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Research Article

Early Primary Gastric Lymphoma with Adverse Prognosis Factors. Is it Benefit Adding Rituximab to CHOP-14?

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ABSTRACT

Objective: Assess if the addition of rituximab to a dose-dense chemotherapy regimen in patients with primary gastric diffuse large B-cell lymphoma (PGL) in early stage, but, associated with worse prognostic factors.

Patients and Methods: Patients with pathological diagnosis of PGL and early stages, but, with elevated levels of beta 2 microglobulin and lactic dehydrogenase, age > 18 years age without upper limit, no gender differences, previously untreated, were recruit in an open label clinical trial, to received CHOP-14 (cyclophosphamide, vincristine, doxorubicin and prednisone, dose dense, every 14 days) and compare with patients that received R-CHOP14 (rituximab + CHOP-14).

Results: Between March 2011 to December 2016, 141 patients were taken entry to the study: no statistical differences were observed in clinical and laboratory characteristics. Complete response (CR) was observed in 68 out of 72 (94.4%) patients in the CHOP-R14, and 67 out of 69 (95.1%) patients in the CHOP14 regimen. Actuarial curves at 5-years show that progression-free survival (PFS) was 89% (95%Confidence Interval (CI) in the CHOP-R14, that did not have statistical differences in the CHOP-14 arm: 92% (95%CI: 83% -97%) (p 0.887); the overall survival were: 90% (95% CI:86%-97%) and 93.4% (95% CI: 86% to 97%) (p 0,665). Toxicities were severe granulocytopenia and infection-related, but no dead were observed. Until now, late toxicities as acute leukemia, second neoplasms and cardiac damage has not been observed.

Conclusion: The use of dose dense regimen (CHOP-14) confirm that is useful in the treatment of PGL associated to worse prognosis factors, the addition of rituximab did not show any benefit.

Introduction

Diffuse large B-cell lymphoma is the most common pathological presentation of non-Hodgkin lymphoma and account between 18 to 35% of non-Hodgkin lymphoma. Gastric lymphoma (PGL) in the most frequent extranodal presentation [1-3]. However, the best treatment has not been defined. Taking in consideration that PGL appear to be limited to the stomach (stage I and II), initial treatment were surgery and radiotherapy; however, relapse were higher, and actually only in selected cases: bleeding, perforation, bad clinical conditions, those therapeutic approaches are employed chemotherapy, CHOP (cyclophosphamide, doxorubicin, vincristine and Prednisone): was considered the gold standard in PGL an early stage: with a complete response of 85 to 93 % of cases, but, even in patients with good prognosis factors at diagnostic, < 60 years old, limited anatomical site, low or low-intermediate clinical risk according to the International Project Index IPI), good performance status (< 1), and small number of patients could have a worse prognosis and have high-risk of relapse, that while can be refractory to salvages, including stem cell transplant [4].

Some years ago, we found that patients with high of lactic dehydrogenase (LDH) and beta 2 microbuline are associated with a worse prognosis in PGL [5]. Thus, we developed an intensive regimen, that increase doses of cyclophosphamide, and doxorubicin, diminished the interval between cycles of 14 instead of 21 days, that achieve good response rate and outcome [6]. Rituximab has been considered as a golden drug in the treatment of DLBCL, but, in PGL, the results were conflictive thus we performed an open label clinical to assess the efficacy and toxicities of a dose dense with and without rituximab [7-10].

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Patients and Methods

Between January 2011 to December 2016, patients with confirmed pathological diagnosis of gastric DLBCL, > 18 years without age limit, no gender differences, early stage I, and elevated levels of LDH and B2M were considered to entry to the study. Staging including, diagnostic was performed with gastric endoscopy, at least 3 sites of tumor were taken, and 6 gastric biopsies of healthy tissues, complete physical examination, complete blood counts, serum chemistry, serum levels of LDH and B2M, computed tomography of thorax, abdomen and pelvis, aspirate and biopsy of bone marrow, viral panel: hepatitis B and C, acquired human immunodeficiency. Immunohistochemistry of malignant tissue included CD20, CD22, MUM1, bcl6. Bcl2, CD10, CD5. Patients that fulfilled the criteria entry, were allocated in a 1:1, to received: CHOP14: Cyclophosphamide, 1000 mg/m^2, $_{IV,}$ day 1; Vincristine 2 mg, standard dose, IV, day 1; Doxorubicin 75 mg/m^2, IV, day 1; Prednisone 100 mg, standard dose per oral, daily, days 1 to 5. They were matched in a proportion to received RCHOP-14; CHOP-14 and Rituximab 375 mg/m^2, IV, day 1.

Each cycle was administered every 14 days, if granulocytes were > 1.5×10^9, and platelets > 100×10^9. To avoid the risk of severe granulocytopenia, granulocyte colony stimulating factor was administered subcutaneous days 12 of each cycle. The regimen was administered every 14 days. Response was assessed according to International criteria. The study was approved by the Scientific and Ethical Committee of our Institute: HO/2011-7, and all patients signed inform consent to participate in the study.

Results

We included 141 cases; the clinical and laboratory dates were no show any statistical difference (Table 1). Overall complete response were 68 out of 72 cases (94.4 %) in the CHOP-R group and 67 (95.01), complete response were 68 patients in CHOP-R and 66 (95.1) in the CHOP group, no statistically differences were observed. Progression free-survival (PFS) were 89% (95% Confidence interval): 81% (-96%) in CHOP R14 and 92% (95%CI: 84% - 95%) in CHOP-14 (p 0.98) and overall survival (OS): 92% (95%CI: 86% - 96%); 93 % (95% CI: 88%-97%), respectively.

Table 1: Clinical characteristics.

	CHOP-R14	CHOP 14	
	No (%)		p
Number	72	69	
Age (years) range	36 - 67	29 - 66	0.625
Median	58.9	58.2	0.876
Sex: male	38 (52.7)	33 (47.8)	0.455
Female	34 (47.2)	36 (52.1)	0.665
Performance status			
0,1	58 (80.5)	58 (84.0)	0.369
2	14 (19,4)	11 (15.9)	0.566
IPI *			
0,1	65 (90.2)	63 (91.3)	0.989
2	7 (9.2)	6 (8.6)	0.887
Bulky disease (> 10 cm)	39 (54.1)	37 (53.6)	0.901
GCB genotype	72 (100)	69 (100)	NA
Elevated lactic dehydrogenase	72 (100	69 (100)	NA
Elevated beta 2 microglobuline	72 (100)	69 (100)	

IPI: International Prognostic Index; GCB: Germinal B Center.

Table 2 show the toxicities; the most common were granulocytopenia, but severe granulocytopenia (grades III and IV) were minimal (< 5%). Infection related granulocytopenia were similar in both arms. No dead relate toxicity were observed. Until now, late adverse events, inclusive acute leukemia and second neoplasms. Cardiac evaluation did no show evidence of cardiac damage.

Table 2: Toxicities.

		No cycles (%)	p
CHOP-R14	432 (100)	414 (100)	
Nausea/vomiting I	110 (25.4)	99 (23.9)	340
Granulocytopenia I-II	296 (68.5)	214 (51.6)	0.08
III-IV	134 (31.0)	102(24.8)	0.567
Infection related			
Granulocytopenia	38 (8.7)	27 (6.5)	334

Discussion

We show the patients with PGL, even in early stage, could have a poor prognosis, if it's associated with serum factors: LDH and B2M, because in this setting of patients, CR could be higher (> 90%), but relapse is frequent and they showed resistant to salvage treatment, including transplant procedures, and it is appeared conventional CHOP or RCHOP will be considered no benefits to these patients. Thus, we explore the use of dose-dense regimen, in a previous study, we show that a dose dense chemotherapy (CHOP-14), will improve outcome, although hematological toxicities were severe, they were controlled. However, CHOP-R is considered as the gold standard in DLBC, and in the best of our knowledge we did not find that rituximab associated to a dose dense CHOP-14 regimen, were employed. The use of rituximab in the treatment of patients with PGL, remain unsolved, thus we show in this paper, that addition of rituximab did not benefit the outcome in these special setting patients: and confirm that a dose dense regimen as CHOP-14 improve outcome. Toxicities, especially hematological were severe, but the use of granulocyte colony stimulating factor, reduce the presence of fatal complications. Until now, late toxicities as acute leukemia, second neoplasms and evidence of cardia damage has been demonstrated. Some studies, including molecular changes has been performed to define a better prognostic model, but, it has not been confirmed [11, 12].

Conclusion

The use of aggressive chemotherapy has been employed with no definitive conclusions, but in the present study we showed that the use of a CHOP-R, is effective, but the use of rituximab remains unsolved in this setting of patients, thus we show, that the addition of rituximab to a dose dense regimen, in PGL with worse prognosis markers, did no adding any benefit.

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Author Contributions

Both authors participated in the design of the study, data acquisition, critical and written the work.

Availability of Dates

Not applicable.

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