Rituximab and Dose-Dense Chemotherapy in Primary Testicular Lymphoma

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Abstract

Background: Treatment of primary testicular lymphoma (PTL) remains unsatisfactory even in patients with good prognosis, as < 30% of patients are alive at 3 years. **Patients and Methods:** We began a phase II study to assess efficacy and toxicity of a dose-dense cyclophosphamide/epirubicin/vincristine/prednisone (CEOP14) regimen with rituximab (CEOP14R) in 38 previously untreated patients with PTL with early-stage (I or II) and low-risk disease, followed by adjuvant radiation therapy and central nervous system prophylaxis. **Results:** Complete response was 86% (similar to historical controls), but improvement in outcome was observed; with actuarial curves at 5 years, event-free survival was 70%, and overall survival was 66%. Toxicity was mild, and the regimen was well tolerated. **Conclusion:** The addition of rituximab to dose-dense chemotherapy improves outcome in this setting of patients who previously had been considered to have the poorest prognosis. It is important that these findings will be validated in multicentric, controlled clinical trials.

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Introduction

Primary testicular lymphoma (PTL) is a rare entity of non-Hodgkin lymphoma, accounting for approximately 1% of all malignant lymphoma, and is the most common testicular malignancy in older men.[1,2] These lymphomas remain a subset of main interest because they have a different biologic and clinical course. Because of the low incidence and the absence of prospective studies, better therapy remains to be found. Commonly, relapse is frequent in extranodal sites, and at this time, prognosis is very poor.[3-5] Initial treatment has ranged from orchiectomy to aggressive therapies, including central nervous system (CNS) prophylaxis and irradiation to iliac and pelvic lymph nodes, including contralateral testis. However, the relapse rate is > 50%, and only between 25% and 37% of patients are alive at more than 3 years.[1,3,6-8] Thus, other therapies need to be explored.

Most PTLs are of diffuse large B-cell lymphoma (DLBCL) histology and are CD20 positive.[1,4] Rituximab, a chimeric antibody, has been proven to be useful and well tolerated in young and older patients with CD20+ DLBCL.[9-12] Thus, we added rituximab to a dose-dense regimen (cyclophosphamide/epirubicin/vincristine/prednisone; CEOP14) followed by extended-field radiation therapy and CNS prophylaxis. The results of these open, longitudinal phase II studies are reported herein.

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Patients and Methods

Between January 2000 and December 2005, patients who fulfilled the following criteria entry were considered candidates for the study: diagnosis of PTL of DLBCL histology and CD20 positivity; early-stage (IE and IIE) disease; previously untreated disease; age > 18 to < 70 years; performance status < 2 according to the Eastern Cooperative Oncology Group criteria; negative immune deficiency virus test, and taking into consideration that the patients will receive rituximab, negative tests for cytomegalovirus and hepatitis B and C virus; normal hepatic, renal, pulmonary, and cardiac (measured with echocardiogram and with a left ventricular ejection fraction > 50%) tests. In all cases, complete immunophenotyping was carried out. Molecular and cytogenetic studies are not available routinely in our institution. All patients completed the staging procedure, which included physical examination; complete blood counts; serum chemistry; liver and renal test; computed tomography of the thorax, abdomen, and pelvis; aspirate and bone marrow biopsy; and lumbar puncture. Cerebrospinal fluid was examined for the presence of malignant cells. All patients were classified according to the International Prognostic Index. The study was approved

Table 1 Patient Characteristics

Characteristic	n (%)
Number of Patients	38 (100)
Median Age, Years (Range)	51.8 (53-70)
Stage (Ann Arbor)	
IE	29 (76)
IIE	9 (23)
Tumor Mass	
< 5 cm	7 (18)
5-10 cm	30 (81)
> 10 cm	1 (1)
ECOG PS	
0-1	26 (68)
2	12 (31)
International Prognostic Index	
Low	12 (31)
Low-intermediate	23 (60)
High-intermediate	3 (8)
Lactate Dehydrogenase Level	
> 2 times normal values	3 (8)
β_2-Microglobulin (> 5.0 pg/mL)	6 (15)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status

Figure 1 Actuarial Curves of Event-Free Survival and Overall Survival in Primary Testicular Lymphoma

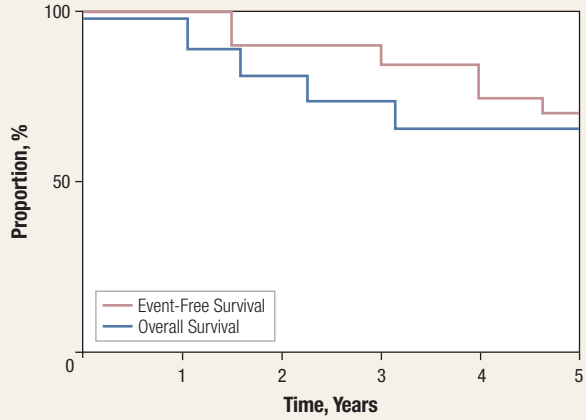

Table 2 Toxicity

Toxicity Measure	Grade n (%)			
	1	2	3	4
Granulocytopenia	49 (21.5)	38 (16)	40 (17.5)	0
Thrombocytopenia	59 (25)	36 (15)	0	0
Anemia	23 (10)	4 (< 1)	0	0
Treatment-Related Infection	24 (10)			
Treatment-Related Death	0			
Delay of Treatment				
Cases	118 (56)			
Median number of days	6.8 (Range, 5-14)			
Mucositis[a]	23 (60)	4 (10)	0	0
Nausea/Vomiting[b]	23 (10)	8 (3)	3 (1)	0
Abdominal/Pain[c]	6 (16)	0	1 (2)	0
Diarrhea[c]	7 (12)	4 (10)	–	–

Number of cycles = 228.
[a]During methotrexate administration.
[b]During chemotherapy.
[c]During radiation therapy.

by our Scientific and Ethical Committee, and patients gave their informed consent to participate in the study.

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It was a prospective, longitudinal, open-label study, the endpoints of which were improvement in event-free survival (EFS) and overall survival (OS). EFS was measured from the time to study entry to any treatment failure, including disease progression or discontinuation of treatment for any reason (disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death). OS was defined as the time from entry in the clinical trial until death from any cause. No attempts were performed to evaluate prognostic factors because most cases represented low or low-intermediate clinical risk, and the population was uniform.

After staging, the patients were allocated in this single-arm, open-label study, and initially they received the following chemotherapy: cyclophosphamide 1500 mg/m^2 intravenously (I.V.) day 1; epirubicin 120 mg/m^2 I.V. day 1; vincristine 1.2 mg/m^2 I.V. day 1; prednisone 60 mg/m^2 orally daily for 5 days; and rituximab 375 mg/m^2 I.V. day 1.

Each cycle was administered every 14 days if platelet and granulocyte counts were normal. Granulocyte colony-stimulating factor (G-CSF) was administered in all cycles at a dose of 5 µg/kg/day to maintain the schedule of chemotherapy. A total of 6 cycles were administered. Dose reduction was not considered. If the patient developed hematologic toxicity grade 1 or 2, treatment was delayed until normal values were documented. If grade 3 hematologic toxicity was observed, delay of treatment and increase in days of G-CSF was the rule. If the patient developed hematologic toxicity grade 4, he or she was removed from the study. Only mucositis grade 3 or 4 warranted treatment modification, with a delay following a dose of intrathecal methotrexate.

If the patients achieved complete response, they started adjuvant radiation therapy: 4 weeks after the last chemotherapy, the patient received a dose of 30 Gy to the entire scrotum and contralateral testis (stage IE) or scrotum, contralateral testis, paraaortic iliac and pelvic lymph nodes (stage IIE). Eight weeks after radiation therapy, patients began CNS prophylaxis with methotrexate 6 g/m^2 day 1, followed by leucovorin rescue 21 mg/m^2, every 6 hours until serum methotrexate was cleared in blood. Hydration and alkaline urine were conserved during treatment. The methotrexate was administered every 28 days for 4 cycles.[6] No further treatment was administered.

Table 3 Recent Results in Testicular Lymphoma

Study	No. of Cases	Median Age, Years	Stage		Treatment	CR, %	EFS	OS
			I	II				
Seymour et al (2001)[17]	18	69	14	8	S + CT: 18 S + RT: 11	NA	23%[a]	32%[a]
Hasselblom et al (2004)[7]	33[b]	69	22	–	S: 5 S + RT: 2 S + CT: 28 S + CT + RT: 3	94	42 Months[a]	47 Months[a]
Avilés et al (2004)[6]	34	64	21	13	S + CT	97	32%[a]	30%[a]
Al-Abbadi et al (2006)[16]	18	58	17	1	NA	NA	NA	76 Months
Vitolo et al (2006)[18]	45	64	36	9	S + CT[c]	98	87%[a]	84%[a]
Sarris et al (2006)[19]	24	60	17	7	S + CT	87	78%[a]	66%[a]
Vural et al (2007)[3]	12[b]	47	3	4	CT: 7[d]	100	84%[a]	100%[a]
Park et al (2007)[4]	45[b]	21	13	–	S:2 S + RT: 1 S + CT: 27 S + CT + RT: 15	77	66%[a]	34%[a]

[a]Median at 3 years in actuarial curves.
[b]Include stages III and IV.
[c]All patients received chemotherapy and rituximab.
[d]Three patients received chemotherapy and rituximab.
Abbreviations: CR = complete response; CT = chemotherapy; EFS = event-free survival; NA = not addressed; OS = overall survival; RT = radiation therapy; S = surgery

For follow-up, patients were evaluated every 2 months during the first 2 years and every 4 months for 3 years additionally. At each visit, physical examination, complete blood count, and serum lactic dehydrogenase and β_2-microglobulin tests were performed. Computed tomography (CT) of the thorax, abdomen, and pelvis were performed every 6 months the first 3 years. Lumbar puncture was performed if clinically indicated.

Response was defined according to the recent response criteria for lymphoma[13]:

Complete response: disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy. Positron emission tomography is not available in our institution; thus, the evaluation was based on CT. No spleen or liver involvement was observed before therapy. Nodal enlargement in stage II disease requires that nodes initially positive will be < 1.0 cm at the restaging. All patients initially had bone marrow negative for infiltration; thus, this study was not repeated.

Partial response: taking into consideration the anatomic site of presentation, this criterion was not evaluable.

Progressive disease: any new lesion or increase by ≥ 50% of the previously involved sites from nadir.

Results

During this time, 3686 cases of lymphoma were diagnosed at the Oncology Hospital, National Medical Center, IMMS, which is a tertiary national reference center, 2997 of which were B-cell lymphoma; 1634 were DLBCL, and of these, 49 were testicular lymphoma. Five cases were stage III and IV, and 6 patients were aged > 75 years and were not considered candidates for the study. Thus, 38 patients were enrolled in the study. In an intent-to-treat analysis, all patients were considered evaluable for efficacy and toxicity. Patient and disease characteristics are shown in Table 1; no clinical differences were observed with previous studies. All patients received at least 6 cycles of the mentioned treatment. Thirty-three patients achieved complete response (86%) and received radiation therapy; the same 33 patients received the planned CNS prophylaxis. Five patients whose were treatment failed or who developed disease progression were treated with salvage chemotherapy, including 2 patients with myeloablative chemotherapy and autologous stem cell transplantation, but all patients died secondary to disease progression. With a median follow-up of 64.8 months (range, 36-84 months), 10 patients developed relapsed disease; in all cases they were in extranodal sites (lung, 3; stomach and nodal disease, 2; disseminated disease, 5). Salvage chemotherapy was used, but prolonged second response was observed in only 2 cases. Thirteen patients (34%) died, all secondary to tumor progression. Actuarial curves at 5 years showed that EFS was 70% and OS was 66% (Figure 1); these survival rates were better when compared with our historical controls.[6] No attempts were performed to evaluate prognostic factors because most patients were low or low-intermediate risk, and it was a uniform population.

Toxicity

Table 2 shows the hematologic and nonhematologic toxicity. Granulocytopenia was observed in 55% of the patients, and treatment-related infection was observed in 24 cases (10%); in all cases, patients responded to broad-spectrum antibiotics and administration of G-CSF. Delay of treatment was observed in 128 cycles, with hematologic recovery in 5-14 days (median, 6.8 days). Dose intensity was not modified, and the patients received about 87% of the planned dose of all chemotherapeutic agents. Nonhematologic toxicity was more frequent during CNS prophylaxis. Delay of radiation, secondary to toxicity for radiation therapy, was necessary in 11 cases (range, 7-15 days; median, 7.8 days). Until now, no evidence of late neurologic or cardiac toxicity has been observed.

Discussion

Primary testicular lymphoma is generally a rare presentation of malignant lymphoma and generally is a disease of older patients (aged > 60 years). Although the majority of patients present with stage I or II and belong to a group with low or low-intermediate clinical risk, they show a high relapse rate and poor survival outcome.[1,5-8] Thus, definitive treatment is not standardized. Bhatia et al performed a review of older results in PTL: the CR response was between 22%

and 68%, but EFS and OS were poor, and < 20% were alive at more than 3 years, but these reports generally did not include prophylactic CNS treatment, and almost 40% of patients were treated with surgery alone.[15] In a retrospective study, similar results were observed.[14] Table 3 shows the more recent results in PTL.[3,4,6,7,16-19] Some studies continue to not use prophylaxis for CNS.[16] Actually, the treatment includes initial orchiectomy, followed by combined chemotherapy containing anthracyclines, with involved-field radiation therapy and CNS prophylaxis, most with radiation therapy and/or intrathecal methotrexate. However, results remain poor. Seymour et al reported an EFS of 23% and an OS of 32%.[17] Hasselblom et al showed that median EFS was 42 months and OS was 47 months[7]; Park et al showed poorer results, with an EFS of 16 months and an OS of 34 months.[4] The study of Vural et al is contradictory, with an OS of 100%, but the number of patients with early-stage disease was 7, and 3 patients had rituximab added to their treatment, but the role of this drug in the response and outcome was not mentioned.[3] In a previous instance, our patients had an EFS of 32% and an OS of 30%.[6] Vitolo et al, in an abstract, reported an uncontrolled clinical trial of 45 patients treated with R-CHOP (rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone), with a real improvement in EFS and OS; the study remains in accrual.[18] The same group reported a retrospective analysis with good results without the use of rituximab. To the best of our knowledge, it is the first prospective study to analyze the efficacy and toxicity of dose-dense chemotherapy and rituximab in PTL; the Vitolo study used standard CHOP. Our results showed that complete response was similar to previous studies,[6] but an improvement was observed in outcome based on EFS and OS.

Toxicity was frequent and severe in some cases, but it was similar to a previous study of R-CHOP in nodal lymphoma[20]; aggressive chemotherapy and rituximab have also been used in elderly patients, with a similar toxicity profile.[9] Dose-dense regimens have been used in an attempt to increase complete response rate and outcome, and toxicity has been considered tolerable because the toxic death rate is < 5%.[10] We considered that R-CEOP14 appears to be a useful and well-tolerated regimen that can be administered in elderly patients with PTL with improvement in outcome. Though controlled, multicentric studies are necessary to validate a therapeutic option, in PTL this will be difficult to achieve because of the low number of cases, even at tertiary reference centers.

Conclusion

The addition of rituximab to dose-dense chemotherapy was well tolerated, even in elderly patients, and improved outcome in patiens with early-stage PTL.

Disclosures

The authors report no relevant financial conflicts of interest.

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