mass (16%). The most commonly represented histological type is diffuse large B-cell lymphoma (DLBCL) (24 patients, 75% of the total), followed by Burkitt's lymphoma (4 patients, 12.5%). B-cell marginal zone lymphoma (MZL) was found in only one patient. Furthermore, there was a case of ovarian involvement by a peripheral T-cell lymphoma, unspecified (PTCL-u).

Table 1. Characteristics and results of treatment of patients affected by Non-Hodgkin lymphoma with ovarian localization

	Total (n= 32)	Involvement type		P value
		Primary (n = 14)	Secondary (n = 18)	
Age (median)	43	44	37	0.150
Range	18–80	31–80	18–66	
Age> 60	4 (12.5%)	3	1	
Histology				
DLBCL	24 (75.0%)	11	13	0.608
BL	4 (12.5%)	1	3	
LBL	2 (6.3%)	1	1	
MZL	1 (3.1%)	1	0	
PTCL	1 (3.1%)	0	1	
B Symptoms	10 (31.3%)	2	8	0.124
Initial manifestations				
Abdominal pain	10 (31.3%)	6	4	0.288
Abdominal distension	6 (18.7%)	3	3	
Palpable mass	6 (18.7%)	3	3	
Vaginal bleeding	4 (12.5%)	1	3	
General ache	4 (12.5%)	0	4	
No Sx	2 (6.3%)	1	1	
Increased serum LDH	19 (59.4%)	8	11	>0.999
Bulky disease	11 (34.4%)	6	5	0.436
Involved side				
Bilateral	13 (40.6%)	4	9	0.289
Unilateral	19 (59.4%)	10	9	
ECOG performance status				
0–1	27 (84.4%)	14	13	0.032
2–3	5 (15.6%)	0	5	
Ann Arbor stage				
I/II	14 (43.7%)	14		<0.001
III/IV	18 (56.3%)		18	
Extranodal involvement ≥ 2	22 (68.8%)	8	14	0.267
International prognostic index				
Low/Low-intermediate	19 (59.4%)	13	8	0.008
High-intermediate/High	13 (40.6%)	1	10	

The latter was included in the group of diseases with systemic dissemination. Bilateral involvement was observed in 13 cases (40.6%) and was seen to be more frequent in patients with secondary lymphoma. Unilateral involvement was found in 19 patients (59.4%), with equal percentage in the right and left ovary.

Diffuse large B-cell lymphoma (DLBCL) treatment outcomes: As regards the treatment of the most frequent histological type, i.e. diffuse large B-cell lymphoma, differs from the treatment of primary and secondary lymphoma. (Table 2.). Of the 11 patients affected by primary diffuse large B-cell lymphoma, 9 undergo surgery to remove the involved ovary and after surgery received the most common systemic chemotherapy treatment, called CHOP, cyclophosphamide, 750 mg/m2, doxorubicin 50 mg/m2 and vincristine 1.4 mg/m2, administered intravenously on day 1, with the addition of prednisolone 100mg administered orally on days 1-5 every 3 weeks and RCHOP, which uses the standard CHOP protocol with the addition of 375 mg /m2 of intravenous rituximab on day 1. Three patients who underwent surgery and RCHOP relapsed during follow-up.

On the other hand, patients treated with CHOP and RCHOP did not show significant differences in the overall treatment results. (Table 2). Among secondary lymphoma patients, many patients (nine) were treated with chemotherapy alone.The remaining four patients also underwent surgery. In contrast to primary involvement, the R-CHOP protocol appears to be superior to CHOP alone in terms of response and relapse rate in the case of secondary involvement, although the number of patients studied is small. Therefore, the OS, i.e. the average overall survival of patients with secondary ovarian lymphoma treated with R-CHOP, was far greater than treatment with CHOP alone, even if it is not statistically significant (P=0.0862).[2] The mean overall survival of the two groups is 9.83 years (95% Confidence Interval: 6.30-13.36) and 9.90 years (95% Confidence Interval: 5.68-14.12). The estimated five-year survival rates for primary and secondary ovarian involvement by DLBCL-type lymphoma are 70.0% and 59.3%, respectively. When survival results were compared between ovarian lymphoma with primary or secondary involvement, there weren't significant difference between OS and PFS i.e. disease-free survival (Fig.1)

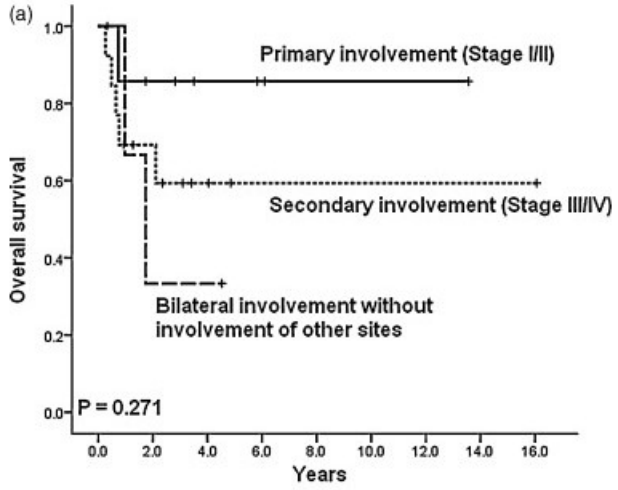

Figure 1. (a) The overall survival of patients with primary DLBCL-type ovarian lymphoma is not significantly different from the survival of patients with secondary DLBCL-type lymphoma (p=0.271). The overall survival of patients with bilateral ovarian involvement or invasion of other sites is lower than that of patients with primary or secondary lymphoma, but on the other hand it is not statistically significant (p>0.05)

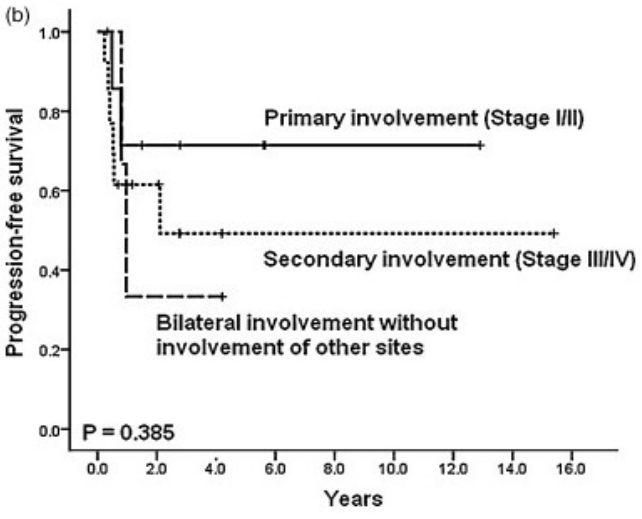

Figure 1. b)There were no significant differences in progression-free survival between primary and secondary DLBCL-type lymphoma patients (p=0.329) who have a similar pattern of bilateral involvement.)

Table 2. Results of the treatment of patients affected by both primary and secondary ovarian lymphoma, DLBCL type

Involvement type	N	CR (%)	PR (%)	Relapse (%)	Death (%)
Primary (n = 11)					
Surgery + RCHOP	6	5(83.3)	1(16.7)	3(50.0)	2(33.3)
Surgery + CHOP	2	2(100.0)	0(0.0)	0(0.0)	0(0.0)
Surgery + IMVP-16	1	1(100.0)	0(0.0)	0(0.0)	0(0.0)
RCHOP	2	1(50.0)	1(50.0)	0(0.0)	1[a] (50.0)
Secondary (n = 13)					
Surgery + RCHOP	3	3(100.0)		1(33.3)	0(0.0)
Surgery + CHOP	1	1(100.0)		1(100.0)	1(100.0)
RCHOP	6	5(83.3)	1(16.7)	2(33.3)	2(33.3)
CHOP	3	1(33.3)	2(66.7)	2(66.7)	2(66.7)

Table 3. Results of treatment in patients with both primary and secondary ovarian lymphoma, but with histological types other than DLBCL

Age	Stage	IPI	Histology	Involvement	Bone marrow invasion	Ovarian involvement	Number of extranodal involvement	Serum LDH	Surgery	Chemotherapy	Response	Relapse	OS	PFS	Survival
31	II	LI	BL	Primary	None	Unilateral	2	Increased	Done	CHOP	CR	Relapse	14.67	8.9	Dead
22	IV	L	BL	Secondary	None	Unilateral	1	Normal	Not done	CODOX	PR	No	127.73	119.8	Alive
45	IV	HI	BL	Secondary	Presence	Unilateral	4	Increased	Done	LMB	PR	Relapse	5.47	2.83	Dead
25	IV	LI	BL	Secondary	None	Unilateral	2	Normal	Done	LMB	PR	Relapse	76.87	4.7	Alive
34	I	L	LBL	Primary	None	Unilateral	1	Normal	Done	HyperCVAD	CR	No	18.03	15.63	Alive
40	IV	LI	LBL	Secondary	Presence	Unilateral	1	Increased	Done	HyperCVAD	CR	No	62.07	58.57	Alive
41	I	L	MZL	Primary	None	Unilateral	1	Normal	Done	CHOP	CR	Relapse	31.8	25.63	Alive
22	IV	HI	PTCL	Secondary	None	Unilateral	3	Increased	Done	CHOP	SD	Relapse	16.63	2.53	Dead

Results of treatment of other less frequent histological types: Four patients were diagnosed with Burkitt lymphoma with primary or secondary ovarian involvement (Table 16). These four patients showed unilateral ovarian involvement. Two of these four patients died after relapse, while the other two show long-term survived. Lymphoblastic lymphoma is observed in 2 patients, respectively in one case it was primary and in the other secondary, both diagnosed after the removal of the involved ovary and the final response after surgery and chemotherapy with the HyperCVAD regimen , was complete remission (CR).

These two patients survived without evidence of relapse. In the analyzed sample there was only one patient affected by peripheral T-cell lymphoma (PTCL-u) who showed a low response to therapy and a low survival, while a case of MZL showed a high survival even after relapse at the time of the data cut-off (Table 3.)

Relapse models: At the end of the initial therapy, 23 patients achieved complete remission. With an average follow-up of 25 months, 14 patients (43.8%) have relapsed and progress in the disease.

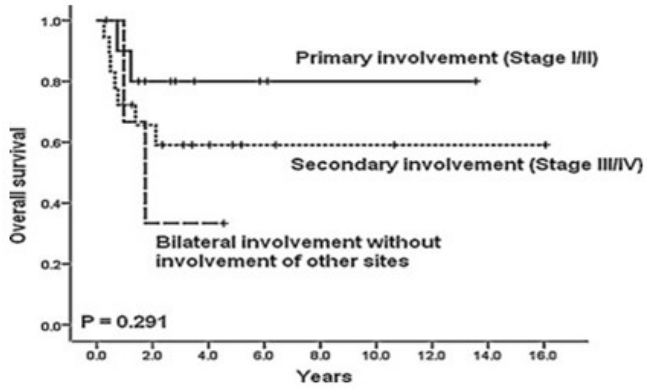

Figure 2. Overall survival of 32 patients was compared between primary and secondary ovarian involvement with the exclusion of bilateral involvement. (p=0.291)

Relapses affected the central nervous system (CNS), bone marrow, lung, adrenal glands and ovary. The most common site of relapse was the CNS with 7 cases observed, and all patients with relapse at the central nervous system level were affected by diffuse large B-cell lymphoma. Ovarian relapse occured in 2 cases: 1) a case had a bilateral onset and subsequent bilateral relapse 2) a second case had an initial unilateral presentation with bilateral relapse. Among all 24 patients with DLBCL-type lymphoma, two patients showed central nervous system involvement at early diagnosis, and subsequent CNS involvement was observed in 5 patients during or after treatment. Clinical figures and results are shown in Table 4. The incidence of central nervous system involvement was 7/24 (29.2%) and of these seven patients all but one had disease stage IV and one patient had primary ovarian lymphoma with CNS involvement. At diagnosis there were 13 patients with bilateral involvement, but only 4 of them had bilateral involvement without any evidence of involvement in other sites. All these 4 cases are DLBCL type, so the overall survival OS was compared with that of primary and secondary ovarian involvement of DLBCL lymphoma. The OS of these patients with bilaterality was lower than the other 2 groups, although it cannot be considered statistically significant (P> 0.005). Since the majority of lymphoma cases (n=24) were DLBCL, the survival analysis of all cases (n=32) also showed a similar outcome to that of DLBCL (Fig.2).

CONCLUSION

ThereforeYun et al looking at the case of 32 patients affected by non-Hodgkin's lymphoma with ovarian involvement, coming from eight different hospitals affiliated with the CISL (Consortium for the improvement of lymphoma survival)and although the number of patients with ovarian involvement was smalldeduced that, contrary to previous reports, patientswith primary ovarian NHL appear to have similar outcomewith patients with other NHL.

Theythus recommend a treatment with curative intent by a combination of chemotherapy regimens appropriate for their specific histology[Dimopoulos*et al*., 1997]Furthemore there was no significant difference in this study in OS (overall survival) and PFS (progression free survival) between primary and secondary lymphoma, hence the survival estimate was between 59.3% at 5 years for secondary ones and 70.0% at 5 years for primary ones.Evaluating that secondary involvement of the ovary was the result of dissemination by a systemic disease, the OS of secondary lymphoma appears to be better than the overall survival expected for stage III/IV DLBCL lymphoma.The fact that patients with secondary ovarian involvement respond better than expected may be related to the introduction of Rituximab in the treatment, but further studies are necessary to test this hypothesis.More works are required to determine the importance ofAAS(Ann ArborStage) and other prognostic factors in primary ovarian NHLin order to minimize toxicity for patients with good prognosis and intensify therapy for those with poor prognosis. [4-5]

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