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Gemcitabine Rituximab Dexamethasone and Thalidomide as Maintenance in the Treatment of Relapse/Refractory Diffuse Large B-cell Lymphoma

Research Article

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Abstract

Background: Although greater advances has been achieved in the treatment of diffuse large B-cell lymphoma, only 35-54% of patients can achieved longer survival. Multiple studies has been performed in the treatment of relapse/refractory lymphoma including stem cell transplant that can offered only in an reduce group patients. Complete response can been observed in 34-56%, but refractory/relapse remain as a problem. We developed an gemcitabine based regimen, that including dexamethasone and rituximab, and thalidomide. Taking in consideration that relapse is frequent, we adding thalidomide at low doses for 18 months as maintenance therapy an low doses.

Results: Complete response was achieved in 113 patients (80.7%); actuarial curves at 5 years in maintenance group was 72.95% that was better that control group: 48,5% ($p<0.01$), overall survival was 68,5% and 41.2%, respectively ($p<0.01$). Toxicity were minimal and well tolerated.

Conclusion: The use of gemcitabine, dexamethasone, rituximab and thalidomide show good results compared with another studies and the addition of thalidomide as maintenance improved significantly the outcome.

Keyword: Diffuse large B-cell lymphoma; Relapse refractory; Gemcitabine; Rituximab; Thalidomide

Drugs: Gemcitabine; Dexamethasone; Rituximab; Thalidomide

Introduction

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphomas actually about 50-55%; although greater advances, including the addition of rituximab, response is achieved in 60-75% of patients, however 30 to 45% relapsed or are primary refractory with a worse prognosis [1]. Different approaches has been employed to improve outcome, as interferon as maintenance therapy [2], interferon associated with cyclophosphamide, vincristine and prednisone [3], rituximab in maintenance [4], rituximab as consolidation [5], but neither of these approaches has been proven to improve outcome. Thus, R/R lymphoma remain as a mayor problem in the treatment of DLBCL. Multiple studies has been performed in the treatment of relapsing/refractory (R/R) lymphomas, in most studies, complete response is achieved between 40 to 65%, actuarial curves at 5-years in Progression-Free Survival (PFS) and Overall Survival (OS) show 25 to 32 % and 29 to 43%, respectively. Actually, Stem Cell Therapy (SCT) is acceptable in those the best treatment but most patients are no candidates, for poor performance status, severe comorbidities, age (>70 years), and the refusal of the patient that has been limited the use of these treatment. Most of the treatments of R/R lymphomas, including anthracyclines, steroids and rituximab, recently new drugs as ibrutinib, lenalidomide and bortezomib has been adding, but, no clear improved in outcome has been observed [6,7] Gemcitabine is a agent that has been developed in the treatment of solid tumors [8,9] and has been demonstrated clinical activity against non-Hodgkin lymphoma; generally combined with cisplatin and dexamethasone [10,11]. Rituximab is a monoclonal antibody anti CD-20, that associated to

anthracyclines-based chemotherapy remain to be the most effectively agent in patients with DLBCL. Have been demonstrated that gemcitabine enhanced the activity of rituximab mediated complement-depended cytotoxicity to B-cell lymphomas, and increased responses and improve outcome [12,13].

However, in most study, a new relapse is common and until now, the presence of relapse suggested the existence of tumor cells, refractory to treatment. Lenalidomide, is an immunomodulator, that has been employed in the treatment of multiple myeloma, and non-Hodgkin lymphoma, used in first line associated R-with CHOP compared with RCHOP+ lenalidomide, show contradictory results in clinical trials. Lenaledomide has been used as maintenance, but no clear benefit has been reported. The mayor problem is that these drug is associated with severe hematological toxicities, caused delay and/or diminished the planned doses, an probably also reduce the efficacy. Thalidomide, is the first immunomodulator, with antitumor activity, that were employed in the treatment of multiple myeloma, with good results previously the time of ASCT. However, was abandoned without any specific reasons. The use of Thalidomide is well tolerated, and we observed good results as maintenance therapy in multiple myeloma and marginal zone lymphoma. Thus, we developed an regimen that include rituximab. gemcitabine and dexamethasone and if the patient achieve Complete Response (CR), thalidomide at moderate doses for 18 month. The end-point was to improve PFS and OS in this setting of lymphomas.

Patients and Methods

Between August 2010 to December 2018, 140 patients were considered candidates to received in a first step: GDR-T (gemcitabine, dexamethasone, rituximab and thalidomide). If the patient achieved CR, they were allocated in an proportion 1:1; to received thalidomide 100mg, oral days 11 to 21 in each cycle, at monthly interval for 18 months. Criteria entry were, pathological confirmation the diagnosis of DLBCL, treated with R-CHOP, that were primary refractory or early relapse (<12 months) age: 30 to <75 years, stage III and IV, performance status ≤2, negatives for immunodeficiency virus, hepatitis B and C, comorbidities well controlled. The study was divided in two steps all patients received Gemcitabine 1500mg/m^2, iv, days 1 and 8 of each cycle, Dexamethasone 40mg, iv, days 1 and 8, rituximab 375mg/m^2 iv, day 1; each cycle was administered every 28 days, for 6 cycles. All patients were restaging to evaluate response type according to the international criteria. Patients that did not achieved CR, were considered to autologous stem cell transplant. The study was approved by the Ethical and Scientific Committee of our Institution, and all patients signed an inform to participate in the study.

Statistical Analysis

PFS: was estimated from complete response until clinical, radiological or laboratory evidence of relapse, Overall Survival (OS) was measured from the time began the treatment to the date for death from any cause.

Results

Initially 140 were included in the Phase A; CR was achieved in 113 cases (76.1%) and were allocated to received maintenance or not. Clinical and laboratory characteristics are show in (Table 1), no statistical differences were reported between received maintenance or not. The 27 cases that did no achieved CR, 13 received ASCT, 10 achieved CR and 6 are alive at a median of 7.2 years (range: 4.6-8.4); 14 cases were treated another salvage regimen or refused any treatment. Hematological toxicities secondary to GDR regimen, are show in (Table 2), no severe toxicity was observed, and none patient die secondary to chemotherapy. Thalidomide did not show any severe toxicity, all were grade I, and were well controlled. Actuarial curves at 5-years that that PFS in maintenance group was 72.95% (95% Confidence Interval (CI)) that were statistically better compared with control group: 48.5% (95% CI: 39.0-50.3%), also Overall Survival (OS) was better 68.5% (95% CI: 68.6-74.9%) in patients that received maintenance therapy: 41.2% (95% CI: 33.6-49%). Until now late toxicities, including a second neoplasm or acute leukemia has not been observed.

Table 1: Clinical and laboratory characteristics.

	Maintenance			
	Total	**Yes**	**Not**	**P**
	No (%)			
Number	113(100)	59(52.2)	54(47.7)	0.67
Age(Median) years	62.5	61.8	66.7	0.801
Range	45-71	48-73	63-73	0.567
Sex: Male	60(53)	29(49.5)	31(57.4)	0.437
Female	53(46.9)	30(52.5)	23(42.5)	0.421
Stage III	10(8.8)	6(10.1)	4(7.4)	0.704
IV	103(91.1)	53(89.9)	50(92.5)	0.665
IPI ≤ 2	98(86.7)	53(89.1)	45(83.3)	0.387
Bulky disease (>10cm)	35(30.9)	18(30.5)	17(31.4)	0.801
LDH > 2 N	31(27.4)	19(32.2)	12(22.2)	0.654
Primary refractory	28(24.7)	15(20.4)	13(24.7)	0.564
Relapse	85(73.2)	44(74.5)	42(75.9)	0.53
Genotype: GCB	95(84.0)	52(88.1)	43(79.6)	0.432
Non-GCB	18(30.5)	11(18.4)	9(16.6)	0.411

Abbreviations: IPI: International Project Index; LDH: Lactic Dehydrogenase; GCB: Germinal Center B-Cell.

Table 2: Hematological toxicities.

	Grade 2	Grade 3
	No (%) *	
Granulocytopenia	60(0.1)	4(0.2)
Thrombocyto-penia	29(10.5)	2(< 1)
Febril neutro-penia	9(0.17)	
Infection related	16(0.53)	

Total of cycles 538.

Discussion

Greater advances has been observed in the treatment of patients with DLBCL, however, primary refractory and relapse remain as a common problem, actually, only 48 to 59% of patients remain alive free disease at 10 years [14,15]. Multiple schedules has been proven, basically including anthracycline based chemotherapy with doses dense, or adding to CHOP or R-CHOP, some of the new drugs, as ibrutinib, lenalidomide, bortezomib, but some Improvement in Response Rate (ORR), DFS and OS did nor show any statistical improved in outcome. Until now, autologous stem cell transplant remain as the gold standard in the treatment of primary refractory or early relapse, but multiple factors limited the use of this treatment. Recently has been introduction of a new type of treatment, the called CART-T cell therapy, initially preliminary results appear to improve the prognosis of R/R DLBCL, but some bias were observed: the number of patients proposed to received the therapy only 60 to 75% of patients received at time, the follow-up were to short and definitive improvement were observed [16].

Moreover, the cost were expensive, and the apparition of acute and late excessive toxicities, specially in system central system, limited the initial exited [17]. Sterner, et al. [18] reported an study, compared CART-T therapy with alternate therapies, although initial response was better with CART-cell therapy, but no statistical differences were observed in PFS and OS [18]. Some years ago, gemcitabine based combined chemotherapy was introducing in this special setting of patients, associate with steroids platinum-derivates; but better benefit has not observed. Recently, has been proven that gemcitabine appears to enhance of rituximab, increased cytotoxic effect in tumor-cells. In our study we observed increased in CR, and improvement in PFS and OS compared with previous studies, without excessive acute toxicities [6,10,13,14]. As mentioned, the major problem is relapse, various attempts, has been employed, neither has been observed that the use of interferon, interferon and chemotherapy and rituximab, employed as maintenance or consolidative has been benefit to these patients [2-5]. Recently, et, reported that the used of lenalidomide employed during induction and followed by 18 months of lenalidomide as maintenance therapy, and an statistical difference in those patients, they employed low doses of lenalidomide, and not delayed or reduced the doses, probably in this instance not is necessary high doses, and continued low doses will be better [15]. In our institution lenalidomide is not available, or these reason we employed thalidomide at low doses, also for 18 months.

The most important is that the use of thalidomide adding a better outcome with improvement PFS and OS, when compared to control group. Toxicities were mild and well controlled, no decrease in dose or delay treatment was observed. Smith, et al. [19] reported that the use of lenalidomide and rituximab have serious adverse effects and suggested that the employed doses will be avoid those high doses [19]. Ji, et al. [20] has been reported a single study and show that addition of thalidomide to CHOP standard in first treatment od DLBCL, and the addition of thalidomide did not increase acute toxicities [20].

Conclusion

We show the results of a single study in an homogenous group of R/R DLBCL patients and response rate is better compared with others studies, without excessive acute and late toxicities, and demonstrated that the use of an immunomodulator can improve outcome, with a prolongation of PFS and OS. Some bias could be observed, it a single center, no external pathological review: but the study was performed in an homogenous population and longer follow-up. It is evident that more studies will be developed to confirm these results.

Conflict of Interest

Both authors did not received grants or funds, and the study was performed with the owner resources of the Instituto Mexicano del Seguro Social.

Contributions

Both authors performed the study design, acquire data, critically revised the context approve the final version and the sending to be published.

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