

Thalidomide Improve Outcomes as Maintenance Therapy in Peripheral T- Cell Lymphoma

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Received: 01 July 2024

Accepted: 12 July 2024

Published: 16 July 2024

J Short Name: COO

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Citation:

Agustin Aviles, Thalidomide Improve Outcomes as Maintenance Therapy in Peripheral T- Cell Lymphoma. Clin Onco. 2024; 7(11): 1-3

Keywords:

Peripheral T-cell lymphoma; Thalidomide; Maintenance; Gemcitabine

1. Abstract

Peripheral T-cell lymphoma (not -specified) is a rare presentation of non-Hodgkin Lymphoma, associated with a worse prognosis. Multiple schedules, including the introduction of new drugs, and until no clear benefit has been observed, and in some, severe toxicities limited the use of these regimens. We performed a gemcitabine based chemotherapy, with two drugs that is considered in the treatment of T-cell lymphomas, etoposide and methotrexate, and introducing the use of maintenance with thalidomide. Progression-free survival (PFS) was better in patients that received thalidomide: 69.9% (95% Confidence interval (CI): 67.2% to 75.4) compared with control group: 48.8% (43.2 % to 54.5 %), ($p < 0.001$); also overall survival (OS): 72.0% (95% CI: 67.7% to

76.9%) compared with control group: 51 % to 69.0%) ($p < 0.001$) Moreover, the PFS and OS were better than most of the published reports, We show that the control group un scheme based in pharmacological drugs, could be better than more toxic schedules. More studies are necessary to confirm our results.

2. Introduction

Peripheral T-cell lymphoma (PTCL) is a group of non-Hodgkin that have a heterogeneous clinical and pathological presentation, account for 10 – 13 % of all non Hodgkin lymphoma, moreover had an aggressive course, until now, the complete response (CR) is < 35 %, with early relapse and only 12-22% of patients survived

more than 5 years. Recently, based on clinicopathological features, immunohistochemistry, genetic features, genomic sequencing have provided information to distinguish the presence of various subtypes; actually 27 subtypes of these lymphomas have been identified. Multiple treatments have been employed, but, most of these regimens have not shown an increase in response and outcomes. CHOP has been employed, with the addition of some drugs, but, these changes have not contributed to improve responses. Pharmacological studies suggested that some drugs: etoposide, methotrexate, immunomodulators, have been more useful in the treatment of these types of lymphoma, some studies employed gemcitabine in place of alkylating agents, and the regimens conserved the efficacy, but less hematological toxicities [1-7]. Recently it has been considered that the cause of early relapse, could be associated with the presence of residual tumor cells. Some studies performed stem cell transplant as consolidative regimen, but, the results were poor and severe toxicities are frequent. Recently reports in T-cell lymphomas as, NK-T cell nasal lymphoma and testicular lymphoma, with excellent results and minimal toxicities, we employed thalidomide at low doses [8-11]. Thus we planned a controlled clinical trial, employing a schedule of chemotherapy, with gemcitabine base associated with two drugs whose pharmacological have better response in T-cell lymphomas (12); the patients that achieved CR were introduced in a controlled study, of a maintenance; these patients were allocated to receive thalidomide or not.

Table 1: Clinical characteristics:

	Total	CR	Maintenance	
			Yes	Not
		(No)	%	
	128 (100)	101(78.0)	50 (49.5)	51 (50.1)
Age Median (range)	50.8(39-61)	57.0(38-66)	57.6(30-63)	58.(38-65)
Male	68 (53.1)	58 (57.0)	26(52)	27(52.9)
Female	60 (46.8)	58(52.7)	24 (45.8)	24 (42.0)
Stage 2	4(3.12)	3 (29.0)	2 (4.0)	1 (1.96)
3	70 (54.6)	59 (57.4)	26 (52.0)	27 (52.9)
4	54 (42.1)	22 (44.0)	23..0)	23 (45.0)
Symptoms , yes	22(17.6)	13 (12.8)	8 (16)	5 (9.8)
LDH , elevated	78 (60.9)	48 (47.5)	23 (46.0)	25 (49.0)
BM2, elevated	84 ((65.6)	51 (52.4)	28 (43.3)	29(56.8)
PS < 2	82 (64.9)	53 (52.4)	21 (42.0)	28 (54.9)

Abbreviations LDH: lactic dehydrogenase, B2M: beta 2 microglobulin

3. Patients and Methods

From May 2009 to December 2018, patients with pathological and immunohistochemistry confirmed were considered to entry to the trial. Criteria entry was followed; age > 18 years with not upper limit, no gender differences, performance status ≤ 2 , normal test from hematological, renal and hepatic, negatives for virus of immunodeficient human, hepatitis and C. In all cases computed tomographic of thorax, abdomen and pelvis, normal cardiac echocardiogram Patients that fulfilled the criteria received initially 6 cycles every 28 days, if CR was achieved, they were allocated in an proportion 1:1 to received or not thalidomide.

Chemotherapy:

Gemcitabine 1000 mg/m², days 1, 8 and 15.

Methotrexate 400 m/m², days 1 and 14, followed by rescue with folinic acid

Etoposide 400 mg /m², days 1 and 14.

Dexamethasone, 40 mg standard doses, days 1 to 4 and 9 to 14. To diminished the risk of severe granulocytopenia, granulocyte colony stimulating factor days 3 to 7, 16 to 19. Maintenance: Thalidomide, oral, 100 mg, days 1 to 21 day, in each every 28 days cycle for 36 months. The study was approved by the Ethical and Scientific Committee of our Institute and all patients signed an inform consent to participate in the study. Progression-free survival, (PFS) was measured from the date began treatment until disease progression, or disease progression: overall survival (OS) was measured from date of diagnosis, to date of death from any cause. Actuarial curves were calculated according to the Kaplan-Meier

methods, the two sided log-rank tests were employed to test the association between variables and PFS and OS. All p values are two sided and $p < 0,05$ were considered statistical significance

4. Results

All patients completed the six cycles programed; CR was achieved in 101 (74.9%). Univariate analysis did not show any statistical differences between the two groups of patients in relation for prognosis (data not show). Fifty-patients received the maintenance group and 51 were the control group, both groups were well balanced. The follow was at an median range of 6.7 (range 7.5 – 11.8) years. Actuarial curves at 10-years, showed that PFS were better in patients that received thalidomide: 69.9 % (95 % Confidence interval, (CI): 63.2 % to 75.4% that the

group did not received maintenance: 48.8 % (95% CI: 43.2% to 54.5 5) (p, 0.001), also OS survival were better in maintenance group 72.0% (95% CI: 67.7 to 76.9 %) compared with control group: 51% (95% CI: 45.5 to 56.0) $p < 0.001$. Granulocytopenia grade 1 and were observed in 32 cycles (4.1%): not severe toxicities were observed. During thalidomide treatment, neurological were minimal and well controlled; no late toxicities were observed and acute leukemia or second neoplasms were observed.

5. Discussion

PTCL is rare presentation, with multiple factors of worse prognosis, thus, most treatments were not effective and the outcome is poor; multiple regimens has been employed, including aggressive combined regimens, and stem cell transplant after chemotherapy,

but, again the prognosis remain poor. Recently, multiples new drugs has been tested in this special setting of patients, and until now, the results were not conclusive, with CR < 50 %, and median survival at 12 months < 25 %(12-15). Some year ago we explore the combination of cyclophosphamide,

methotrexate, etoposide, and dexamethasone (CMED), and show that this regimen is better compared with the CHOP conventional [7]. Also, we found that the gemcitabine-based regimen, following with maintenance with thalidomide, offer excellent results in T-cell lymphomas: NK-T cell nasal lymphoma and testicular lymphoma [8,9] Thus, show performed an study, treat patients with an regimen that employed drugs that could be useful in T-cell lymphoma PTCL and introduction the use of a maintenance phase, with thalidomide. Our results were excellent, CR, PFS and OS, were better when compared with the most recent reports, including novel agents. Acute toxicity was minimal, probably for the preventive use of granulocyte stimulating factor. We decided to employed gemcitabine, that has been useful in T-cell lymphomas, and based in pharmacology of etoposide and methotrexate that has been considered that are benefit in T-cell lymphomas. The use of maintenance therapy in PTCL has not been explored, but, thalidomide is an immunomodulator, extensive employed as maintenance therapy in multiple myeloma, but, suddenly, at the appearance of lenalidomide , these drug is useful, but acute: lymphopenia ,neutropenia, has been associated with severe viral and bacterial infections, and the most important, it was associated in an 30% with the development a second neoplasms. Moreover, patients whose did not received maintenance, have a better PFS and OS, compared with others studies. In most instances, as PTCL, when response is poor, I considered that more specific drugs, and moderate doses, could be benefit, and avoid the risks of severe toxicities observed with the novel agents. Also, the observation that some neoplasms have early relapse, can be associated with the presence of residual tumor cells, thus the use of maintenance therapy, but, these

approach will be carefully evaluated to avoid the risk, the risks of unnecessary toxicities. Is evident that is necessary that the results of this study will be confirmed for another trials Both authors performed t design, analyzed data, confirmed the results. Both authors declare that did not have conflict of interest and was performed with the resources of the Instituto Mexicano del Seguro Social.

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