

Short Communication

Radiotherapy Associated With Gemcitabine, Etoposide, Methotrexate and Dexametasone and Maintenance with Thalidomide Improves Outcomes in Patients with Nk-T Cell Nasal Lymphoma

Agustin Aviles*, and Sergio Cleto

*Oncology Research Unit Hematology Department; Oncology Hospital, National Medical Center, IMSS, Mexico****Corresponding author**

Agustin Aviles, Avenida Cuauhtemoc 330, Colonia Doctores, Zip 6620, Ciudad de Mexico, Mexico

Submitted: 11 November 2023**Accepted:** 20 November 2023**Published:** 21 November 2023**ISSN:** 2333-6684**Copyright**

© 2023 Aviles A, et al

OPEN ACCESS**Keywords**

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

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.

INTRODUCTION

Extra nodal 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 asparaginases 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.

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 cytoplasmic epsilon, CD 7 and CD 16; also they expressed cytotoxic -granule -associated protein, granzyme B, T-cell – restricted intracellular antigen (TIA-1), and perforin. 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, hypo pharynx, 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 dehydrogenase, 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.

TREATMENT

Gemcitabine 1000 mg/m², 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 diminish 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 beam of 6.0 were administered with intensity-modulated radiotherapy with a total dose of 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 field's 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) was 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-Meier method, and correlation analysis was performed using the log-rank test. A value of < 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 not 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 observed. 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 relapses 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 than maintenance group: 83, 5% (95%CI: 75.2 -89.1%) (P < 0.001). Also overall survival (OS) was worse in the group that did not receive 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

Table 1: Clinical and laboratory characteristics

	At diagnosis	CR		
		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		
	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			

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 explored in this type of lymphoma, probably because in other lymphomas types, multiple agents have 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.

CONCLUSION

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.

ACKNOWLEDGEMENT

The work did not receive 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 of the version of manuscript. The work was performed in the Oncology Hospital, National Medical Center, IMSS, is a tertiary reference center for our Institution for cancer patients we have a median of 534 patients with Non-Hodgkin lymphoma and 21 patients with Nasal lymphoma. Our statistical service, considered that it is very difficult to performed statistical table.

REFERENCES

- Allen PB, Lechowicz MJ. Management of NK/T-cell lymphoma nasal type. *J Clin Oncol Pract.* 2019; 15:513-520.
- Hernandez-Ruiz E, Alavrado -Ibarra M, Lien-Chang LEJ, Banda-Garcia L, Aquino-Salgado JL, Barragan-Ibanez G, Ramirez-Romero EF, et al. Epidemiology and clinical characteristics of non-Hodgkin lymphoma in Mexico. *World j Oncol.* 2021; 12: 28-33.
- de Oliveira -Costa R, Pereira J, Covas-LLAP, Guimarães Baiocchi OC. Extranodal NK/T-cell lymphoma nasal type. *Front Oncol.* 2023; 13:1175545.
- Yan Z, Wang Z, Yao S, Zhou E, Lui Y, Yao Z. Treatment of extranodal NK/T-cell lymphoma: From past to future. *Front Immunol.* 2023; 14: 1088685.
- Haverkos BM, Pan Z, Gru AA, Freud AG, Rabinovitch R, Xu-Welliver M, 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 Malig Rep.* 2016; 11: 514-522.
- Zhang L, Sula L, Jia S, Nan F, Li Z, Cao J, et al. The DGP (dexamethasone, gemcitabine and pegasparginase) regimen for treatment of extranodal natural killer t-cell lymphoma nasal type. *Oncotarget.* 2016; 7: 58396-58404.
- Ghione P, Qi S, Imber BS, Seshan V, Moskowicz A, Galasso N, 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.
- Xu PP, Xion J, Cheng S, Zhao X, Wang CF, Cai G, et al. A Phase II study of methotrexate, dexamethasone, etoposide a pegaspargase dsnwixed with radiotherapy in the treatment of newly designed stage I and II extranodal nodal natutal NK T-cell killer lymphoma nasal type. *EBioMedicine.* 2017; 25: 41-49.
- Cao J, Lan S, Shen L, Si H, Zhang N, Li H, et al. A comparison of treatment modalities for nasal NK T-cell in early stage: The efficacy of CHOP regimen based concurrent chemoradiotherapy. *Oncotarget.* 2017; 8: 2036-20370.
- Yamaguchi M, Miyazaki K. Current treatments approaches for NK T-cell lymphomas. *J Clin Exp Hematol.* 2017; 57: 98-108.
- Sun Y, Li L, Zhang L, Li X, Wang X, Fu X, et al. Outcomes of GCPT (gemcitabine, cisplatin prednisone and thalidomide) versus CHOP in newly diagnosed peripheral T-cell lymphoma patients. *Ther Adv Med Oncol.* 2020; 27: 1758835920923829.
- Chang Y, Li L, Zhang L, Duan W, Li X, Fu X, et al. The efficacy and safety of gemcitabine, cisplatin, prednisone, thalidomide versus CHOP in patients with newly diafnosis peripheral T-cell lymphoma with analysis of biomarkers. *Br J Haematol.* 2017; 178: 772-780.
- Aviles A, Neri N, Fernandez R, Huerta-Guzmán J, Nambo MJ. Combined therapy in untreated in nasal NK-T cell lymphomas: results of a clinical trial. *Med Oncol.* 2013; 30: 637.