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Original Article

Combined Modality Treatment with "Dexamethasone, Methotrexate, Ifosfamide, L-Asparaginase, and Etoposide" Chemotherapy and Involved Field Radiotherapy for Early Stage Natural Killer/T Cell Lymphoma with Local Tumor Invasiveness: A Single-institution Study from India

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Abstract

Context: Patients with early stage extranodal natural killer/T-cell lymphoma, nasal type (ES-NKTCL) and local tumor invasiveness (LTI) show poor treatment outcomes with standard approaches. Dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) is an intensive, highly active protocol mainly studied in advanced/recurrent disease. No prior study has utilized this protocol in high-risk ES-NKTCL. **Methods:** Between 2011 and 2016, all patients with ES-NKTCL with LTI at presentation were uniformly treated at our institute with a combination of SMILE chemotherapy for 5–6 cycles, and involved-field radiotherapy (IFRT). Records of these patients were retrospectively reviewed. **Results:** Sixteen patients were identified, 69% stage IE and 31% stage IIE. The majority of patients had B-symptoms (75%), paranasal sinus (PNS) invasion (81%), facial skin invasion (56%), palatal perforation (69%), or orbital extension (56%). 12/16 had B-symptoms, and 6/16 had elevated lactate dehydrogenase. All patients received the entire planned 5–6 cycles. IFRT was delivered after a mean 4 cycles. Complete remission was achieved in 13/15 (87%) patients. At a median follow up of 18.5 months, 1-year progression-free survival and overall survival was 84% and 94%, respectively. Grade 3–4 toxicity was seen in 81%, most commonly neutropenia (75%), anemia (44%), and thromobocytopenia (31%). Six patients required dose adjustments (predominantly in the first 1 or 2 cycles). No treatment-related mortality was noted. **Conclusion:** SMILE with RT is a toxic but tolerable protocol for ES-NKTCL with LTI with high efficacy. Prospective studies are warranted.

Keywords: *Asparaginase, chemotherapy, lymphoma, methotrexate, natural killer cells*

Introduction

Extranodal natural killer/T-cell lymphoma, nasal type (NKTCL) is an aggressive lymphoma with a strong geographical predilection seen predominantly in Asian and South American populations. These lymphomas generally present as destructive lesions of the nose and nasopharynx and surrounding areas.[1] The majority of patients (70%–90%) present with localized disease restricted to this location (Ann Arbor stage IE/IIE) and are considered to have early stage NKTCL (ES-NKTCL). The optimal therapy of these patients is controversial. Radiotherapy (RT) is generally considered mandatory for cure, with chemotherapy added either sequentially or concurrently.[2] Very low-risk patients may do well with RT alone.[3]

Among the most important prognostic factors in ES-NKTCL is local tumor invasiveness (LTI). This entity is generally defined as tumor that extends to adjacent structures such as PNS, skin, or palate. Multiple studies indicate that LTI is among the most consistent and powerful prognostic factors in ES-NKTCL.[4-15] The significantly worse treatment outcome of ES-NKTCL with LTI has led some oncologists to propose that the staging of ES-NKTCL be modified to reflect the importance of this prognostic factor,[16] and treatment be tailored according to risk scores that take LTI into account.[3,5]

NKTCL patients respond poorly to anthracycline-based chemotherapy due to high expression of P-glycoprotein in the malignant cells resulting in a multi-drug resistant (MDR) phenotype.[2,17]

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L-asparaginase based protocols have been attempted in ES-NKTCL with good results. However, the number of patients with LTI have been few or unreported in these studies.[18,19] In view of the poor outcomes of patients with LTI, they are candidates for consideration of more intensive treatment approaches, as are generally used in advanced disease. The protocol dexamethasone, high-dose methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) is among the most aggressive non-MDR regimens for ES-NKTCL. The protocol has been used predominantly in the advanced/recurrent setting, and experience in ES-NKTCL is limited.[20-23] We hypothesized that use of SMILE (a more aggressive protocol) as a component of multimodal therapy may lead to improved clinical outcomes in this group of high-risk patients.

Materials and Methods

Patient selection and staging evaluation

Treatment records of all patients with histopathologically proven ES-NKTCL, who were treated at our cancer center from 2011 to 2016 were retrospectively reviewed. All patients underwent a complete baseline staging including complete blood count, liver and kidney function tests, serum lactate dehydrogenase (LDH), contrast-enhanced computed tomography (CECT) of PNS, neck, chest, abdomen and pelvis; nasal endoscopy with biopsy; and bone marrow aspiration and biopsy. Additional evaluation including magnetic resonance imaging or whole body 18-F fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET-CT) was done as felt necessary. LTI was defined as the presence of disease extending into neighboring structures or organs, or involvement of multiple, contiguous primary sites. International Prognostic Index (IPI) and Korean Prognostic Index (KPI) was calculated for all patients.[14]

Treatment

All patients with ES-NKTCL with LTI at presentation were uniformly treated at our institute with a combination of chemotherapy with SMILE regimen [Table 1] for 5–6 cycles, and involved-field radiotherapy (IFRT). RT (45–50 gray/25 fractions/5 weeks) was introduced in the treatment protocol usually after the completion of 3–4 cycles of initial chemotherapy. Patients required in-patient admission for each cycle of chemotherapy, whereas intramuscular L-asparaginase and subcutaneous growth factors were given on out-patient basis as per protocol. Patients with poor performance status at presentation (PS 3–4) or those who suffered significant toxicity underwent dose modifications of offending chemotherapeutic drugs. All patients received prophylactic antimicrobial prophylaxis with acyclovir and cotrimoxazole (withheld during methotrexate administration and introduced after clearance) during the entire duration of therapy. Local RT was usually planned by three-dimensional conformal technique. Intensity modulated RT was used when necessary for sparing of critical organs at risk. The response was assessed by CECT scan; patients with clinical suspicion of an active disease or equivocal findings on CECT underwent FDG PET-CT scan and histological examination, if feasible. Toxicity was assessed as per Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

IBM SPSS statistics version 20 was used for statistical analysis. Overall survival (OS) was defined as the period from the date of diagnosis to the date of death from any cause. Progression-free survival (PFS) was defined as the period from the date of diagnosis to the date of radiological or clinical progression of the disease. Kaplan-Meier analysis was performed to evaluate OS and PFS. All analyses were censored on 31 August 2016.

Results

Baseline characteristics

Records of 33 patients with NKTCL treated at our center during 2011–2016 were retrieved, from which the following were excluded: 6 patients did not have pathologically proven NKTCL, 5 patients who did not receive SMILE chemotherapy, 3 patients with advanced disease, and 3 patients who received SMILE as salvage but not as the first line. The remaining 16 patients constituted the study group. Baseline characteristics of the 16 patients are described in Table 2.

Table 1: Dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide chemotherapy protocol

Drug	Daily dose	Route	Days of protocol
HDMTX	2 g/m^2	IV over 6 h	1
Leucovorin	15 mg × 4	IV or oral	2-4
Ifosfamide	1.5 g/m^2	IV	2-4
Mesna	300 mg/m^2 × 3	IV	2-4
Dexamethasone	40 mg	IV or oral	2-4
Etoposide	100 mg/m^2	IV	2-4
L-asparaginase (*Escherichia coli*)	6000 IU/m^2	IM	8, 10, 12, 14, 16, 18, 20
G-CSF	300 mcg	SC	6 till WBC >5000

G-CSF – Granulocyte colony stimulating factor; HDMTX – High dose methotrexate; IM – Intramuscular; IV – Intravenous; SC – Subcutaneous; WBC – White blood cell

Table 2: Baseline characteristics of patients included in the study (total patients-16)

Parameter	*n* (%)
Age in years (median, range)	31 (19-55)
Female gender	6 (38)
Symptom duration in months (median, range)	5.5 (1-24)
B-symptoms	12 (75)
Stage	
IE	11 (69)
IIE	5 (31)
IPI	
0	9 (56)
1	3 (19)
2	4 (25)
3	0
4	0
5	0
KPI	
0	3 (19)
1	6 (38)
2	5 (31)
3	2 (13)
4	0
ECOG performance status	Available for 13/16 patients
0	0
1	7 (54)
2	4 (31)
3	2 (15)
4	0
Palatal perforation	11 (69)
Paranasal sinus invasion	13 (81)
Orbital extension	9 (56)
Facial skin invasion	9 (56)
Oropharyngeal extension	3 (19)
Intracranial extension	2 (13)
Lymph node involvement	5 (31)
Elevated LDH	6 (38)

B-symptoms - Defined as unexplained weight loss of >10% of the body weight in the 6 months previous to presentation; unexplained fever with temperature >38°C; or night sweats. ECOG – Eastern Cooperative Oncology Group; IPI – International Prognostic Index; KPI – Korean Prognostic Index; LDH – Lactate dehydrogenase

In general, patients presented late, with median symptom duration of 5.5 months (range 1–24 months). The majority of patients had B-symptoms at presentation (75%). All patients had LTI reflected variously as PNS invasion (81%), facial skin invasion (56%), palatal perforation (69%), orbital extension (56%), oropharyngeal extension (19%), or intracranial extension (13%). Eleven (69%) patients had stage IE disease and 5 patients (31%) had stage IIE disease with cervical lymph node involvement.

Risk scores were calculated for all patients [Table 2]; most patients had an IPI score of 0–1 (12, 75%) whereas 4 patients (25%) had an IPI score of 2. KPI scores were calculated to be 0, 1, 2, and 3 in 3, 6, 5, and 2 patients, respectively. Elevated serum LDH was noted in 38% of patients. Baseline PS was available for 13/16 patients; approximately half the patients (54%) were PS 1 and the rest were PS 2–3.

Treatment and toxicity

One patient is still on therapy on the date of data analysis, having received 4 cycles of SMILE so far. The remaining all received the entire planned 5–6 cycles (five patients received five cycles each, the remaining ten received six cycles each). Conformal RT was delivered to a dose of 45–50 gray in 25 fractions over 5 weeks after a mean of 4 cycles of chemotherapy.

Toxicity with SMILE was substantial but manageable [Table 3]. Thirteen patients (81%) suffered grade 3–4 toxicity. Most of the toxicities were hematological, including grade 3–4 neutropenia, anemia, and thrombocytopenia in 75%, 44%, and 31% of patients, respectively. Four patients (25%) suffered febrile neutropenia. Grade 3 anaphylaxis, encephalopathy, and mucositis was seen in one patient each. Three deaths occurred as a result of disease progression, and no treatment-related deaths were noted in this study.

Ten patients (63%) required no dose adjustment over the entire protocol. Six patients required dose adjustments as follows: three patients required dose adjustment in the first cycle in view of poor PS; two patients required dose adjustment in both first and second cycles in view of poor PS; and one patient had omission of L-asparaginase in the last two cycles due to the risk of anaphylaxis. All other cycles were delivered at full doses in all patients.

Clinical outcomes

Response

One patient is currently on treatment. Thirteen patients achieved complete remission translating to a CR rate of 87%. Two patients progressed on therapy. Among them, one died of progressive disease while the other is alive, having achieved a partial remission to salvage gemcitabine, asparaginase and oxaliplatin (GELOX) and currently awaiting high-dose chemotherapy.

PFS and OS

At a median follow up of 18.5 months (range 6–56 months), four patients progressed at 4, 7, 12 and 19 months from diagnosis. The 1-year and 2-year PFS are 80% and 70%, respectively [Figure 1]. Three patients died at 6, 13, and 21 months from diagnosis. The 1-year and 2-year OS are 94% and 74%, respectively [Figure 2].

Discussion

ES-NKTCL with LTI is an aggressive, difficult to treat malignancy. Our cancer center, located in North India,

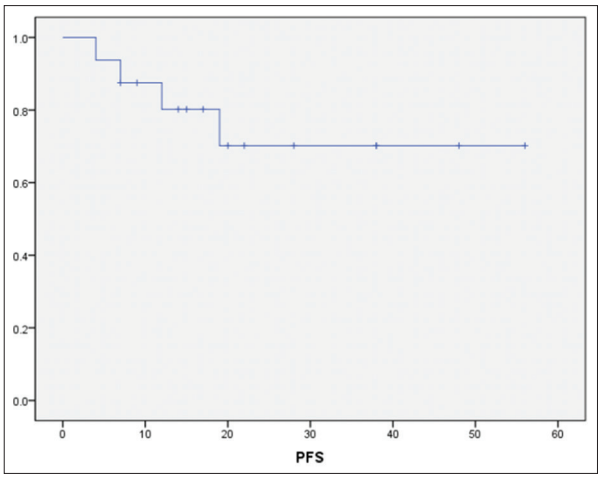

Figure 1: Progression-free survival for the cohort by Kaplan-Meier analysis

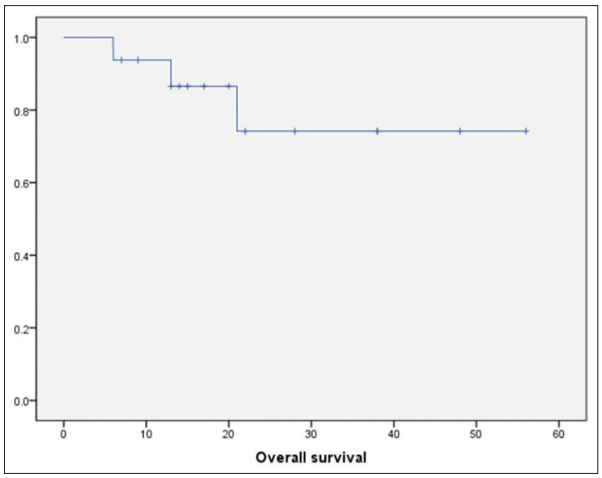

Figure 2: Overall survival for the cohort by Kaplan-Meier analysis

Table 3: Grade 3-4 toxicity as per Common Terminology Criteria for Adverse Events 4.0 (total patients - 16)

Grade 3-4 toxicity	*n* (%)
Any	13 (81)
Neutropenia	12 (75)
Febrile neutropenia	4 (25)
Thrombocytopenia	5 (31)
Anemia	7 (44)
Mucositis	1 (6)
Encephalopathy	1 (6)
Anaphylaxis	1 (6)

provides-free service to socioeconomically vulnerable populations from neighboring states. Due to limited cancer awareness, the paucity of diagnostic and treatment facilities and economic limitations, the vast majority of patients with NKTCL attending our center present late with either ES-NKTCL with LTI or with advanced-stage NKTCL. The heavy disease burden is reflected in the fact that the majority had features such as PNS invasion (81%), facial skin invasion (56%), palatal perforation (69%), or orbital extension (56%).

The treatment of these patients is challenging. The majority of previous studies of ES-NKTCL which have looked at LTI as a prognostic factor have reported poorer outcomes for these patients.[4-15] In fact, it has been commented that the prognosis of these patients is closer to advanced stage NKTCL than early stage.[16] The natural conclusion that follows is that standard treatment approaches for these patients may be inadequate and more aggressive and intensive therapy should be attempted. This leads to the question of how this intensification may be accomplished. Anthracycline-based chemotherapy is now considered less effective and modern chemotherapy for patients with NKTCL includes a backbone of L-asparaginase and other non-MDR drugs.[2] Ways to combine non-MDR chemotherapy with RT include concurrent chemoradiation (CCRT) or sequential chemotherapy and RT. CCRT with non-MDR protocols has delivered improved outcomes (78% OS at 2 years with dexamethasone, etoposide, ifosfamide, and carboplatin - "DeVIC"; 86% OS at 3 years with etoposide, ifosfamide, cisplatin, and dexamethasone - "VIPD") in unselected ES-NKTCL patients compared to historical controls.[24,25] Timely CCRT is often difficult to implement outside a trial setting due to logistic reasons; further, tolerability in patients with the active up front disease is also a concern. Thus, sequential therapy is generally preferred.[2] Sequential therapy with asparaginase, vincristine, and prednisolone or GELOX with RT have resulted in 2-year OS rates of 86%–89%.[18,19] However, in all these studies, patients with LTI have been very few[19] or unreported.[18,24,25] The poor prognosis and aggressive course of ES-NKTCL with LTI indicate that these patients warrant a more intensive approach, analogous to that utilized for advanced stage NKTCL. Hence, we selected SMILE, which is considered the most aggressive chemotherapy protocol for NKTCL to treat this population.

By utilizing a combination of SMILE and IFRT, we achieved a 1-year PFS and OS rates of 84% and 94%, respectively. The 2-year PFS and OS rates were 70% and 74%, respectively. These outcomes are notably better than described in historical series of ES-NKTCL with LTI.[6-10,12] Longer follow up will clarify whether this favorable clinical outcome will be maintained, but it is notable that the majority of relapses of NKTCL tend to occur within the first 2 years.[26]

An important limitation of SMILE is the high toxicity associated with this protocol.[20-22] In our study, 81% of patients suffered grade 3–4 toxicity, predominantly hematological. However, the majority of patients could complete the planned chemotherapy, and there was no treatment-related mortality. While it is undebatable that SMILE is a toxic protocol, we believe that if managed carefully in large volume centers with considerable experience and good quality supportive care, toxicity is manageable [Table 4].[27] For instance, Yamaguchi *et al*.

Table 4: Comparison of adverse events to previous studies using dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide (SMILE)

	Reference			Current study
	[20]	[22]	[21]	
Number of patients	38	87	21	16
Any Grade III-IV	100%	NR	NR	81%
Treatment-related deaths	5%	6%	At least 14%	0%
Neutropenia	100%	67%	86%	75%
Febrile neutropenia/infection	61%	31%	NR	25%
Thrombocytopenia	64%	42%	52%	31%
Anemia	50%	NR	29%	44%
Encephalopathy	3%	NR	NR	6%
Mucositis	13%	NR	10%	6%
Anaphylaxis	NR	1%	NR	6%
Nephrotoxicity	5%	1%	5%	0%
Hyperbilirubinemia	11%	7%	10%	0%
Comments	No deaths after modification of infection surveillance protocol and inclusion criteria	4/5 patients who died had refractory lymphoma	Unusually high toxicity in SMILE arm[27] 19% did not complete a single cycle, 14% died during cycle 1, only 57% received >4 cycles	

NR – Not reported; SMILE – Dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide

noted that modification of their infection surveillance protocol was useful in preventing deaths among patients on SMILE regimen.[20] To sum up, adequate experience, appropriate use of chemotherapeutic agents, dose modifications whenever needed, prophylactic antimicrobial therapy and close surveillance for infections can help in achieving a good clinical outcome in patients with ES-NKTCL with this aggressive combined modality treatment.[23,27]

Conclusion

Combined modality treatment with SMILE chemotherapy and IFRT is a toxic but tolerable protocol for the treatment of patients of ES-NKTCL with LTI with high efficacy. Prospective studies of this treatment approach are warranted in this patient subgroup.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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