Nasopharyngeal/nasal type NK/T lymphoma: Analysis of 23 cases and current review of the literature

Nazofarengeal/nazal tip NK/T lenfomaları:
23 olgunun analizi ve güncel literatür incelemesi

Yosra Ben Youssef, M.D.,[1] Iheb Bougmiza, M.D.,[2] Zahreddine Bouabid, M.D.,[5] Bechir Achour, M.D.,[1]
Haifa Regaieg, M.D.,[1] Badreddine Sriha, M.D.,[3] Malek Belkadhi, M.D.,[4]
Halima El Omri, M.D.,[1] Abderrahim Khelif, M.D.[1]

[1]Department of Clinical Hematology, Farhat Hached University Hospital, Sousse, Tunisia;
[2]Department of Family & Community Medicine, Farhat Hached University Hospital, Sousse, Tunisia;
[3]Department of Pathology, Farhat Hached University Hospital, Sousse, Tunisia;
[4]Department of Radiology, Moknine Hospital, Tunisia;
[5]Department of Otorhinolaryngology, Farhat Hached University Hospital, Sousse, Tunisia

Objectives: This study aims to identify the presenting symptoms, treatment and outcome of patients with nasal natural killer T (NK/T)-cell lymphoma and to find possible differences in survival based on Ann-Arbor stage and international prognostic index (IPI).

Patients and Methods: Computed tomography and biopsy results of 23 patients (15 males, 8 females; mean age 41 years; range 22 to 72 years) with extranodal NK/T-cell lymphoma who were treated at the department of clinical hematology between 1995 and 2011 were retrospectively analyzed.

Results: The median time from onset of clinical symptoms to histological diagnosis was five months. Most patients presented with nasal obstruction (69%) and rhinism (52%). The site of extranodal NK/T-cell lymphoma primarily involved nasal cavity in 39%. Orbital extension was observed in 26%. Lymphomas were classified as stage IE in 30.4%, stage IIE in 47.8% and stage IVE in 21.7%. Nineteen patients received treatment: 10 received chemotherapy plus radiotherapy, nine received chemotherapy only. We used several regimens of chemotherapy including some protocols containing etoposid, L-asparaginase and others without this drugs. Univariate analysis showed that lower IPI score, low Ann-Arbor stage and responsiveness to treatment with both chemotherapy and radiotherapy were significant factors influencing both OS and PFS.

Conclusion: Nasal type NK/T-cell lymphoma showed a poor response to the conventional anthracycline-based chemotherapy, thereby an investigation for a novel therapy is urgently needed to improve survival.

Key Words: Chemotherapy; nasal cavity; natural killer T cell lymphoma; prognostic factors; radiotherapy.

Amaç: Bu çalışmanın amacı, nazal doğal katil T hücreli (NK/T) lenfoma olan hastalarda semptom, tedavi ve sonuçları belirlemek ve Ann-Arbor evre ve uluslararası prognostik indeks (IPI) temelinde muhtemel farklılıkları saptamaktır.

Hastalar ve Yöntemler: Ekstranodal NK/T hücreli lenfoma olan ve 1995-2011 yılları arasında klinik hematoloji bölümünde tedavi edilen 23 hastanın (15 erkek, 8 kadın; ort. yaş 41 yıl; dağılım 22-72 yıl) bilgisayarlı tomografi ve biyopsi sonuçları retrospektif olarak değerlendirildi.

Bulgular: Klinik semptomların başlangıcından histolojik tanıya kadar geçen medyan süre beş aydı. Hastaların birçoğunda burun tıkanıklığı (%69) ve genizden konuşma (%52) şikayeti vardı. Ekstranodal NK/T hücreli lenfoma, hastaların %39'unda nazal kavite tutulumluydu. Hastaların %26'sında orbital ekstansiyon görüldü. Lenfoma hastaların %30.4'ünde evre IE; %47.8'inde evre IIE ve %21.7'sinde evre IVE olarak sınıflandırıldı. On dokuz hasta tedavi edildi; bunların 10'una kemoterapi artı radyoterapi; dokuzuna yalnızca kemoterapi uygulandı. Bir kısmı etoposid, L-asparaginaz içeren protokoller, bir kısmı ise bu ilaçları kapsamayan protokollerden oluşan çeşitli kemoterapi rejimleri kullanıldı. Tek değişkenli analiz düşük IPI skoru, düşük Ann-Arbor evresi ve hem kemoterapi hem de radyoterapiye yanıt verme durumunun, OS ve PFS'yi etkileyen önemli faktörler olduğunu gösterdi.

Sonuç: Nazal tip NK/T hücreli lenfoma, konvansiyonel antrasiklin bazlı kemoterapiye kötü yanıt verdiği için, sağkalımı iyileştirmek için yeni bir tedavinin araştırılması gerekmektedir.

Anahtar Sözcükler: Kemoterapi; nazal kavite; doğal katil T hücreli lenfoma; prognostik faktörler; radyoterapi.

Extra nodal natural killer T-cell (NK/T) lymphoma nasal type (ENKTL), is a rare subtype of non Hodgkin's lymphoma (NHL) accounting for 1% of all malignant lymphomas and 74% of lymphomas arising within the nasal cavity and paranasal sinuses in Korea.[1] It is prevalent in Asia and South America but exceptionally rare in western countries.[1-4]

Extra nodal natural killer T-cell lymphoma is a very aggressive disease, characterized by local destruction and refractoriness to treatment. The presentation can mimic primary otorhinolaryngologic pathology so that misdiagnosis is possible.[5]

This disease entity is categorized as an angiocentric T-cell lymphoma due to its characteristics of angiocentricity and angioinvasion according to the revised European American lymphoma classification and a frequent association with Epstein-Barr virus (EBV) infection.[6-10]

Pathologically, these tumors are composed of a polymorphous mixture of inflammatory cells admixed with atypical lymphocytes having hyperchromatic, enlarged, and convoluted nuclei. Immunohistochemical features show that the tumor cells most frequently express CD2+, CD3-, CD3€+, CD56+ and CD57-.[6,8]

It is well known that P glycoprotein, which is a product of the multi drug resistance 1 (MDR1) gene related to multidrug resistance, is expressed on tumor cells of ENKTL, leading to the concern that (MDR) might be an obstacle to successful treatment with anthracycline based chemotherapy (CT).[11-13]

Due to the small number of cases of this type of lymphoma, valuable randomized controlled trials are lacking, and the optimal treatment still remains unclear.

The goal of this study was to review the cases of ENKTL diagnosed at our institution to add to the current knowledge of the presentation, workup, treatment and outcome of this disease, and to determine if there was a significant difference in survival by stage, and international prognostic index (IPI) score.

PATIENTS AND METHODS

Between January 1995 and December 2011, 23 Tunisian patients (15 males, 8 females; mean age 41 years; range 22-72 years) who were diagnosed with NK/T-cell lymphoma at the Farhat Hached University Hospital, were included in this retrospective cohort study. All patients had histologically-confirmed NK/T-cell lymphoma according to the World Health Organization (WHO) classification.

Nasal NK/T-cell lymphoma was defined as lymphomas occurring within nasal cavity and/or upper aerodigestive tract such as oral cavity, palate, larynx, pharynx, and tonsil.

Demographic information, presenting signs and symptoms, histopathologic reports with immunophenotypic analysis, and EBV infection evaluation, investigation, stage disease, treatment and outcome, including response rate, relapse site, relapse treatment and overall survival were recorded. Staging was performed according to the Ann Arbor staging system. Cases were classified according to the IPI.

Diagnosis of NK/T-cell lymphoma was based on the detection of cytoplasmic CD3 (CD3€) positivity, and surface CD3 negativity, CD56 and cytotoxic granule associated proteins EBV positivity.

All neoplastic samples included in this study were subjected to determination of EBV tumor infection using in-situ hybridization of EBV encoded small RNA (EBERs). In all samples immunostaining for latent membrane protein 1 (LMP1) was performed with anti LMP1 antibody on formalin-fixed, paraffin embedded tissue.

Treatment

The anthracycline based CT regimen used was as follows: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), intensive conventional chemotherapy (ACVBP regimen), and ifosfamide, vindesine, aracytine, methotrexate (IVAM).

The non anthracycline based CT was DHAP (dexamethasone, cytarabine, cisplatin) and SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide).

CHOP regimen consisted of cyclophosphamide (750 mg/m^2 given i.v. day 1), doxorubicin (50 mg/m^2 i.v. day 1), vincristine (1.4 mg/m^2 but not more than 2.0 mg i.v. day 1) and prednisolone (100 mg po days 1-5). The CT cycles were repeated at 21st day intervals.

ACVBP regimen consisted of doxorubicin (75 mg/m^2 i.v. day 1), cyclophosphamide

(1200 mg/m² given i.v. day 1), vincristine (1.4 mg/m² but not more than 2.0 mg i.v. day 1; 5), bleomycin (10/m² i.v. day 1, 5) and prednisolone (60 mg/m² po days 1-5). The CT cycles were repeated at 14 days intervals.

GELT (groupe d'étude des lymphomes tunisiens) protocol (Tunisian study gro: consists in 4 ACVBP cycles, followed by 2 cycles of high dose methotrexate (3 g/m²), leucovorin (acide folinique rescue: 30 h after the initiation of methotrexate), than 4 cycles of (ifosfamid 1.5 g/m² + etoposide 300 mg/m² day 1) and 2 cycles of cytarabine (100 mg/m² for 4 consecutive days).

IVAM regimen consisted of ifosfamid (1.5 g/m² i.v. day 1-5), etoposide (150 mg/m² i.v. day 1-3), cytarabine (100 mg/m² i.v. day 1-3), methotrexate (3 mg/m² i.v. day 5), acide folinique rescue (50 mg/m² i.v. every six hours for 12 doses), the CT cycles were repeated at 28 day intervals.

DHAP regimen consisted of dexamethasone (40 mg i.v. days 1-4), cytarabine (2 g/m² i.v. day 2), and cisplatine (100 mg/m² i.v. day 1).

SMILE regimen was as follows: (dexamethasone 40 mg i.v. day 2-4) methotrexate (2 g/m² i.v. over 6 h day 1), ifosfamid (1.5 g/m² i.v. day 2-4), L-asparaginase (6000 UI/m² i.v. on days 8, 10, 12, 14, 16, 18 and 20) etoposid (100 mg/m² i.v. days 2-4), leucovorin (acide folinique rescue: 30 h after the initiation of methotrexate), mesna uroprotection (300 mg/m²) simultaneously with ifosfamid and at 4 and 8 hours after wards, granulocyte colony-stimulating factor (G-CSF) was initiated if the white blood cell (WBC) count decreased to less than 2000/mm³, the CT cycles were repeated at 29 day intervals.

The dose intensity and CT cycles varied according to patient's status. Involved-field radiotherapy (IFRT) was given at physian's discretion following CT; it was begun three weeks after the completion of planned CT. The total RT dose was 45 Gy or more administered over five weeks by conventional fractionation schedule (1.8 Gy/fraction, 5 fractions/week).

Response criteria

Tumor response to treatment was assessed according to Stanford response criteria described by Cheson et al.[14] Complete remission (CR) was defined as no evidence of residual disease; partial response (PR) was at least a 50% reduction in the tumor burden before initiation of treatment; local failure (LF) was defined as primary tumor persistent or relapsed after initial treatment. Systemic failure was described as any clinical, laboratory or radiological data indicating active diseases in extra nasal organs.

Statistical analysis

Overall survival (OS) and rates were estimated by the product limit Kaplan-Meier method.

Overall survival was measured from the start of initial treatment until time to death of any causes or until last follow-up.

Progression free survival was measured from the start of initial treatment until time of first local or distant progression or relapse, or until last follow-up or death.

Statistical significance was calculated by the log.rank.test.

Univariate analysis was performed to define the prognostic factors influencing survival rate.

Prognostic factors included «B» symptoms, paranasal and or systemic extension, lactate dehydrogenase, Ann Arbor stage, and IPI, response.

A *p* value of less than 0.05 was considered statistically significant. All data were analyzed using the SPSS (SPSS Inc., Chicago, Illinois, USA) for Windows 18.0 version software program.

RESULTS

The main characteristics of patients are listed in Table 1.

The median time from onset of clinical symptoms to histological diagnosis was five months (range 1-17 months).

The majority (n=16) suffered from nasal obstruction, rhinitis (n=12), epistaxis (n=6), and nasal tumor (n=5).

According to the Ann Arbor staging system, seven patients were classified as stage I disease, 11 were stage II, and five were stage IV disease. Among the patients with stage IV disease, the most distant affected organs were liver (n=3), bone marrow (n=2).

The nasal cavity was the most frequently involved primary organ in 16 patients. Orbital extension was seen in six cases.

Table 1. Patients characteristics

Patient	Age/sex	PS score	Symptoms	B symptoms	Initial site	Paranasal/systemic extension	LDH level	Ann Arbor stage	IPI	Initial treatment	RT	Relapse site	Relapse treatment	PFS	Outcome	OS
1	26/M	0	NO, headache, rhinism orbital oedema, epistaxis, hear pain, nasal twang	–	Nose	Nasopharynx maxillary sinus sphenoid sinus hard palate	Normal	IIE	0	CHOPx2 IVAMx3	–	–	–	12	F, D	12
2	48/M	2	Dysphagia, rhinism nasal twang	+	Palate, nose	Pharyngeal, cavum	Normal	IIE	1	CHOPx3	+	Nose	IVAMx4 DHAPx1	48	CR, R, D	50
3	38/M	1	NO, nasal twing	–	Nose	Palate	Normal	IE	0	ACVBPx4 ifosfamide+VP16:x4 cytosine arabinosidex2 (GELT)	+	–		59	CR, A	60
4	26/M	3	Rhinism	+	Paranasal sinus	–	Normal	IE	1	ACVBPx4 ifosfamide+VP16:x4 cytosine arabinosidex2 (GELT)	+	–		31	CR, lost to follow-up	32
5	41/M	2	Rhinism, NO, epistaxis nasal tumor	+	Nose	Pharyngeal, cavum	Elevated	IIE	2	CHOPx5, DHAPx1	–			4	PR, F, D	4
6	69/M	2	Nasal tumor nasal twang	–	Nose	Orbit	Normal	IIE	2	CHOPx6	–	–	–	9	CR, lost to follow-up	9
7	69/M	4	Headache, hear pain	+	Palate	Nose maxillary sinus orbit ethmoidal sinus hepatic lesions	Elevated	IVE	4	CHOPx6	–	–	–	5	F, D	5
8	41/F	1	Nasal obstruction epistaxis	–	Nose	–	Elevated	IE	1	ACVBPx4 ifosfamide+VP16:x4 cytosine arabinosidex2 (GELT)	+	Palate	Smilex2 radiotherapy	36	CR, A	87
9	39/F	0	Nasal tumor	–	Nose	–	Normal	IE	0	ACVBPx4 ifosfamide+VP16:x4 cytosine arabinosidex2 (GELT)	–	–		45	CR, A	46
10	60/F	3	Nasal tumor orbital oedema	+	Nose	Orbit, upper lip	Normal	IIE	2	CHOPx3	–	–	–	2	F, lost to follow-up	2
11	53/M	4	NO nasal tumor headache fever	+	Palate	Maxillary sinus nose splenic and hepatic lesions	Elevated	IVE	3	CHOPx1	–	–	–	1	F, D hepatic failure	1
12	71/M	4	Mandibular tumor	–	Mandibular	Hepatic, lung	Elevated	IVE	4	–	–	–	–	1	F, D	1
13	41/F	3	NO headache epistaxis, orbital oedema	–	Nose	Maxillary sinus orbit ethmoidal sinus frontal sinus	Normal	IIE	1	CHOPx8	+	–	–	13	CR, lost to follow up	13
14	28/F	1	NO, rhinism, epistaxis	+	Nose	Maxillary sinus ethmoidal sinus palate frontal sinus Bone morraw extension	Normal	IVE	1	ACVBPx2	–	–	–	3	F, D	3
15	46/F	1	NO, rhinism, epistaxis facial pain	–	Nose	Maxillary sinus Ethmoidal sinus	Elevated	IIE	1	ACVBPx4	+	Nose	ACVBPx4 RT	3	CR, lost to follow-up	96
16	34/F	1	NO, rhinism, nasal twang	+	Cavum	–	Normal	IE	0	ACVBPx4	+	–	–	108	CR, A	108
17	55/M	3	Fever, rhinism, NO	+	Nose	Maxillary sinus, ethmoidal sinus, palate, frontal sinus	Elevated	IIE	2	–	–	–	–	1	D	1
18	30/M	3	NO rhinism fever orbital oedema	+	Nose	Cavum maxillary sinus orbit palate	Elevated	IIE	2	ACVBPx4, IVAMx2	–	–	–	4	F, D	4
19	35/M	1	NO, headache	–	Nose	Maxillary sinus, orbit ethmoidal sinus	Elevated	IIE	1	ACVBPx4, CHOPx6	+	–	–	84	CR, D gastric adenocarcinoma	84
20	34/M	1	NO, rhinism, headache, orbital oedema	–	Nose	Maxillary sinus, ethmoidal sinus, palate, frontal sinus	Elevated	IV Medullary	2	–	–	–	–	3	D	3
21	36/M	3	NO, jugal tumor	+	Maxillary sinus	Upper lip	Normal	IIE	1	CHOPx1, ACVBPx2	–	–	–	5	F, D medullary extension	5
22	57/F	1	NO, rhinism	–	Nose	–	Elevated	IE	1	–	+	–	–	1	F, D colic angiomatosis	1
23	22/M	1	NO, rhinism, fever, jugal tumor	+	Larynx	–	Elevated	IE	1	Smilex2	+	Larynx		17	CR, R, D	18

NO: Nasal obstruction; IPI: International prognostic index; PS: Performance status; LDH: Lactate dehydrogenase; RT: Radiotherapy; PFS: Progression-free-survival; OS: Overall-survival; CR: Complete remission; PR: Partial remission; F: Failure; D: Dead; A: Alive.

In terms of PS score nine patients presented with a poor Eastern Cooperative Oncology Group (PS ≥2).

B symptoms occurred in 12 patients. The serum lactate dehydrogenase (LDH) was elevated in 12 cases. The IPI was low risk (≤1) in 14 cases, and high in nine cases.

The diagnosis of ENKTL was made after more than one biopsy in eight cases, histological features showed polymorphic lymphocytic infiltrate and prominent necrosis in all cases, and often angioinvasion (40%); all samples were positive for CD3. Ninety samples were detected for EBER, 16 samples were positive.
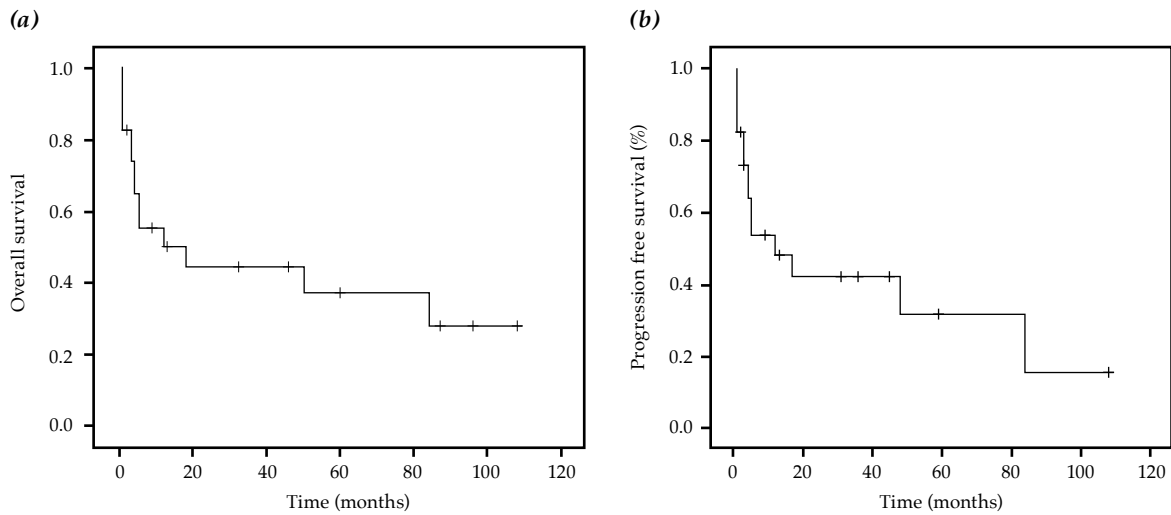
(a)

(b)

Figure 1. *(a) Overall surv ival curve, (b) Progression free survival curve.*

Treatment

Nineteen patients received CT alone (n=9) or in combination with RT (n=10), one patient was treated with RT alone.

Regimens containing anthracyclines were adopted in 18 patients (10 patients were treated with CHOP, 3 patients with IVAM, 10 patients with ACVBP).

Four patients received respectively DHAP regimen in two cases, SMILE in two cases.

Outcome

Twelve patients responded- 11 achieved a CR, and one a PR, while the other eight patients were refractory to treatment. Among the 12 responsive patients, three patients relapsed and died respectively at four, 18 and 50 months from diagnosis.

Causes of death

Fourteen patients died in our series, among them two died of colic angiomatosis after RT in one case, and gastric adenocarcinoma in one case. Twelve patients died of disease progression (local, regional, or systemic).

Survival

The median OS for all patients was nine months (range, 1-108), the median PFS was five months (range, 1-108). The actuarial Kaplan-Meier curve
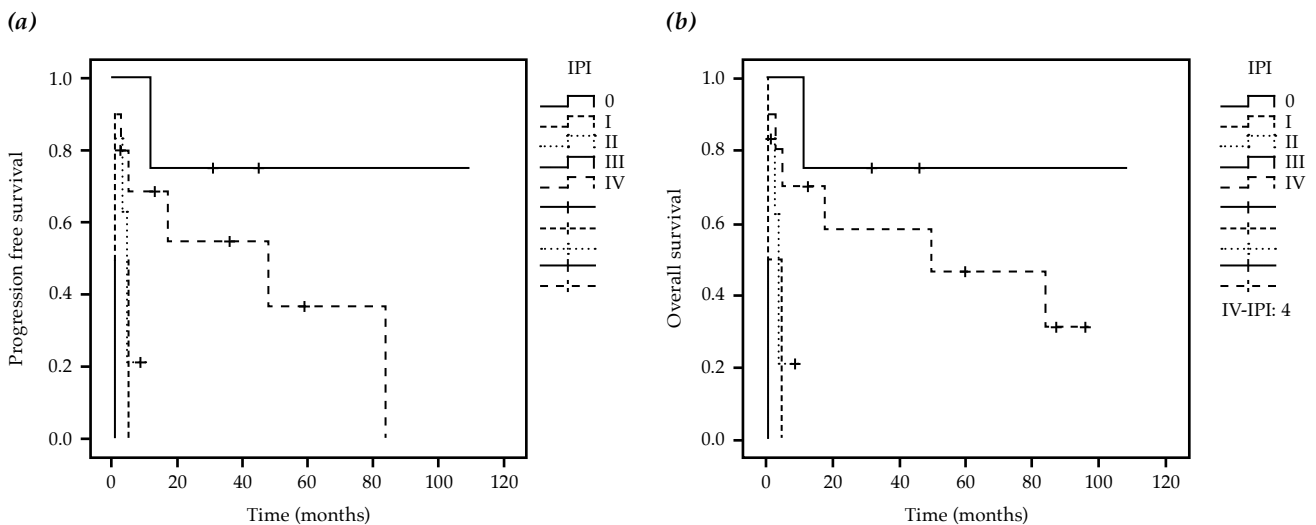
(a)

(b)

Figure 2. *Progression free survival according to international prognostic index score **(a)** (P value: 0.011), OS according to international prognostic index score **(b)** (P value: 0.001).*
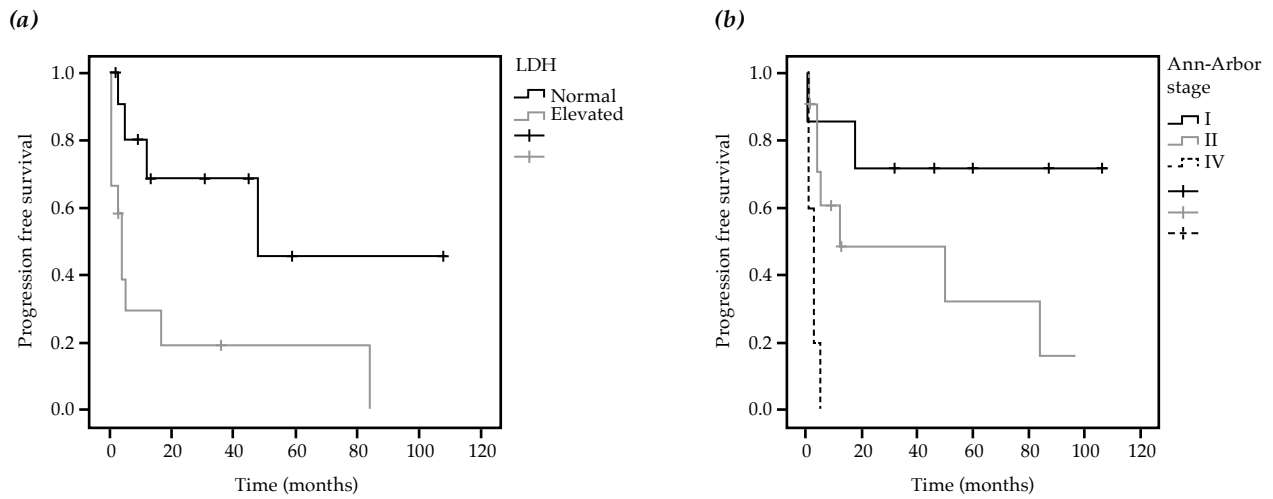
(a)

(b)

Figure 3. *Overall survival according to Ann Arbor stage* **(a)** *(P value: 0.001) progression free survival according to Ann Arbor stage* **(b)** *(P value: 0.001).*

shows a PFS of 31.8% at five years (Figure 1a) and an OS of 37.1% at five years (Figure 1b).

Prognostic factors

At univariate analysis the following parameters were evaluated: IPI score (0-1, versus ≥2), LDH (normal versus elevated), B symptoms, Ann Arbor stage, regimens containing CT+RT versus CT alone, and extranasal invasion or no, CR or no.

Lower IPI score, low Ann-Arbor stage, achievement of CR and responsiveness to treatment with both CT and RT were found to be the significant factors influencing both OS and PFS (Figures 2, 3, 5, 6).

Patients with normal serum LDH level are shown to have better PFS (Figure 4).

The low number of patients did not allow a multivariate analysis.

DISCUSSION

Extranodal NK/T-cell lymphoma, nasal type purses an aggressive clinical course with poor prognosis.[15] The incidence of the disease varies considerably in different parts of the world but it remains a rare disease, the incidence reported by Tababi et al.[16] is around one case per year.

ENKTL can occur at any age, but essentially affects subjects during the fourth and fifth decade,[16] in the study of Tababi et al.,[16] the mean age of patients was 52 years (range 35-81), this disease is more frequent in men than women with a sex ratio M/F of 6.5,[16] the sex ratio M/F was 1.87 in our study.

Initial symptoms are nonspecific, nasal obstruction is most common followed by purulent or bloody rhinorrhea, facial swelling, numbness, crusting. Other symptoms include fever, weight loss, general malaise, sore throat or aural fullness.[2]

In some cases, signs due to infiltration of local structures, such as cranial nerve palsies due to intraorbital or skull base extension.[16]

Bone marrow involvement is uncommon, though it may disseminate rapidly or be complicated by a hemophagocytic syndrome.[2,10]

On physical examination, patients may present with destructive lesions such as septal perforation, non healing ulcers and oral sinonasal fistulae.[2]
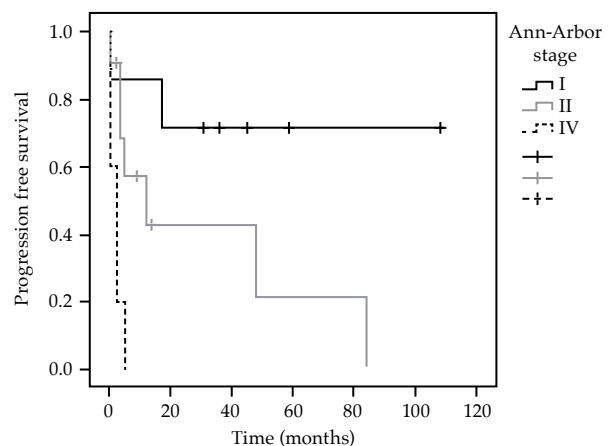
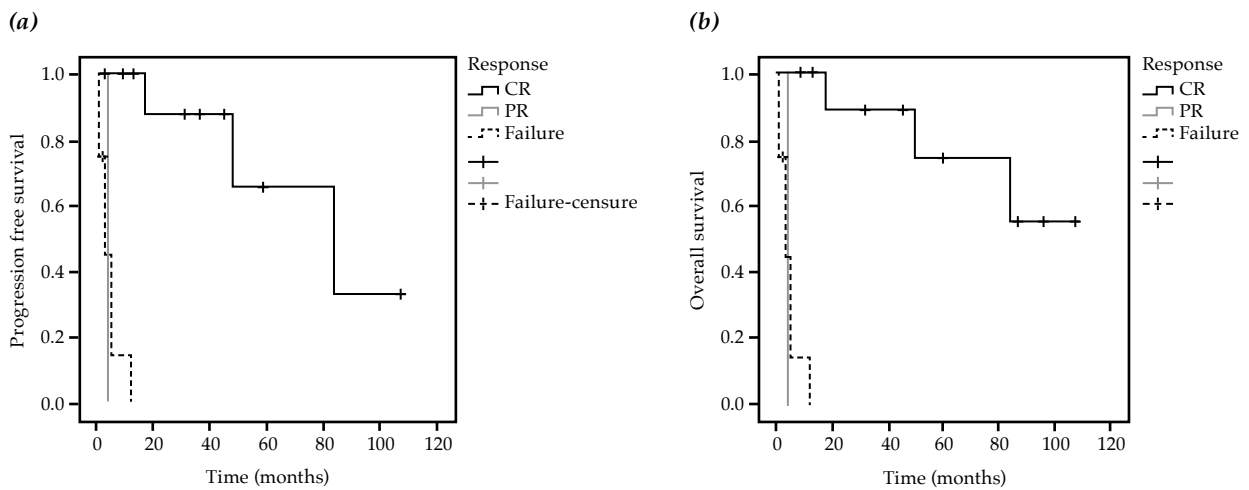**Figure 4.** *Progression free survival according to lactate dehydrogenase level (P value: 0.017)*

(a)

(b)

Figure 5. *Progression free survival status* ***(a)*** *(P value: 0.000) overall survival (OS) status* ***(b)*** *(P value: 0.00) of patients based on whether they achieved complete remission (CR) or not.* PR: Partial response.

Diagnosis of NK/T-cell lymphoma may be delayed in the event of non specific symptoms, so we need a high index of suspicion in the diagnosis of NK-cell lymphomas. Deep biopsies outside necrotic tissue must be obtained. The search for EBV is important as its presence is a factor for poor prognosis.[5] It is now generally accepted that a large number of biopsies must be performed to confirm the diagnosis of ENKTL.[16]

Computed tomographic scans are particularly helpful in evaluating the extension of the destruction and the involvement of sinuses and orbits, of the commonly reported finding include cloriding mucosal thickening, opacification and nasal septal perforation. Magnetic resonance imaging (MRI) may be superior in determining in the amount of tumor tissues versus reactive inflammatory disease. Gadolinium enhancement is also moderate and heterogeneous and is useful to evaluate the anatomical relations of the tumor with intracranial structures.[3,10]

When the diagnosis of ENKTL has been confirmed, a staging assessment must be performed prior to any treatment. The Ann-Arbor staging system is problematic for NK/cell lymphomas, because it does not take into account the tumor size, an important determinant in locally invasive tumors.[7]

To overcome this problem, a staging system devised for conventional sinonasal B-cell lymphoma has been tested in nasal NK-cell lymphomas. Initial results showed that stage T_1/T_2 diseases had superior outcomes compared with stage T_3/T_4 diseases.[8,10]

The IPI which considers not only the stage but also the age, performance status and the LDH, has been found to be prognostically relevant in nasal NK-cell lymphoma.[10] In our series patients with low IPI 1 or less were shown to have a better PFS, (p=0.011).

A staging system combining the tumor size, the Ann-Arbor staging and IPI may be appropriate and remains to be validated.[8]

ENKTL purses an aggressive clinical course with poor prognosis. Several recent clinical investigations have reported five-year OS ratios
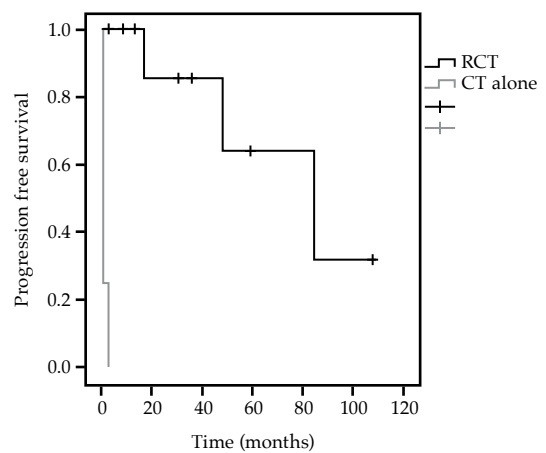
Figure 6. *Progression free survival status of patients based on whether patients were treated with radiotherapy plus chemotherapy (RCT) or chemotherapy (CT) alone.*

ranging from 36% to 49% for patients with stage I-II disease.[15] Up to now; optimal treatment strategies have not been fully recognized.

Although RT and CT are both effective for ENKTL, approximately 50% of the patients still fail in locoregional recurrence or systemic disease progression.[7]

The expression of MDR gene and high levels of P glycoprotein in NK cells underlies the resistance to anthracyclines and vinca alkaloids.[17]

Chemotherapy alone does not seem to play a role in the treatment of these patients, probably due to the lack of efficacy of conventional treatment.

The SMILE regimen is promising for these patients. It contains the steroid dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide. The components of SMILE are multidrug resistance unrelated agents.[12] Etoposide shows both in vitro and in vivo efficacy for EBV associated lymphoproliferative disorders and for NK-cell neoplasms.[12]

L-asparaginase induces the selective apoptosis of NK-lymphoma cells in vitro.[12]

Indeed, successful therapeutic results in NK-cell lymphoma have been reported for L-asparaginase either alone or in combination with other methods of CT.[12]

In light of the high relapse rate with RT alone, combination of CT and RT is the current standard care in patients who can tolerate systemic treatment.

External beam RT with a minimum dose of about 52 Gy delivered according to classical fractionation is recommended for localized stages I and II.

The SMILE was used in two cases in our study resulting in a complete remission in one patient and a relapse in the other patient.

Other so called "salvage chemotherapy protocols" are used in the absence of response to first line CT or in case of relapse consisting of etoposide, ifosfamide, methotrexate, prednisolone,[18] and bortezomib associated with CHOP,[19] possibly followed by autologous bone marrow transplantation (ASCT).

Allogenic HSCT, with the potential benefit of graft versus lymphoma (GVL) effect is a sound option for patients with advanced disease, but small series have shown that it is a potentially curative option.[20]

Unrelated cord blood stem cell transplantation could be considered as alternative source of stem cells for NK/T-cell lymphoma patients with no suitable donor even though the disease is in refractory phase.[4,21]

In conclusion, this study has some limitations. Firstly the cycles of CT applied to the patients were not the same; secondly the dose of RT was variable to some patients.

Finally due to the variances in patient's status and the institutional protocol, the time points to add RT among these patients are not consistent. Despite these pitfalls, we believe this study has provided some important information about the importance of initial CT with etoposide or association of L Asparaginase. In our center we have recently used the SMILE regimen.

Owing to the unsatisfactory results of conventional treatment, RT and/or CT, prospective data on larger series of patients treated homogenously also with innovative approaches is needed in order to establish the best treatment for this very aggressive lymphoma.

Declaration of conflicting interests

Funding

REFERENCES

1. Lee J, Suh C, Park YH, Ko YH, Bang SM, Lee JH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. J Clin Oncol 2006;24:612-8.
2. Zeglaoui I, Belcadhi M, Sriha B, Bouzouita K. Nasal NK/T-cell lymphoma in the paediatric population. Two case reports B-ENT. 2009;5:119-23.
3. Mestiri S, Zeglaoui I, Sriha B, Belcadhi M, Bouzouita K, Korbi S. Extra-nodal T lymphomas of the nasal cavities and sinuses. Ann Otolaryngol Chir Cervicofac 2008;125:188-92. [Abstract]
4. Mori Y, Aoki T, Takenaka K, Yamauchi T, Yamamoto A, Kamezaki K, et al. Successful treatment of refractory advanced nasal NK/T cell lymphoma with unrelated cord blood stem cell transplantation incorporating focal irradiation. Int J Hematol 2010;91:107-11.
5. Mani R, Belcadhi M, Krifa N, Sriha B, Elomri H, Ben Ali M, et al. NK/T-Cell lymphoma of nasopharynx. Ann Otolaryngol Chir Cervicofac 2006;123:189-93. [Abstract]

6. Li YX, Yao B, Jin J, Wang WH, Liu YP, Song YW, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol 2006;24:181-9.

7. Ma HH, Qian LT, Pan HF, Yang L, Zhang HY, Wang ZH, et al. Treatment outcome of radiotherapy alone versus radiochemotherapy in early stage nasal natural killer/T-cell lymphoma. Med Oncol 2010;27:798-806.

8. Kwong YL. Natural killer-cell malignancies: diagnosis and treatment. Leukemia 2005;19:2186-94.

9. Bossard C, Belhadj K, Reyes F, Martin-Garcia N, Berger F, Kummer JA, et al. Expression of the granzyme B inhibitor PI9 predicts outcome in nasal NK/T-cell lymphoma: results of a Western series of 48 patients treated with first-line polychemotherapy within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. Blood 2007;109:2183-9.

10. Gill H, Liang RH, Tse E. Extranodal natural-killer/t-cell lymphoma, nasal type. Adv Hematol 2010;2010:627401.

11. Suzuki R. Treatment of advanced extranodal NK/T cell lymphoma, nasal-type and aggressive NK-cell leukemia. Int J Hematol 2010;92:697-701.

12. Yamaguchi M, Suzuki R, Kwong YL, Kim WS, Hasegawa Y, Izutsu K, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci 2008;99:1016-20.

13. Kim SJ, Kim K, Kim BS, Kim CY, Suh C, Huh J, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol 2009;27:6027-32.

14. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.

15. Yong W, Zheng W, Zhu J, Zhang Y, Wang X, Xie Y, et al. L-asparaginase in the treatment of refractory and relapsed extranodal NK/T-cell lymphoma, nasal type. Ann Hematol 2009;88:647-52.

16. Tababi S, Kharrat S, Sellami M, Mamy J, Zainine R, Beltaief N, et al. Extranodal NK/T-cell lymphoma, nasal type: report of 15 cases. Eur Ann Otorhinolaryngol Head Neck Dis 2012;129:141-7.

17. Lee J, Kim WS, Park YH, Park SH, Park KW, Kang JH, et al. Nasal-type NK/T cell lymphoma: clinical features and treatment outcome. Br J Cancer 2005;92:1226-30.

18. Kim BS, Kim DW, Im SA, Kim CW, Kim TY, Yoon SS, et al. Effective second-line chemotherapy for extranodal NK/T-cell lymphoma consisting of etoposide, ifosfamide, methotrexate, and prednisolone. Ann Oncol 2009;20:121-8.

19. Lee J, Suh C, Kang HJ, Ryoo BY, Huh J, Ko YH, et al. Phase I study of proteasome inhibitor bortezomib plus CHOP in patients with advanced, aggressive T-cell or NK/T-cell lymphoma. Ann Oncol 2008;19:2079-83.

20. Pagano L, Gallamini A, Trapè G, Fianchi L, Mattei D, Todeschini G, et al. NK/T-cell lymphomas 'nasal type': an Italian multicentric retrospective survey. Ann Oncol 2006;17:794-800.

21. Yokoyama H, Yamada MF, Ishizawa K, Yamamoto J, Tomiya Y, Harigae H, et al. Successful treatment of advanced extranodal NK/T cell lymphoma with unrelated cord blood transplantation. Tohoku J Exp Med 2007;211:395-9.