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Follicular Lymphoma Controled Clinical Trial with Integral Therapy In Untreated Patients

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1. Abstract

Follicular lymphoma (FL) is the second most frequent non-Hodgkin lymphoma, and until now the best treatment has not been defined, most studies show an excelent Overal Survival (OS), but relapse is observed at very short time. Thus, actually the goal of most studies is to Increase Progression-free survival (PFS)

1.1. Patients and Methods

We developed an regimen on patients with FL, untreated, stage III-IV, to include: 6 cycles of CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone), if the patient achieve Complete response (CR) patients received 375 mg/m2 at monthly cycles (days 1,8,15) for six months. Subsequently were allocated in a proportion1:1: thalidomide, 100 mg, oral, days 1 to 21, at monthly interval for 3 years.

1.2. Results

CR was achieved in 701 (91%); 343 patients received thalidomide an 358 were the control group. PFS in maintenance group was 88% (95% Confidence Interval: 82%-965) and OS was 93% (95CI: 87%-97%), that were statistical better that the control group: 69% (61%-77%) <and71 % (95CI :67%-73%) respectively. Severe acute and late toxicities were not observed.

1.3. Conclusion

The use of a continuous chemotherapy: induction, consolidation with rituximab and maintenance with low doses of thalidomide, achieve excellent response because significantly increase PFS and OS.

2. Introduction

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma: is most common in > 50 years and advanced stages (III and IV). Recently progress in the understanding on the biology of this lymphoma led to modest progress in the treatment, however, results can be no concordant. The knowledge in tumor environment and clonal changes ,contributed to define the best treatment to

improve outcomes [1-4]. However, until now, specific treatment has not was defined; in early stages (I, II) the use of radiotherapy is the best option, with complete response (CR) in > 90%, and overall response > 10 years [5]. In early stages, combined anthracycline -based, chemotherapy achieved CR in

most of 85 %, but, continued relapse remain as an problem, specially, because relapse is most frequent at < 2 years of treatment delivery. Thus, has been considered that this relapse could been associate to resistant-tumor cells. Thus, maintenance treatments appear to be necessary. Various treatment has been

employed, chemotherapy at low doses, interferon, ant rituximab, that increase OS, but not progress-free disease (PFS), and is necessary that the novel treatments maintain the response, but accumulative toxicities, as severe neutropenia, viral infections, and probably second neoplasms are common, and as

necessary to reduce the doses, or stop maintenance, and probably influence in the outcome of this patients [5-13]. Thus, we development a new therapeutic approach, used a different time the treatment and employed, to treat to maintain cell lymphoma under

continues attack, employed adjuvant radiotherapy and thalidomide as maintenance. The first end point I to increase the PFS, to avoid the use of more aggressive treatment in the patient relapse.

3. Material and Methods

From March 2001 to December 2014, patients with confirm pathology and histochemistry of follicular lymphoma, that were untreated and fulfilled the following criteria entry were considered to entry at the study; normal complete blood counts, serum chemistry, serum determinations of lactic dehydrogenase

and beta 2 microglobuline, negative test for viral of immunodeficient human, virus B and C. Computed tomography of thorax, abdomen and pelvis, Evaluation of cardiac state with electrocardiogram, ecocardiogram. All studies will be normal, performance status < 2: if the patient had some comorbidities, it were under control The study was approved by the Scientific and Ethic Committee and all patients signed an consent inform to participate in the study.

4. Response Criteria

Complete response (CR): was defined as disappearance of all detectable clinical and radiologic of nodal disease, normalization al abnormal laboratory test, secondary to tumor activity, were normal. For criteria in these study, partial response was considered failure. Progresion free-surviva PFS) l, was considered from the time of initial treatment until the first, clinical, laboratory or radiological studies, were observe or death secondary to other cause; overall survival was considered to the time of diagnosis to the die secondary to either cause.

5. Treatment

5.1. Phase I

Six cycles of CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) at conventional doses, every 21 days. At the end, complete restage were performed. Patients with nodal bulky disease (tumor mass> 10 cm) received involved field radiotherapy at doses of 25 Gy.

5.2. Phase II

All patients in CR were receive an consolidation, with Rituximab standard doses, days 1, 8 and 14 days every 28 day cycle, for 2 years.

5.3. Phase III

After rituximab, the patients were allocated to received maintenance in a proportion 1:1, of thalidomide, 100 mg oral, days 1 to 21 in monthly interval. To avoid bias, the study was finished in December 2014, but, the final results were evaluate until July 2024, to had s minimal time of observation of 10 years.

6. Results

A total of 768 patients entry in the study; the baseline characteristics are show in the Table 1, no statistical differences were observed in these characteristics, only female were most common probably because it is a single center and homogenous population. CR was achieved in 701 (91.5%). All patients received rituximab at complete doses. The patients that received maintenance, did received the planned phase. Actuarial curves at 10-years, show the PFS was better in patients that received Thalidomide: 88 %(95% Confidence interval (CI): 82 % to 96%) compared with control group: 69 % (95%:63%-77%) ($p < 0.001$), also OS was better 93 % (95%: 87%-97%) compared with control group: 75% (95 % CI 67%-73%) ($p<0.001$). We did not found any prognostic factor, except the use of maintenance, that can influence these data (dates no show). Only 11 patients, 5 with control group and 6 in maintenance need adjuvant radiotherapy; the group were small to found influence in PFS and OS.

Table 1: Clinical characteristics.

	No (%)	CR	Maintenance	
			Yes	No
Age (years) range	768 (43-79)	701 (48-78)	343 (48-79)	358 (45-77)
Median	64.7	91.0	58	61
Sex: Male	398 (46.1)	328 (46.7)	160 (46.6)	168 (46.9)
Female	410 (53.3)	373(53.2)	183 953.3)	190 (53.0)
PS * 0	384 (50.0)	336 (47.4)	153 (44.6)	161 (46.9)
1	299 (38.9)	209 (44.0)	153 (44.6)	169 (47.2)
2	85 (12.1)	54 (7.7)	37 (10.7)	28 (7.8)
Stage III	215 (27.9)	189 (26.9)	121 (34.9)	124 (34.6)
IV	553 (72.0)	512 (73.0)	242 (70.5)	234(65.3)
B symptoms	164 (21)	150 (21.3)	88 (25.5)	89 (24.4)
IPI ** 1	306 (39.8)	289((41.2)	140(40.8)	166 (45.1)
2	368 (47.9)	332(43.3)	156(50.0)	176(53.1)
3	90 (11.7)	88 (12.5)	40 (11.6)	50 (13.9)
4	4 (5.1)	2 (2.8)0	0	2 (5.5)
LDH *** High	200 (26.1)	169 (24,1)	89 (2.5)	80 (2.2)
B2M **** High	177((23.3)	135 (19.2)	67 19.5)	66(18.4)

6.1. Toxicity

Neutropenia grade I and II were observed during CHOP administration, but, no significance in delay treatment was necessary, another, including cardiac damage and second neoplasms has not has been observed. Rituximab were well tolerated, with minimal effects that no affect the dosage and time of the drug. Patients that received Thalidomide has neurological grade I, 23 cases, were observed, in all cases the drug was diminished to 50 mg, for 1 to 3 months, when the drug were newly taken, no toxicity was observed.

7. Discussion

FL has is a clinical and pathological heterogenous presentations, is a very sensitive neoplasm to different treatments, and have easy response to a many therapeutics approaches, achieved CR in most of 80 % of cases, but, relapse is also common, and in most cases before 2 months. In the other hand, 80% of

patients, can are alive > 10 years, because FL response to more lines of, until 6 or 8. It isa possible because FL response, but. Accumulative side effects an late toxicities are common. Multiple studies has been conducted, introduction of new drugs; but not statistically differences has been observed [5-13].

Some years ago, we performed various studies, and observed that relapse is common in nodal sites with a tumor mass > 10 cm; and that addition of adjuvant radiotherapy increase PFS and OS [9]. Also, the use of maintenance employed low-doses of cyclophosphamide, or interferon also, show modest results [7,8]. The use of maintenance appear to be the better option, and multiple agents as considered, but, most of these drugs have a greater possibility of had severe toxicities, acute and late, and are more expensive. Thalidomide, was the first immunomodulator agent in multiple myeloma, that improve outcomes, con tolerated toxicities toxicities well controlled and late events are very rare. However, without any specific reason, thalidomide was supplied for another immunomodulator: lenalidomide, that are associate with frequent acute toxicities: severe infections, immunodefiency, and second neoplasms. When we developed the study, we considered that taking in consideration the low growth

the tumor cells, is better employ the same drugs, but in an low administration. As show in these that PFS and OS were better in patients who received Thalidomide compared with the control group with minimal acute and late toxicities, Thus, we suggested that use of treatment in FL, will be considered at minimal effective doses, but, for prolonged time, It is clear that more studies are necessary to confirm these results.

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