

Short Communication

Treatment and Outcomes of Centrofacial NK/T Cell Lymphoma Nasal Type: A Report of 8 Cases and Literature Review

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Keywords

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Abstract

Purpose: Extra nodal natural Killer T cell lymphomas nasal types (NKTCL) are rare. Their prognosis is poor. Treatment is still not codified. We report the treatment and evaluation of a series of 8 patients with a review of the literature.

Patients and methods: Between february 1993 and december 2012, 8 patients with centrofacial NKTCL were treated in the CHU of Sfax in Tunisia .The average age of patients was 41.5 years with a sex ratio of 3. The diagnosis of NKTCL was confirmed by histological analysis completed by immuno histochemical study. All patients underwent combined treatment: chemotherapy with anthracyclines followed by radiotherapy at a dose of 40-45 Gy.

Results: After primary treatment, 4 patients achieved complete remission and 2 patients achieved partial remission. Two had progression during radiotherapy. The median follow-up was 28.5 months (range: 8-168 months). Only one patient is a live with complete remission. The cause of death was the lymphoma in 6 cases. One patient was died with complete remission.

Conclusion: The treatment of NKTCL, nasal type lymphoma is not standardized. Radiotherapy has a key role in the treatment of localized disease in combination with chemotherapy. However, the best sequence of radiation and chemotherapy has to be defined.

INTRODUCTION

Extranodal natural Killer T cell lymphomas (NKTCL) nasal types are uncommon. They represent 1.85% of aggressive lymphomas [1,2]. In Asia, this proportion is higher ranging between 25% and 39% [3, 4]. NKTCL generally occurs in male adults with a median age of 50 years [1,5]. It first affects the nasal cavity, nasopharynx, paranasal sinuses and larynx [5-7]. The lymphoma can then spread in surrounding tissues and organs, to the regional lymph nodes or to distant organs such as the skin, gastro-intestinal tract, lungs and testes [5,7,8]. The prognosis of this lymphoma is poor with a 3-years overall survival (OS) of 46.3% and a 5-years OS of 42% [6]. The treatment depends on the stage. For localized early stage, combined chemotherapy-radiotherapy is the standard treatment [9-11]. For advanced

stages, the poly chemotherapy is the main stay of treatment [12].

We retrospectively reviewed the clinical features and treatment outcomes of 8 patients treated in the department of radiotherapy of the Habib Bourguiba Hospital for centrofacial NKTCL.

PATIENTS AND METHODS

A retrospective chart review of 8 patients with centrofacial NKTCL managed in the department of radiotherapy of the Habib Bourguiba Hospital in Sfax Tunisia, between January 1993 and December 2012.

PATIENTS' CHARACTERISTICS

All patients had NKTCL of nasal type, that was confirmed

on histology and immunohistochemistry. Characteristics of patients and disease are summarized in table 1. A marked male predominance was observed, with a sex ratio of 3 (6 Male/ 2 Female). Mean age was 41.5 years and median age was 38.5 years (range: 24-65 years).

The circumstance of discovery was nasal obstruction in the majority of cases (5 patients) associated with epistaxis in tow cases and exophthalmoses in one case. One patient consulted for a cervical node, one patient for dysphonia and one for dysphagia. B symptoms were present in three cases. Inspection of the face revealed a hemi-facial edema in three cases. Cervical node involvement was noted in three cases. Nasal endoscopy, performed in all patients showed a burgeoning tumor in 5 cases. Examination of the oropharynx demonstrated necrotic ulceration in one case and burgeoning tumor in two cases. Cervical node was present in three cases.

Biopsies were performed in all patients and histological examination completed by immunohistochemical study confirmed the diagnosis of NK/T-Cell lymphoma, nasal type.

TREATMENT

All patients had combined treatment: chemotherapy followed by radiotherapy.

Almost all patients (7 patients) had 3 cycles of CHOP regimen: cyclophosphamide, doxorubicin, vincristine and prednisone. Only one patient had 4 cycles of ACVP regimen: doxorubicin, cyclophosphamide, vindesine, and bleomycine, prednisone, followed by 4 cycles of Holoxan-etoposide.

All treatment protocols in radiotherapy used a conventional fraction schedule of 2 Gy/ day, five days a week. The planned total dose to the planned area was 40-54 Gy. Cervical nodes were included in the target volume only when they were involved.

FOLLOW-UP

Patients were evaluated before each cycle of chemotherapy and weekly during radiotherapy for response and toxicity. Then, they were evaluated every 3 months for the first 2 years, every 6 months for the following 3 years and annually thereafter.

Complete physical examination with direct examination of tumor bed was required at each follow-up. In addition, computed tomography of the head and neck area was required annually.

Overall survival (OS) was measured from the diagnosis until time of the death from any cause, or until the final follow-up.

RESULTS

Treatment

The treatments received are summarized in Table 2.

All patients had combined treatment: chemotherapy followed by radiotherapy.

Almost all patients had 3 cycles of CHOP regimen. Only one patient had 4 cycles of ACVP regimen followed by 4 cycles of Holoxan-etoposide.

Six patients received the prescribed total dose of radiotherapy. Two patients stopped radiotherapy at a dose of 18 Gy (died) and 14 Gy (skin metastasis).

Outcomes

After the initial treatment, 4 patients were in complete remission and 2 were in partial remission. Two patients were in progress during radiotherapy.

The median follow-up was 28.5 months (range: 8-168 months). One patient is still alive in complete remission. The cause of death was lymphoma in 6 cases. One patient died in complete remission.

DISCUSSION

Extranodal NK/TCL, nasal type, are clinical entities which preferentially arise in the nasal cavities and sinuses (70%). They can also arise in waldeyer's ring (38%), in the oral cavity (14%) or the larynx and the hypopharynx (10%) [13]. They represent a rare pathology but the number of reported new cases is on increase due to a better knowledge of this disease [14-16]. Extranodal NK/TCL essentially affects men during the fourth and fifth decades with a sex ratio varying between 2 and 6.5 [15,17]. In our series, the mean age was 41.5 years and the sex ratio was 3.

Table 1: patients' characteristics.

	Sex	Age	PS	Antecedents	Presenting symptoms	B symptoms	Nodal involvement	LDH
1	M	24	1	0	Right cervical node	Yes	Yes	3XN
2	F	54	1	0	Dysphonia	Yes	No	N
3	M	65	1	Hypertension	Nasal obstruction Epistaxis	No	No	N
4	M	40	1	Diabetes	Nasal obstruction Exophthalmoses Blindness	No	No	N
5	M	37	1	0	Upper dysphagia	No	No	N
6	M	35	1	0	Nasal obstruction	No	No	N
7	M	38	2	0	Nasal obstruction Alteration of PS Right cervical node	Yes	Yes	2XN
8	F	39	1	0	Nasal tumefaction and obstruction epistaxis	No	Yes	N

M : male ; F : Female ; PS : Performance Status ; LDH : Lactate dehydrogenase ; N : normal

Table 2: treatment modalities and outcomes.

	Chemotherapy	Radiotherapy	Response	Outcome	OS (months)
1	4 cycles ACVP 4 cycles Holoxan, Etoposide	Waldeyer ring + cervical nodes 54 Gy	Local progression	Died at 18 Gy	12
2	3 cycles CHOP	Waldeyer ring 44 Gy	Complete remission	Complete remission	18
3	3 cycles CHOP	Waldeyer ring 40 Gy (stopped at 14 Gy)	Skin metastasis	Died	8
4	3 cycles CHOP	Facial + cervical nodes 40 Gy	Complete remission	Died from other cause	168
5	3 cycles CHOP	Waldeyer ring + cervical nodes 40 Gy	Complete remission	Died	42
6	3 cycles CHOP	Facial + cervical nodes 50 Gy	Complete remission	Died	113
7	3 cycles CHOP	Facial + cervical nodes 45 Gy	Partial remission	Died	8
8	3 cycles CHOP	Facial + cervical nodes 40 Gy	Partial remission	Died	39

CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; ACVP: doxorubicin, cyclophosphamide, vindesine, bleomycine, prednisone

Table 3: protocols and results of 2 prospective trials of concurrent chemo-radiotherapy.

Reference	Nb of patients	Stage	Protocol	CR rate	PFS	OS
KIM 2009 [27]	30	IE-IIIE	Concurrent radiotherapy (40-50.8 Gy ; 1.8-2 Gy/fraction) chemotherapy (cisplatin 30 mg/m ² weekly) Three cycles of VIPD were scheduled after CCRT	73.3%	85.1% at 3 years	86.2% at 3 years
YAMAGUCHI 2009/2012 [28]	33	IE-IIIE	Concurrent radiotherapy (50 Gy ; 2 Gy/ fraction) chemotherapy (3 cycles DeVIC)	77%	63% at 5 years	78% at 2 years 73% at 5 years

Nb : number ; VIPD : etoposide, ifosfamide, cisplatin and dexamethasone; CCRT : concurrent chemo-radiotherapy ; CR : complete response ; PFS : progression free survival ; DeVIC : dexamethasone, etoposide, ifosfamide, and carboplatin

The clinical presentation of the disease is non-specific and can often be misleading. In fact, presenting symptoms consist on non-specific nasal symptoms (epistaxis, nasal obstruction, and nasal discharge), dysphagia, dysphonia, facial edema or hemifacial pain.

A large number of biopsies are necessary to confirm the diagnosis of extranodal NKTCL, nasal type. The characteristic feature of this lymphoma is the presence of vascular lesions with tumour cells arranged in perivascular cuffs with vascular thrombi [18]. Immunophenotyping reveals expression of T lymphocytes as well as NK lymphocyte cell markers. The most typical immunophenotype of extranodal NKTCL, nasal type, is: CD2+, CD56+ with intracytoplasmic expression of anti-CD3 antibody and negative expression of CD3 on the cell surface [19]. It should be noted that despite progress in immunochemistry and molecular biology, extranodal NKTCL, nasal type, still remains a diagnosis of exclusion due to the absence of any specific clinical and histological features [15].

The treatment of extranodal NKTCL, nasal type, is difficult and complex. Treatment strategies are adopted from retrospective analyses and from phase II studies. It's generally admitted that for localized disease, combined chemotherapy-radiotherapy is the standard approach [10,20,21]. For disseminated NKTCL, chemotherapy is the mainstay of treatment [20].

LOCALIZED EARLY-STAGE NKTCL LYMPHOMAS

NKTCL is radiosensitive. In studies using radiotherapy alone (at least 50 Gy), overall response rates range from 77%

to 100%, with complete response varying between 52% and 100% [22,23,24]. However, the systemic relapse rates were as high as 25% to 40% [22]. Thus, radiation therapy alone was considered insufficient treatment and the combination of chemotherapy has emerged as a logical strategy to both increase the local and the systemic control rate. However, it should be noted that for patients intolerant of chemotherapy, because of serious co morbidities, radiotherapy alone (at least 50 Gy) may be acceptable if PET/CT clearly shows localized disease [20]. For chemotherapy, anthracycline-based regimens (4 cycles of CHOP regimen) followed by involved-field radiotherapy were largely employed but they were unsatisfactory [20,25].

In our study, 7 patients received chemotherapy with CHOP regimen. Radiotherapy was delivered to a total dose of 40-50 Gy. A complete response was achieved in 50% of cases.

Kim and al. [25] reports, in their retrospective study of 17 patients treated for localized stage I/II NKTCL by 4 cycles CHOP regimen followed by involved-field radiotherapy (45 Gy), a complete response rate of 58% with a 3- years OS of 59%. Sixty five per cent of those patients had disease progression during CHOP. These disappointing results may be related to the intrinsic properties of the lymphoma and to the non optimal dose of radiotherapy.

In fact, available data suggest chemoresistance of this type of lymphoma to protocols regimens CHOP or CHOP-like and this could be explained by the expression of the PGP (P-glycoprotein) in the tumor, which is an efflux protein, part of a multi-drug resistance (MDR) system [26-29].

Currently, the protocols based on L-asparaginase are widely used since this substance has been identified to be independent of the mechanism of resistance (MDR) of tumor cells [26,27,28,29]. A recent phase II study included 26 patients of localized stage nasal lymphoma who were treated with chemotherapy LVP regimen (L-asparaginase, vincristine and prednisolone) [29]. A radiation dose of 56 Gy was delivered after two cycles of chemotherapy. At the end of treatment, a complete response was achieved in 81% of cases with an overall survival and a 2-years progression-free survival respectively of 88.5% and 80.6%. The treatment-related toxicity was not very important with grade 3 leukopenia observed in only 2.7% of patients. Another chemotherapy regimen using GELOX (gemcitabine, oxaliplatin and L-asparaginase) also showed equivalent results with overall survival and progression-free survival at 2 years estimated at 86% [33].

In the SMILE study, a more intensive protocol based on L-asparaginase (dexamethasone, methotrexate, ifosfamide, etoposide and L-asparaginase) was used [29]. In this study, the response time was shorter: after only two cycles of chemotherapy with a complete response rate achieved in 90% of cases when associated with radiation therapy (50 Gy). The treatment-related toxicity was important with grade 3 neutropenia found in 61% of patients, grade 3-4 thrombocytopenia in 42% of patients and treatment-related mortality in 7% of cases. This led to a reduction in doses of chemotherapy in 30% of patients.

It is thus clear that radiotherapy has a key role in the management of Localized early-stage NKTCL lymphomas in combination with chemotherapy protocols using L-asparaginase. However, the optimal sequence of radiotherapy and chemotherapy has to be defined. Two prospective studies [27,28] showed the results of a treatment with concomitant chemoradiotherapy. These results are summarized in Table 3. Both studies showed that concomitant chemoradiotherapy increase the complete response rate and overall survival at 2 years compared with radiotherapy alone. Overall survival rates were 86% at 3 years and 70% at 5 years. However, these protocols were also associated with an important hematological toxicity.

Unless the promising results of those 2 studies, it still no clear evidence that concomitant radiotherapy/chemotherapy is necessary, as sequential chemotherapy/radiotherapy gives comparable results [20].

ADVANCED-STAGE AND RELAPSED/REFRACTORY NKTCL

Combination chemotherapy is the mainstay of treatment. The SMILE regimen is the most used currently [12, 30].

The prognosis of extranodal NKTCL, nasal type, is very poor with 5-years OS ranging between 10% and 45% [31,32]. In our series, the overall survival was 28.5 months. Only 2 patients survived for 5 years.

CONCLUSION

At the actual scientific knowledge, anthracyclines based regimens must be replaced with L-asparaginase based regimens. Radiotherapy is a mainstay of the treatment for localized disease.

It should not be retarded by chemotherapy. Concurrent protocols showed promising results but they may be reserved for patients with no co morbidities. Despite the therapeutic advances, the prognosis of NKTCL, nasal type, remain poor with an overall 5-year survival ranging between 10% and 45%.

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