International Journal of Clinical Science and Medical Research

ISSN(print): 2770-5803, ISSN(online): 2770-582X

Volume 03 Issue 12 December 2023

DOI: https://doi.org/10.55677/IJCSMR/V3I12-01/2023, Impact Factor: 6.967

Page No : 223-226

The Role of Thalidomide as Maintenance in Nasal Lymphoma

Agustin Aviles[1], Sergio Cleto[2]

[1,2] Oncology Research Unit, Hematology Department ; Oncology Hospital, National, Medical Center, IMSS, Ciudad de Mexico.

ABSTRACT

NK T-cell lymphoma nasal type, is a rare presentation of malignant lymphoma, and until now the best treatment has not well defined, the use of radiotherapy it is considered the best treatment , but relapse is common, and use of chemotherapy is necessary. We performed an open label clinical trial , combined the best cytotoxic agents that had employed, aggressive radiotherapy , and introduced the use of maintenance , with low doses of thalidomide. Between August 2010 to December 2018, 166 patients fulfilled the criteria entry; early stage, previously untreated, were enrolled. They received 3 cycles of gemcitabine, methotrexate, etoposide and dexamethasone, following for intensive modulated radiotherapy: 50 Gy in 25 sessions, and another 3 additional cycles of chemotherapy. Patients who achieved complete response were allocated to received thalidomide, oral, 100 mg daily , days to 21 in each cycle of 28 days; and no further treatment (control group) Complete response was obtained in 131 cases (81 %); actuarial curves at 5-years, showed that progression-free survival was worse : 60.8 (95% Confidence Interval (CI): 56.3% to 63.6%) in patients that did not received maintenance: 60.8% : 83.5% (95%CI: 75.2%- 89.1%)($p < 0.001$), also overall survival were worse in patients that not received maintenance : 56.8% (95% CI: 49.3% to 61.5%) compared with maintenance group: 77.8% (95%CI: 72.3% to 89.6%) $p < 0.001$. Acute toxicities were minimal and well controlled, no late toxicities has been observed.

Conclusion: We show in the present study that the use of the best individual drugs , aggressive radiotherapy improve the complete response rate, and the used of thalidomide employed as maintenance improve outcome, well controlled toxicities. Is evident that other studies were performed to define if the present regimen is the best option in these special setting of patients.

Published Online: December 07, 2023

KEYWORDS:

Nk t-Cell lymphoma, NK T-cell lymphoma nasal type, Maintenance therapy, Radiotherapy

INTRODUCTION

Extranodal nasal type NK t-cell lymphoma (ENKT) lymphoma is a presentation of malignant lymphoma, is rare in North-America and Europe, but is most frequent in Asia and Latin America; this clinical presentation represent a clinical, pathological and immunohistochemistry heterogenous disease and nasal presentation is the most common form of disease (stage I and II). Although initial presentation is localized, good performance status, low clinical risk, the prognosis is worse. Initially complete response (CR) I achieved in more of 60 % of patients, relapse is common, and overall survival (OS) at 10 years is < 35 %. Multiples treatment regimens has been performed, and until now, no exists an schedule that would be considered the better. When derivatives de asparaginase were introduced, improvement in response and outcome, but the drug was associated with excessive toxicities, and is not available in most countries (1-5).

Radiotherapy is considered the basis of any treatment, employed before, or after chemotherapy, and with the introduction of best techniques and programs that machines, the tolerance is excellent and toxicities, acute and later, were well controlled. Gemcitabine, etoposide, methotrexate and dexamethasone has been the drugs most employed, with different results (6-8), thus we conducted an open label Phase study to assess efficacy and toxicity of this schedule, intensive modulated radiotherapy was administer after 3 cycles, and we adding thalidomide to assess if maintenance with immunomodulator drug can improve outcome.

Corresponding Author: Agustin Aviles

Cite this Article: Agustin Aviles, Sergio Cleto (2023). The Role of Thalidomide as Maintenance in Nasal Lymphoma. International Journal of Clinical Science and Medical Research, 3(12), 223-226

PATIENTS AND METHODS

Between August 2010, to December 2018, 166 patients were including in the study, they have the classical immunophenotype of NK T-cell lymphoma: cells were positive for CD2, CD 56, and cytoplasmatic epsilon, CD 7 and CD 16; also they expressed cytotoxic -granule -associated protein, granzyme B, T-cell -restricted intracellular antigen (TIA-1), and performin. In situ hybridization for EBV-encoded.

All patients were enrolled if they complete the following staging: primary tumor involving the nasal cavity and nasopharynx (Stage I) or palate sinuses, tonsils ,hypopharynx , and hard palate (stage II), age > 18 years with no upper limit, no gender differences, performed status ≤ 2; previously untreated , negative for immunodeficiency virus test, as well as hepatitis A and B.

All patients underwent clinical staging evaluation, complete blood counts, serum analysis, determination of lactic deydrogenase, beta 2 microglobulin. Computed tomography of neck, thorax, abdomen and pelvis, magnetic resonant in some patients: aspirate and biopsy of bone marrow. The study was approved for the Ethical and Scientific Committee of our Institution, all patients signed an informed consent to participate in the study. The study was performed in the Oncology Hospital, National Medical Center, IMSS, that is a tertiary reference center, when the media annual of non-Hodgkin lymphoma is 490, and 22 were nasal lymphoma.

TREATMENT

Gemcitabine 1000 mg/2, iv, was administered days 1 and 8 of each cycle; methotrexate 600 mg/m2, day 1, following for folinic acid rescue, etoposide 400 mg/m2, days 1 and 2, and dexamethasone 40 mg standard dose . days 1 to 4. Each cycle was administered every 14 days. To diminished the risk severe hematological toxicities, granulocyte colony-stimulating factor, was administered at a dose of 5ug/day, days 2 to 12.

After 3 cycles, radiotherapy were administered with a photon bean of 6.0 were administered with intensity-modulated radiotherapy with a total dose 0f 50Gy in 25 fractions, over 5 weeks. In patients with nasal lymphoma limited to anterior part of the nasal cavity, the clinical target volume of extended fields radiotherapy encompass the bilateral nasal cavity , nasopharynx , frontal ethmoid sinus, and bilateral ipsilateral maxillary sinus. In patients with extended involvement (Stage II), the conformal radiotherapy was extended to include the paranasal and other adjacent organ structures.

After 3 weeks that radiotherapy was administered, 3 cycles of chemotherapy were administered. Patients that achieved complete response (CR), were allocated in an proportion 1: 1, to received maintenance: thalidomide 100 mg, oral, standard dose, days 1 to 21 of each 28 days cycle, for 18 months Statistical analysis Progression-free survival (PFS) w measured from the start of any treatment to the first local or distal disease evidence, until the last follow-up (December 2018). Overall survival (OS) was defined as the interval from the initiation of treatment to the date of death from any cause or last follow-up. Survival analysis was performed using the Kaplan-Meir method, and correlation analysis was performed using the log-rank test. A value 0f < 0.05 was considered statistically significant and all p values corresponded to two-tailed significant tests.

RESULTS

Between August 2010, to December 2018, 170 patients were evaluated, 4 were excluded, two did no confirm the diagnosis and 2 refuse the treatment, thus 166 patients were included . Table 1 show the main clinical and laboratory characteristics, no statistical difference were observes. Complete response was achieved in 131 cases (81%). The median follow-up was 68.9 (range 46 – 99)months. Relapse was observed in 11(16.9 %) patients in maintenance and 23 (34.8), (P < 0.001) in no maintenance group. Neither relapse occur in the first 30 months, and after 70 months no relapse has been observed. Relapse did not occur in sites that received radiotherapy. Actuarial curves at 5- years show that Progression-free survival (PFS) was 60.8 % (95% Confidence interval (CI) 51.3 to 63.6 %) that were worse that maintenance group : 83,5% (95%CI: 75.2 -89.1%) (p < 0.001). Also overall survival (0S) was worse in the group that did not received thalidomide: 56.5% (95%CI: 49.3 – 61.1%), compared with maintenance group: 77.8% (95% CI: 72.3- 84.6%) (p < 0.001).

Table 2 show the toxicities, in 996 cycles administered, no toxicity grade 3 or 4, were observed, the most common were hematological toxicities, the use of radiotherapy, 41 cases of mucositis, grade 1 and 2, were observed in the 166 (24.6%) patients. Thalidomide was well tolerated, no delay or reduction of dose were necessary. :Late toxicities were not observed until now.

DISCUSSION

NK-T cell nasal lymphoma, is a rare presentation of non-Hodgkin lymphoma, and probably it is the cause that controlled trials are scarce and the best treatment has not been defined. Initially radiotherapy have been advocated as the best treatment, because complete response were higher, and limited toxicities. But, with large follow-up, relapse was common, and it is clinical situation, the prognosis were worse (Thus, is evident that residual tumor cells, outside the radiotherapy, is the cause of relapse. Thus, adding chemotherapy will be necessary, but, although multiples schedules were proved, improve the outcome has not been observed. Some annotations could be considered, the best therapeutics approaches include some of this studies were gemcitabine, methotrexate, etoposide, and steroids, Derivatives of l-asparaginase show benefit, but, acute toxicities limited the use of these drugs, and in some cancer centers is not available. We show in this study, that the use of the combined chemotherapy improve response rate and

outcome Different therapeutic approaches have been reported for this disorder, and the use of radiotherapy following adjuvant chemotherapy appears to be the best approaches in term of survival (9-13).

We search if some proposed prognostic factors, as age, stage, high clinical risk (with different proposal) , can influence the prognostic, but any of the mentioned factors show that can influence response rate and outcome (data no show).Of date, relapse has not been observed in the radiotherapy site, thus, radiotherapy retain the useful in local disease.

In the best of our knowledge, maintenance has not been explore in this type of lymphoma, probably because in another lymphomas types, multiple agents has been tested as maintenance , without any clear benefit. Thalidomide, is an immunomodulator, that has been tested specially in multiple myeloma. Some recent reports,where thalidomide was adding during induction treatment , show that this drug can be employed in NK T-cell lymphoma. Taking in consideration that most studies employed large doses of thalidomide, it was associated with acute toxicity, and reduction of dose of delayed time of administration, thus we began with relative minor doses; that were well tolerated. The use of thalidomide increase PFS and OS, and with minimal and well tolerated.

Thus, we show the results of an uniform population of NK T-cell nasal lymphoma, employed a combination of radiotherapy, chemotherapy and introduced the use of maintenance phase with an immunomodulator , with improve outcomes; it is evident that more studies, that explore a maintenance phase, to confirm the results of this clinical trial.

CONFLICT OF INTEREST: Both authors disclose any conflict of interest .

ACNOWLEDEGMENT: The work did not received any outside support and was performed with the owner resources of the Instituto Mexicano del Seguro Social.

AUTHORSHIPS: Both authors contribute in conception and design of the work, acquisition and analysis of data for the interpretation of dates of the work. Drafting revision and critically for intellectual concepts and final approval pf the version of manuscript.

REFERENCES

1. Allen PB, Lee HO, Wicz MJ.: Management of NK/T-cell lymphoma nasal type. J Clin Oncol Pract 2019;15:513-520
2. Hernandez-Ruiz E, Alavrado E, Ibanez M et al.: Epidemiology and clinical characteristics of non-Hodgkin lymphoma in Mexico. World j Oncol 2021:12:28-33.
3. Oliveira -Costa R, Pereira J, Covas-LLAP, et al.: Extranodal NK/T-cell lymphoma nasal type. Front Oncol 2023: 13:1175545.
4. Yan Z, Wang Z, Zhou E et al.: Treatment of extranodal NK/T-cell lymphoma , Front Immunol 2023: 14:1038685,
5. Haverkos BM, Pan A, Gror A, et al.: Extranodal NK/T-cell lymphoma nasal type an updated of epidemiology , clinical presentation and natural history in North America and European cases, Curr Hematol Maling Res. 2016:11:514-522.
6. Zhang L, Sula L, Jia S, et al.: The DGP (dexamethasone, gemcitabine and pegasparigenase) regimen for treatment of extranodal natural killer t-cell lymphoma nasal type . Oncotarget 2018:7; 58394.
7. Ching P, Sho Nau Q, et al.: Modified Smile (m-smile) and intensity modulated radiotherapy for extranodal NK/T-cell nasal type in a single center population, Leuk Lymphoma 2020;61:3331-3341.
8. Xu PP,Xion J, Cheng S,et al.:A Phase II study of methotrexate, dexamethasone, etoposide an pegaspargase dsnwiched with radiotherapy in the treatment of newly designed stage I and II extranodal nodal natutal NK T-cell killer lymphoma nasal type, Biomed ‘2017:25:41049.
9. Nang Y, Wang CQ, Sun P, et al.: A comparison of treatment modalities for nasal NK T-cell in early stage, Oncotarget 2017:8:2036-20370.
10. Tsege E, Zhang WE, Knowng YC, et al.: Current treatments approaches for NK T-cell lymphomas . J Clin Exp Hematopatol 2017:57:98-108.
11. Sun Y, Li L, Zhang L, et al.:Outcomes of GCPT (gemcitabine, cisplatin prednisone and thalidomide) versus CHOP in newly diagnosed peripheral T-cell lymphoma patients. Ther Adv Med Oncol 2016:17:1063;
12. Liu Y, Li L, Zhang L et al.: The efficacy and safety of gemcitabine, cisplatin, prednisone ,thalidomide versus CHOP in patients with newly diafnosis peripheral T-cell lymphoma with analisis of biomarkers, Br J Haematol 2017:178: 773-780.
13. Aviles A, Neri N, Fernandez R et al.> Combined therapy in untreated in nasal NK-T cell lymphomas. Med Oncol 2013:30:637.

Table 1. Clinical and laboratory characteristics

	At diagnosis	CR	Maintenance	
		No (%)	Yes	Not
Number	166 (100)	131 (78.9)	65 (49.6)	66 (50.3)
Gender				
Male	91 (54.8)	80 (87.9)	34 (47.6)	34 (42.3)
Female	75 (45.1)	50 (78.4)	34(52.3)	36 (54.5)
Age (years)				
Median	48.3	47.3	49.6	50.2
Range	43-58	47-55	46.9	52.0
PS *				
1	112 (67.4)	80 (71.4)	39 (60)	41(62.2)
2	54(32.9)	51 (38.9)	26(48.1)	25 (46.3)
Stage				
I	40 (24.4)	31 (29.6)	10 (15.3)	21(31.8)
II	126 (75.9)	31 (24.6)	55 (84.2)	55 (8.3)
LDH > 2N* *	42 (24.4)	23 (54.6)	12 (28.5)	11(28.1)
B2M >2N* **	48 ((28.9)	29 (22.1)	15 (31.2)	14((21.2)

*Performance status, * lactic dehydrogenase > 2 normal value, *** Beta 2 microglobulin , > 2 normal values.

Table 2. Toxicities *

	Grade 1	Grade 2	Grade 3
		No (%)	
Granulocytopenia	84 (8.3)	21 (2.1)	0
Anemia	31 (3.1)	7 (0.7)	0
Thrombocytopenia	26 (2.6)	0	0
Fever related-granulocytopenia	8 (0.8)	0	0
Infection	7 (0.7)	3 (0.3)	0

Total of cycles: 996