NK/T Cell Lymphoma: A Tertiary Centre Experience

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Abstract Extranodal NK/T-cell lymphoma (ENKTL), nasal type, is a rare type of non-Hodgkin lymphoma that is commonly seen in East Asian countries and is associated with Epstein-Barr virus infection. This is a retrospective study where we describe nine cases of ENKTL; nasal type diagnosed and treated at our center over a period of 2 years. These cases were analyzed retrospectively for clinical presentation (age, sex, site of involvement), immunophenotype, treatment, response and toxicity profile. Sino-nasal symptoms (blocked nose, headache, epistaxis, regurgitation) were the most common presenting complaints ($n = 8$). Almost 67 % ($n = 6/9$) of the cases were referred from Bhutan. Necrosis and angiocentricity were the commonest histological features. Depending on the stage of the disease patient were initially treated with chemotherapy (SMILE/CHOP) and Radiotherapy (IFRT). We describe our experience of management of ENKTL, where we observe that Bhutan could be endemic region for this rare tumour.

Keywords NK/T cell lymphoma · T-cell lymphomas in India · SMILE therapy · SMILE in NK/T cell lymphoma

Introduction

Extranodal NK/T-cell lymphoma (ENKTL), nasal type is a rare, very distinct type of lymphoproliferative disorder known to arise from the NK/T cells. Previously called as angiocentric lymphoma in the REAL classification, this disorder was renamed as NK/T cell lymphoma, nasal type in the WHO classification 2008. It has got a specific geographical predilection for Asian and South American populations where it may comprise 2–7 % of all non Hodgkin lymphomas [1–3]. This disease is known for its predominant involvement of the nasopharynx, strong association with Epstein–Barr virus (EBV) and carries a poor prognosis with a 5 year cumulative probability of survival ranging from 30 to 40 %. [4, 5] One of the postulated reasons is the high concentration of P-glycoprotein on natural killer (NK) cells which leads to multi-drug resistance, hence response to traditional anthracycline containing regimens is poor. Incorporation of drugs like L Asparaginase which bypass the effect of P-glycoprotein has improved the outlook for this disease. Here we describe our experience in management of this disease.

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Materials and Methods

This is a retrospective study carried out at our center over a period of 3 years from 2011 to 2014, and included 9 patients with histopathological diagnosis of NK/T-cell lymphoma. Data on clinical history, physical examination, performance status, baseline haematological and biochemical parameters, histology, imaging and bone marrow studies were collected from the computer database. The study included biopsy/excision material of patients registered within the hospital as well as those referred from

outside. The cases were reviewed by two pathologists (NA/IA). Tissue was processed in 10 % formalin, and 4 µm paraffin sections were stained with hematoxylin and eosin (H & E). Immunohistochemistry (IHC) along with appropriate positive and negative controls was performed in all cases using a Ventana Benchmark XT auto-stainer with antibodies obtained mainly from Dako (Glostrup, Denmark). In situ hybridization for EBER was performed using a Ventana EBER-ISH detection kit on a Ventana Benchmark XT auto-stainer. Formalin fixed, paraffin-embedded tissue Sections (4 µm) were floated on silane-coated slides and incubated at 60° C for 3–4 h. De-paraffinised slides were further processed in the Ventana auto-stainer, which included conditioning, treatment with Protease II for 8 min, application of an INRORM EBER probe and Blue Detection reagent, and counter staining with Ventana Red Stain II. A known EBV LMP1 positive lymphoma was used as positive control.

Treatment records were reviewed and the nature of treatment, duration, toxicity and nature of responses were collected and rates of complete remission, overall survival and progression free survival were calculated for this cohort. Response evaluation was done as per standard criteria. Toxicity has been documented as per Common Terminology Criteria for Adverse Events version 4.0. Progression was defined as the time at which a second line therapy was started or death due to any cause.

Results

Patients

A total of 09 patients were diagnosed with NK/T cell lymphoma over a 3 year period (Table 1) and included 5 females and 4 males. The median age of this cohort was 39 years (range 29–64 years). Six patients from this cohort were residents of Bhutan. The other three cases were of Indian ethnicity (West Bengal). Sino-nasal symptoms (blocked nose, headache, epistaxis, regurgitation) were the most common presenting complaints ($n = 8$). B symptoms were noted in over one-third of the patients ($n = 4/9$). An ulcerative, necrotic mass lesion in the nose and/or hard palate along with cervical lymphadenopathy was the commonest physical finding ($n = 8/9$). Haepatosplenomegaly was seen in a single case. Only two patients had poor performance status at presentation. Seven out of these 9 patients had elevated LDH, 3/9 patients had advanced stage disease (stage III/IV) and 2/9 patients had high IPI (>3). None of the patients had bone marrow involvement. The median follow up was 10 months (range 03–36 months).

Morphology/Immunophenotype

Morphologically, the neoplastic cells were predominantly medium sized in most cases. Ulceration (6/8), necrosis (7/8) and vascular invasion (4/8) were the common histopathologic findings (Table 1). All cases were positive for CD56 and CD3 except one case which was negative for CD3 (UPN1). This case was CD2+, CD56+, CD30 (focal and weak) positive and negative for CD20 and PAX5. EBER status of this case was not available for evaluation. Weak and focal CD30 expression was documented in all these cases. EBER-ISH/LMP1 was done in 6 patients and was positive in all 6 patients. The MIB proliferation index ranged from 40 to 90 %.

Treatment

Four out of nine patients received CHOP as the first line treatment (Table 2) and the rest received a regimen comprising Methotrexate, L-Asparaginase and Etoposide (SMILE) as the first line therapy [6]. The median number of cycles received by patients was 6 (range 1–6) in the CHOP group and 3 (range 1–4) in the SMILE group. Additionally two patients received SMILE as salvage therapy. Five patients received further radiotherapy to the nasal primary with a median dose of 50.4 gy.

Response

Majority of patients on CHOP ($N = 3/4$) progressed on therapy, except one who achieved CR and continues to remain in CR after 34 months of follow up. Of these 3 progressive cases, 2 were salvaged with SMILE + radiotherapy while one was palliated due to poor general condition. The two patients who received salvage therapy achieved CR after 4 cycles of SMILE followed by radiotherapy.

Amongst the five patients who received SMILE as first line therapy two achieved complete response, one died due to therapy related complications (gram negative sepsis), another had progressive disease and one patient had severe toxicity after the 1st cycle and hence could not receive further chemotherapy. The median overall survival (OS) and progression free survival (PFS) of this entire cohort was 10 months (range 03–36 months) and 5.5 months (range 01–34 months). The median PFS following therapy with SMILE was 9 months.

Toxicity

CHOP was generally well tolerated with no major haematologic or non haematologic toxicity. On the other hand, haematologic toxicity was ubiquitous following

Table 1 Patient characteristics and pathological findings at baseline (n = 9)

Parameter	UPN1	UPN2	UPN3	UPN4	UPN5	UPN6	UPN7	UPN8	UPN9
Age/sex	30 M	31 F	29 F	39 M	56 F	41 F	64 M	30 M	55 F
Ethnicity	Bhutan	Bhutan	Bhutan	Indian	Bhutan	Bhutan	Indian	Bhutan	Indian
ECOG	3	3	2	1	1	2	1	1	1
Symptoms	D, O	E	BN	BN	BN, E	U palate, NR	LA, ES	BN	BN, E
Signs	M, LN	U palate	M, LN	M, U palate	M, LN	U palate, post pharyngeal wall	HSM, A	M	M, U palate
Haemoglobin (Gm/Lit)	102	94	110	84	97	121	117	164	116
WBC count ($\times 109/\text{Lit}$)	6.4	5.2	6.1	6.1	2.6	7.6	10.7	5.4	10.4
Platelet count ($\times 109/\text{Lit}$)	293	500	325	320	201	241	148	285	128
LDH (313–618 U/Lit)	707	1195	832	663	879	521	782	638	540
Stage (Ann Arbor)	IIAE	IVAE	IIAE	IAE	IIAE	IIAE	IVB	IAE	IAE
IPI	2	4	1	1	1	1	3	1	0
Vascular invasion	–	+	+	–	–	+	NA	+	+
Ulceration	–	+	–	+	+	+	NA	+	+
Necrosis	+	+	+	+	+	+	NA	+	+
CD3	–	+	+	+	Focal+	+	+	+	+
CD56	+	+	+	+	+	+	+	+	+
CD30	Focal+	+	NA	+	+	+	+	+	Focal+
EBER/LMP1	NA	+	+	+	+	+	NA	NA	+

D dysphagia, *O* odynophagia, *E* epistaxis, *BN* blocked nose, *U* ulcer, *NR* nasal regurgitation, *LA* loss of appetite, *ES* early satiety, *M* mass in nasopharynx, *L* lymphadenopathy, *HSM* hepatosplenomegaly, *A* ascitis, *NA* not available

Table 2 Treatment, response and toxicity profile of these cases

Patient	First line treatment	No. of cycles received	Response to first line	Second line	No. of cycles	Response to IInd line treatment	Toxicity
UPN1	CHOP	6	Progression	SMILE	4	CR	N, T
UPN2	CHOP	1	Progression	Palliation	NA	NA	Nil
UPN3	CHOP	4	Progression	SMILE	3	CR	N, T
UPN4	CHOP	6	CR	Nil	NA	NA	Nil
UPN5	SMILE	3	Progression	Nil	NA	NA	N, T, thrombosis
UPN6	SMILE	1	TRM	Nil	NA	NA	N, T, TRM
UPN7	SMILE	2	Due to toxicity shifted to second line	L-CHOP	1	Progression	N, T
UPN8	SMILE	4	CR	Nil	NA	NA	N, T
UPN9	SMILE	3	CR	Nil	NA	NA	N, T, thrombosis

N neutropenia, *T* thrombocytopenia, *TRM* therapy related mortality, *NA* not available, *CR* complete remission

therapy with SMILE. All patients developed Grade IV neutropenia and 6/7 patients developed grade IV thrombocytopenia. Deep venous thrombosis was seen in two patients and in both these cases, this was related to central

vascular access devices. There were no instances of pancreatitis or liver dysfunction in this cohort. There was one treatment related death in a patient who received SMILE (gram negative sepsis).

Discussion

NK/T-cell lymphoma is a distinct clinico-pathologic entity associated with EBV and is more commonly seen in Asian and South American populations.

An interesting observation from this series is the clustering of patients from region of Bhutan ($n = 6/9$, 66 %). Bhutan is a small landlocked country in south East Asia with a population of 776000 (*Source*: Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, *World Population Prospects: The 2012 Revision*). There is no published data on epidemiology of lymphomas from Bhutan. NK/T cell lymphoma comprised 26 % ($n = 6/23$) of all cases of non-Hodgkin lymphomas in patients of Bhutanese ethnicity treated in our center. Of the only 2 large series comprising of 37 cases and 84 cases of ENKTCL described from India, only one study has actually documented the ethnicity of the patients with these neoplasms. Almost half of the cases in that study were from western India where as East India (West Bengal/Assam) constituted 20 % of the overall ENKTCL [7, 8].

NK/T cell lymphoma is a disease of young adults and most patients present with sino-nasal symptoms. A necrotic, ulcerating mass in the nasopharynx is the most common clinical finding which is similar our findings. Generalised lymphadenopathy and hepatosplenomegaly are usually features of disseminated disease. These cases were previously referred to as “non-nasal NK/T cell lymphoma”. However modern imaging with PET CT has shown that most if not all “non-nasal NK/T cell lymphomas” have an occult nasal primary. [9].

Histopathology of the tumour commonly shows angiocentricity and angio-destruction leading to extensive necrosis and ulceration. The tumour cells have a cytotoxic T-cell phenotype and are for CD2, CD3, CD56 and EBV. However CD3 negative cases have been previously reported. [7] In this present series all cases were positive for CD56 and CD3 except one patient in whom CD3 was negative. EBER was positive in all cases wherever available.

Congruent with other studies, standard anthracycline based chemotherapy was ineffective in 3 out of 4 patients progressing on CHOP in this present series [10]. The median PFS following therapy with CHOP was 4.5 months (range 2–34 months). Patients treated with L-Asparaginase based regimen showed better response with CR rate of 50 %. In patients with early stage disease the CR rate was better at 66 %. Patients with advanced disease (higher stage, high IPI) tended to do poorly irrespective of the modality of treatment. These figures are comparable with previously published studies on L-Asparaginase based therapy for NK/T cell lymphoma [11].

Haematologic complications are the most common toxicity associated with SMILE therapy and this usually requires dose reduction in subsequent cycles. The other reported toxicities include hepatotoxicity and pancreatitis, although none of the patients in this cohort developed these toxicities. L-Asparaginase may induce a pro-coagulant state and result in thrombosis. This is particularly problematic as patients receiving treatment with SMILE often require central venous access devices.

NK/T cell lymphoma is a radio-sensitive disease. In initial studies, when used as the only treatment modality, complete responses were observed in 52–100 % of patients with a overall response rate between 77 and 100 %. [5, 12, 13] However the rates of systemic relapse were as high as 45 %. [5] Therefore it is not recommended to use radiotherapy alone in management of this disorder. Additionally the dose and radiation fields are important considerations. It is recommended to use at least 50 Gy over an extended field incorporating the para-nasal sinuses, nasopharynx and palate for optimum results [5, 12, 14].

In this series we describe our experience of management of a small series of ENKTCL from eastern India. Our data suggests that Standard anthracycline based chemotherapy is ineffective and suggest that patients with limited stage disease be treated with combination chemotherapy with L-Asparaginase based regimens along with radiotherapy to the nasal primary. In addition we observe that Bhutan could be endemic region for this rare tumour. This though is a first report of NK/T cell lymphoma in patients of Bhutanese origin and would require a large study to confirm these initial observations.

Compliance with Ethical Standards

Conflict of interest There is no conflict of interest to declare.

Ethical standards This is a retrospective studies, therefore for this type of study formal consent is not required.

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