EUROPEAN HEMATOLOGY ASSOCIATION

EHA-TSH Hematology Tutorial

Clinical Case – Session 5: Treatment approaches in NK/T cell lymphoma nasal type

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Ankara, Türkiye
June 29-30, 2024

Disclosure

- I have no actual or potential conflict of interest in relation to this program/presentation.

Clinical history

- A 51-year-old woman presented with persistent nasal obstruction, dysphagy and dysphonia (May 2020)
- Her previous medical history was irrelevant
- A mass was detected in the arytenoid cartilage and nasal cavity on clinical examination and imaging
- Also, careful clinical examination showed skin lesion on proximal 1/3 lateral region of the left arm (6.7x4.5 mm in size showed later in ultrasound)
- There was no palpable lympadenopathy

Clinical history

- PET/CT scanned nodular thickening in the **left arytenoid cartilage** characterized by intense FDG uptake with a transaxial wide diameter of approximately 1.5 cm (SUVmax = 12.3)
- A mass with soft tissue density was noted which filled most of the **right nasal cavity** and was characterized by intense FDG uptake, with an anteroposterior length reaching approximately 2.5 cm (SUVmax = 18.7)
- Two focal lesions with increased FDG uptake, restricted to the **skin**, were noted in the 1/3 proximal and lateral, 1/3 distal parts of the **left arm**
- There were no other sites of increased FDG activity

Clinical history

- The punch biopsies taken from the lesion adjacent to the right nasal cavity and the left arytenoid cartilage, and the excisional biopsy taken from the lesion in the fatty tissue in the proximal left humerus confirmed NK/T-cell lymphoma, positive for Epstein-Barr virus

Clinical history

- Stage IV according to Ann Arbor

<Stage I(E) disease (usually of the upper aerodigestive tract) plus isolated distant involvement>

- Stage IV according to the CA ENKTCL staging system

- IPI intermediate low-risk
- PINK intermediate risk
- NRI high risk

IPI: international prognostic index
PINK: prognostic index natural killer cell lymphoma
NRI: nomogram revised index
the most widely used predictive models

The Chinese Southwest Oncology Group and Asia Lymphoma Study Group (CA) ENKTCL staging system

Stage	Description
I	Lesions confined to the nasal cavity or nasopharynx No local invasion No lymph node involvement
II	Lesions confined to the nasal cavity or nasopharynx Local invasion No lymph node involvement Non-nasal disease
III	Lesions with regional lymph node involvement
IV	Non-regional lymph node involvement Lymph nodes above and below diaphragm Widespread disease

Fig. 18.4

ENKTCL, extranodal natural killer/T-cell lymphoma.

No bone marrow involvement

On TTE: left ventricular ejection fraction 60%

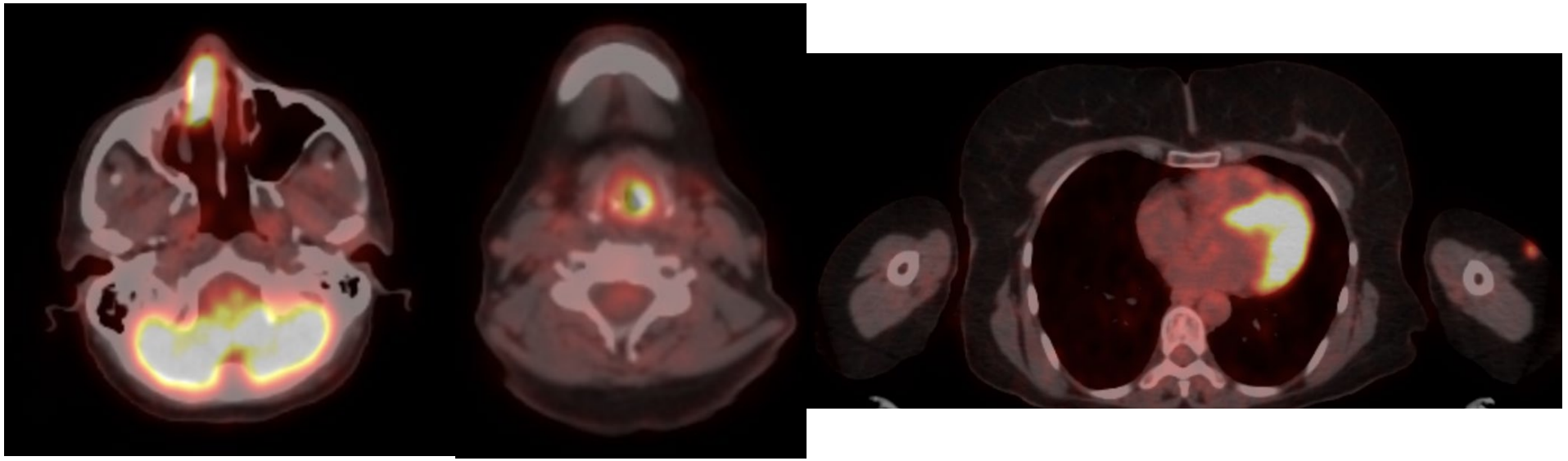
Plasma EBV-DNA negative

Clinical history

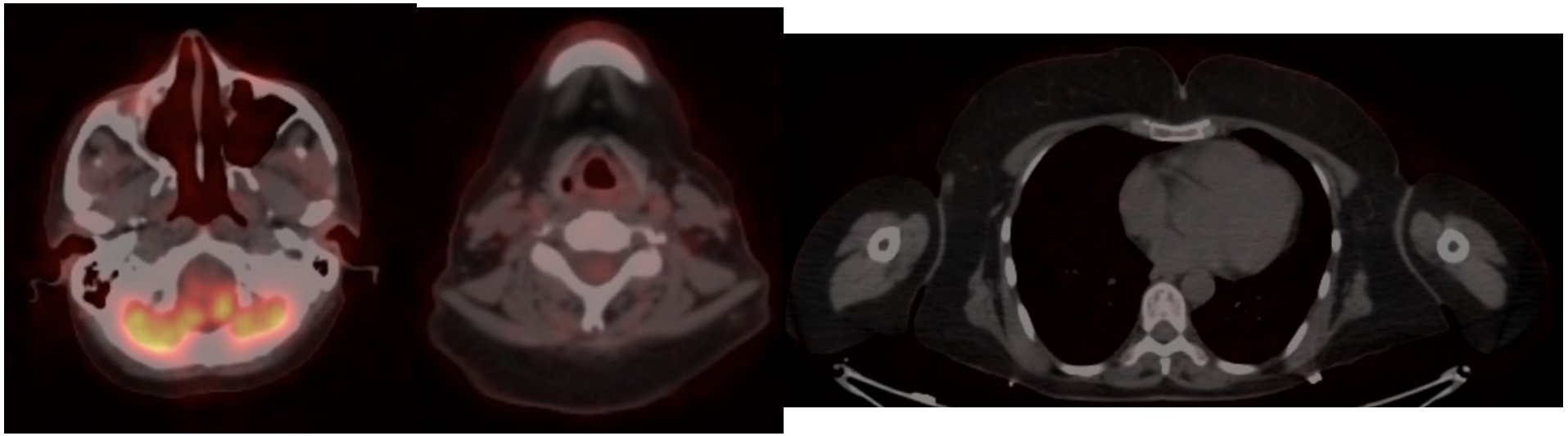
- Advanced stage nasal type extranodal NK T cell lymphoma (ENKTCL)
- Fit (ECOG 0)
- Disseminated disease

- We initiated SMILE protocol (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide)
- After second course therapy, complete response was achieved

(September 2020)



Before treatment



After second course therapy

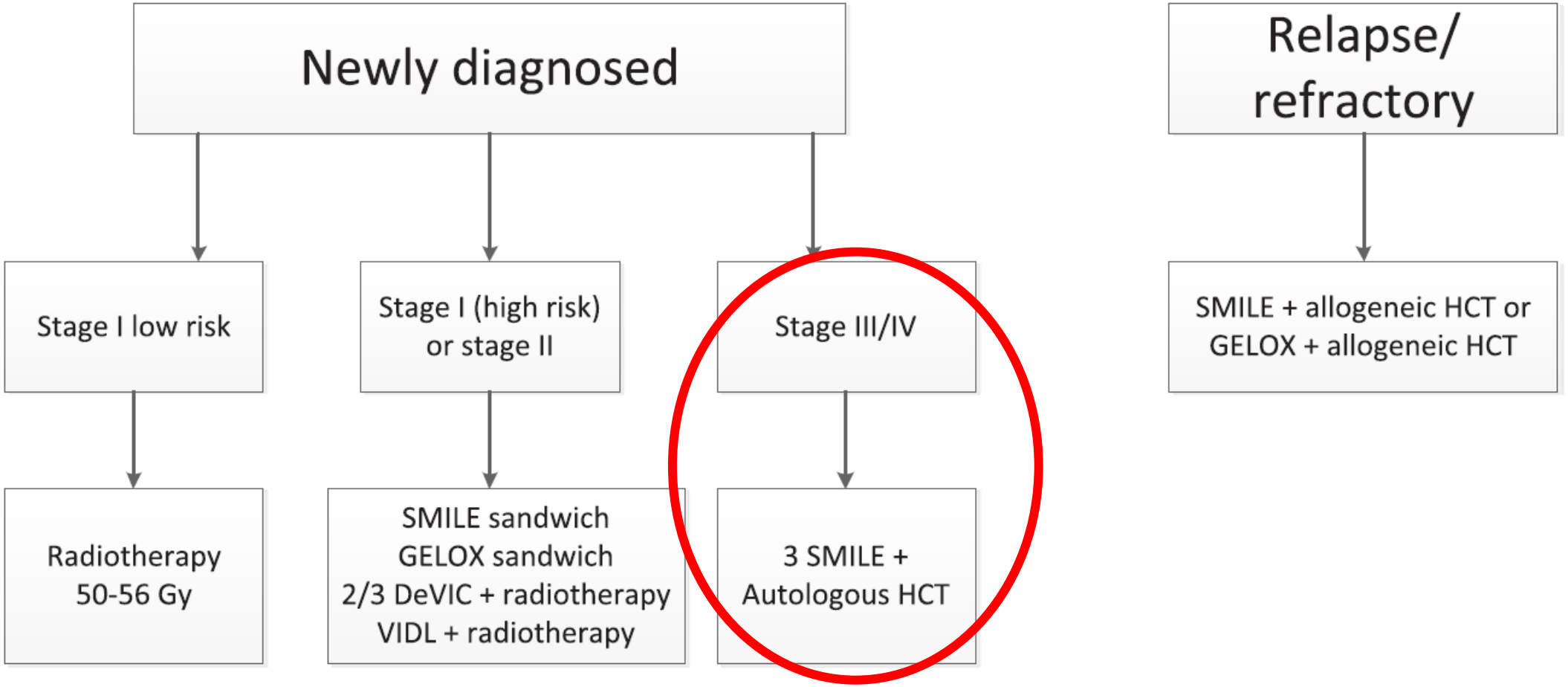


Figure 2. Proposed treatment algorithm. DeVIC = dexamethasone, etoposide, ifosfamide, and carboplatin; GELOX = gemcitabine, oxaliplatin, and L-asparaginase; HCT = hematopoietic cell transplantation; SMILE = dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; VIDL = etoposide, ifosfamide, dexamethasone, and L-asparaginase.

van Doesum JA, Niezink AGH, Huls GA, Beijert M, Diepstra A, van Meerten T. Extranodal Natural Killer/T-cell Lymphoma, Nasal Type: Diagnosis and Treatment. Hemasphere. 2021;5(2):e523

Clinical history

- The patient underwent stem cell mobilization with G-CSF <$7.73x10^6$/kg CD34(+) > (28.6cc DMS0)

- Then the 3rd course of SMILE started

She had no HLA-matched donor

Clinical history

ECOG 0
KARNOFSKY 100
EBMT 0
SORROR 0

- Autologous stem cell transplantation was performed on **November 3, 2020**

- Conditioning BEAM (carmustine, etoposide, cytarabine, melphalan)

- +9… neutrophil engraftment
- +10… platelet >20000 /mm3
- +13… platelet >50000 /mm3

- Complete remission was maintained in the posttransplant 3rd month
- Then, she was followed up in remission throughout 26 months

Clinical history

- There was a relapse in January 2023
- PET/CT showed involvement in bilateral nasal mucosa, bilateral tonsillar area, left vocal cords, bilateral cervical lymph nodes and spleen
- No bone marrow involvement
- Stage IIIE according to Ann Arbor

Clinical history

- After **two course DeVIC** (dexamethasone, etoposide, ifosfamide, carboplatin) protocol →
- On interim PET/CT, the involvement in bilateral nasal mucosa, bilateral tonsillar region, left vocal cords and spleen was completely regressed. The involvement in bilateral cervical lymph nodes had almost completely regressed

- Then, the patient was treated with **50 Gy radiotherapy**, followed by **2 more courses of DeVIC** (sandwich approach)
- Complete response was achieved

Clinical history

- She was then allografted from her HLA-haploidentical son donor using myeloablative conditioning on January 17, 2024.
- Conditioning: Flu-Bu-TT (fludarabine-busulfan-thiotepa)
- GVHD prophylaxis

  -rabbit ATG

  -PTCy, Cyclosporine, MMF
- Defibrotide prophylaxis was added to the protocole for prevention of sinusoidal obstruction syndrome

Clinical history

- The last visit (June 15, 2024) (at day +150)
  - Haemoglobin concentration (Hb) 10.0 g/l
  - WBC 2.8 x 10^9/l
  - Neutrophils 1.4 x 10^9/l
  - Platelet count 80 x 10^9/l

CMV-PCR negative
Molecular chimerism %99, XY chimerism 100
No active GVHD
Bone marrow aspiration biopsy
cellularity 50%, megakaryocytes with normal morphology were seen, no dysplasia, no disease involvement

Discussion

- NKTCL is a rare, EBV-related non Hodgkin lymphoma
- It develops from transformation of NK-cells or cytotoxic T-cells, rarely both
- It shows a geographical predilection for Asian and South American populations
- NKTCL can be nodal or extranodal

Montoto S, Dreyling M, Ballova V. ESMO Lymphomas: Essentials for Clinicians Third Edition, 2024

Discussion

- More than two thirds of NKTCLs are localised at diagnosis and most frequently located in the nasal and upper airway region
- Nasal type is more prevalent in men in their 5th decade
- Disseminated disease occurs in 10%-20% of ENKTCLs, involving sites such as testis, skin, intestine, soft tissue and bone marrow (rarely) and may be complicated by HPS
- Despite the predominant nasal location, spread to the cerebrospinal fluid (CSF) is uncommon

Montoto S, Dreyling M, Ballova V. ESMO Lymphomas: Essentials for Clinicians Third Edition, 2024

Discussion

- NKTCL shows an angiocentric and angiodestructive pattern
- EBV infection and subsequent genetic alterations in infected cells are central to ENKTCL development
- Positivity for EBV with in situ hybridisation is necessary for diagnosis

The circulating EBV in the peripheral blood can often be detected, providing another method of disease monitoring

Tse E, Zhao WL, Xiong J, Kwong YL. How we treat NK/T-cell lymphomas. J Hematol Oncol. 2022;15(1):74.

Discussion

- Staging distinguishes between localized disease versus advanced disease

- Ann Arbor staging system → staging ENKTCL and is useful for planning RT
- Site, local invasion and lymph node involvement seems more accurate in estimating survival

Localized NKTL is curable but most persons with advanced disease have a poor prognosis

Table 1. Detailed description of The Chinese Southwest Oncology Group and Asia Lymphoma Study Group (CA) ENKTL staging system.

Stage	Description
I	Lesions confined to the nasal cavity or nasopharynx
	No local invasion
	No lymph node involvement
II	Lesions confined to the nasal cavity or nasopharynx
	Local invasion
	No lymph node involvement
	Non-nasal disease
III	Lesions with regional lymph node involvement
IV	Non-regional lymph node involvement
	Lymph nodes above and below diaphragm
	Widespread disease

Table 2. Comparison of prognostic/predictive models.

Model	Prognostic factors (points)	Definition (points)	Development/validation era		Accuracy[a]	
			Anthracycline	No anthracycline	C-statistic	AUC for 5-year survival
IPI	Age >60 years (1); Increased LDH (1); PS ≥ 2 (1); Stage-III/IV (1); Extra-nodal disease ≥2 (1)	Low-risk (0–1) Intermediate low-risk (2) Intermediate high-risk (3) High-risk (≥4)	Development	–	0.62	0.61
KPI	B-symptoms (1); Stage-III/IV (1); Increased LDH (1); Regional lymph node involvement (1)	Group 1 (0) Group 2 (1) Group 3 (2) Group 4 (≥3)	Development	Validation	0.64	0.68
PINK	Age >60 years (1); Stage-III/IV (1); Distant lymph node involvement (1); Non-nasal disease (1)	Low-risk (0) Intermediate-risk (1) High-risk (≥2)	–	Development and validation	0.61	0.63
NRI	Age >60 years (1); Stage-II (1); Stage-III/IV (2); PS ≥ 2 (1); Increased LDH (1); With PTI (1)	Low-risk (0) Intermediate low-risk (1) Intermediate high-risk (2) High-risk (3) Very high-risk (≥4)	Development	Validation	0.70	0.72

AUC area under curve, *LDH* lactate dehydrogenase, *PS* performance status, *PTI* primary tumor invasion.

International Prognostic Index

Korean Prognostic Index

Prognostic Index of Natural Killer Lymphoma

Nomogram -revised Risk Index

PINK-E

Adopting a dynamic approach that incorporates evolving parameters, such as plasma EBV DNA and PET/CT imaging

Wang H, Fu BB, Gale RP, Liang Y. NK-/T-cell lymphomas. Leukemia. 2021;35(9):2460-2468.
Tse E, Zhao WL, Xiong J, Kwong YL. How we treat NK/T-cell lymphomas. J Hematol Oncol. 2022;15(1):74.

Principles of Treatment

- NK-cells express high levels of P-glycoprotein, leading to a multidrug resistance (MDR) phenotype
- Anthracycline-containing (CHOP or CHOP-like) regimens are MDR-dependent and ineffective
- So, anthracycline-containing regimens should be avoided in NKTCL
- non-MDR–dependent therapies should be the first choice of therapy, examples of which are asparaginase- or platinum-based therapies which induces apoptosis of NK-cells in vitro
- Also, NKTCLs are radiosensitive

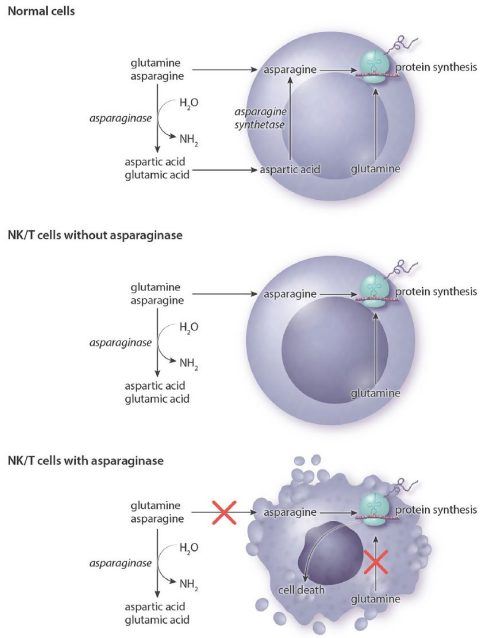


Figure 3. Mechanism of action of asparaginase. The lack of asparagine synthetase in NK/T-cells means that they are dependent on exogenous asparagine and glutamine. By degrading asparagine and glutamine to aspartic acid and glutamic acid, asparaginase inhibits essential intracellular protein synthesis and triggers cell death. NK = natural killer.

Table 2 Major regimens used in NK/T-cell lymphomas, listed in alphabetical order according to acronyms

Regimens	Drugs and schedule
AspaMetDex	*E. coli* L-asparaginase: 6000 U/m^2, IM, days 2, 4, 6, 8
	Methotrexate: 3000 mg/m^2, IV, day 1
	Dexamethasone: 40 mg, oral, days 1–4
DDGP	Dexamethasone: 15 mg/m^2, IV, days 1–5
	Cisplatin: 20 mg/m^2, IV, days 1–4
	Gemcitabine: 800 mg/m^2, IV, days 1, 8
	Pegaspargase: 2500 IU/m^2, IM, day 1
DeVIC (2/3)	Dexamethasone: 40 mg, IV, days 1–3
	Etoposide: 67 mg/m^2, IV, days 1–3
	Ifosfamide: 1000 mg/m^2, IV, days 1–3
	Carboplatin: 200 mg/m^2, IV, day 1
DICE-L-asp	Dexamethasone: 20 mg/m^2, days 1–4
	Ifosfamide: 1200 mg/m^2, IV, days 1–3
	Cisplatin: 25 mg/m^2, IV, days 1–4
	Etoposide: 60 mg/m^2, days 1–4
	L-asparaginase: 6000 U/m^2, days 6–11
GELAD	Gemcitabine: 1000 mg/m^2, IV, day 1
	Etoposide: 60 mg/m^2, IV, days 1–3
	Pegaspargase: 2000 U/m^2, day 5
	Dexamethasone: 40 mg, days 1–4
GELOX	Gemcitabine: 1000 mg/m^2, IV, days 1, 8
	E. coli L-asparaginase: 6000 U/m^2, IM, days 1–7
	Oxaliplatin: 130 mg/m^2, IV, day 1
LVP	L-asparaginase: 6000 IU/m^2, IV, days 1–5
	Vincristine: 1.4 mg/m^2, IV, day 1
	Prednisolone: 100 mg, oral, days 1–5
MEDA	Methotrexate: 3000 mg/m^2, IV, day 1
	Etoposide: 100 mg/m^2, IV, days 2–4
	Dexamethasone: 40 mg, IV, days 2–4
	Pegaspargase: 2500 U/m^2, day 4
MESA	Methotrexate: 1000 mg/m^2, IV, day 1
	Etoposide: 100 mg/m^2, days 2–4
	Dexamethasone: 40 mg, IV, days 2–4
	Pegaspargase: 2500 U/m^2, IM, day 4
P-GEMOX	Pegaspargase: 2500 IU/m^2, IM, day 1
	Gemcitabine: 1000 mg/m^2, IV, days 1, 8
	Oxaliplatin: 130 mg/m^2, IV, day 1
SMILE	Dexamethasone: 40 mg, IV or oral, days 2–4
	Methotrexate: 2000 mg/m^2, IV, day 1
	Ifosfamide: 1500 mg/m^2, IV, days 2–4
	E. coli L-asparaginase: 6000 U/m^2, IV, days 8, 10, 12, 14, 16, 18, 20
	Etoposide: 100 mg/m^2, IV, days 2–4
VIDL	Etoposide: 100 mg/m^2, IV, days 1–3
	Ifosfamide: 1200 mg/m^2, IV, days 1–3
	Dexamethasone: 40 mg, IV, days 1–3
	L-asparaginase: 4000 IU/m^2, IM, days 8, 10, 12, 14, 16, 18, 20
VIPD	Etoposide: 100 mg/m^2, IV, days 1–3
	Ifosfamide: 1200 mg/m^2, IV, days 1–3
	Cisplatin: 33 mg/m^2, IV, days 1–3
	Dexamethasone: 40 mg, IV or oral, days 1–4

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van Doesum JA, Niezink AGH, Huls GA, Beijert M, Diepstra A, van Meerten T. Extranodal Natural Killer/T-cell Lymphoma, Nasal Type: Diagnosis and Treatment. Hemasphere. 2021;5(2):e523

Stage I/II Nasal NKTCL

Assessment of medical fitness is important for treatment choice

- asparaginase-containing regimens combined with radiotherapy
- concurrent chemoradiotherapy vs sequential chemotherapy and radiotherapy
- radiotherapy doses below 50 Gy linked to higher locoregional relapse rates

Table 3 Outcome of patients with NK/T-cell lymphomas treated with asparaginase-containing regimens

Regimens	Status	Stage	ORR	CR (%)	PFS	OS	References
VIDL + RT	Newly diagnosed	I/II	90%	87	5 year: 60%	5 year: 73%	[61]
LVP + RT	Newly diagnosed	I/II	89%	81	5 year: 64%	5 year: 64%	[64]
GELOX + RT	Newly diagnosed	I/II	96%	74	5 year: 74%	5 year: 85%	[67]
P-GEMOX [+ RT for stage I/II]	Newly diagnosed	I/II	94%	80	2 year: 77%	2 year: 83%	[68]
	Newly diagnosed	I/II	94%	64	3 year: 66%	3 year: 81%	[69]
	Relapsed/refractory		81%	52	3 year: 24%	3 year: 58%	[76]
DICE-L-asp	Newly diagnosed	I/II	100%	91	5 year: 82%	5 year: 89%	[70]
MESA	New diagnosed	I/II	92%	89	2 year: 89%	2 year: 92%	[30]
SMILE [+ RT for stage I/II]	Newly diagnosed	I/II	90%	69	Not reported		[73]
		III/IV	Not reported	54	4 year: 60%	5 year: 47%	
	Relapsed/refractory		77%	66	4 year: 68%	5 year: 52%	
DDGP	Newly diagnosed	III/IV	95%	71	1 year: 86%	1 year: 90%	[77]
AspaMetDex	Relapsed/refractory		78%	61	2 year: 40%	2 year: 40%	[74]
MEDA	Relapsed/refractory		77%	61	1 year: 62%	1 year: 69%	[75]
GELAD	Newly diagnosed	I/II	94%	92	2 year: 90%	2 year: 94%	[71]

ORR: Overall response rate; CR: complete remission; PFS: progression-free survival; OS: overall survival; RT: radiotherapy; VIDL: etoposide, ifosfamide, dexamethasone, L-asparaginase; LVP: L-asparaginase, vincristine, prednisolone; GELOX: gemcitabine, L-asparaginase, oxaliplatin; P-GEMOX: pegaspargase, gemcitabine, oxaliplatin; DICE-L-asp: dexamethasone, ifosfamide, cisplatin, etoposide, L-asparaginase; MESA: methotrexate, etoposide, dexamethasone, pegaspargase; SMILE: dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide; DDGP: dexamethasone, gemcitabine, cisplatin, pegaspargase; AspaMetDex: L-asparaginase, methotrexate, dexamethasone; MEDA: methotrexate, etoposide, dexamethasone and pegylated asparaginase; GELAD: gemcitabine, etoposide, pegasparaginase, dexamethasone

Tse E, Zhao WL, Xiong J, Kwong YL. How we treat NK/T-cell lymphomas. J Hematol Oncol. 2022;15(1):74.

Stage III/IV Nasal and Non-Nasal NKTCL

- The standard-of-care for advanced stage is asparaginase based combination chemotherapy
- Therapeutic goals include achieving undetectable plasma EBV DNA and a PET/CT Deauville score ≤ 3 at both interim and end-of-treatment
- CNS involvement can occur in stage III/IV
- Intermediate-dose methotrexate regimens (SMILE or SMILE-like) reduce the risk of CNS involvement

Wang H, Fu BB, Gale RP, Liang Y. NK-/T-cell lymphomas. Leukemia. 2021;35(9):2460-2468.

Table 3. Therapies for advanced NKTL.

Regimen	*N* subjects	Response	Survival (95%CI)	Adverse events (Grades-3/-4)				Ref.
				↓ WBC	Anemia	↓ Platelets	Liver	
CCRT-DeVIC	27	20 CR 1 PR	2-year 78% (57, 89%) 5-year 70% (49, 84%)					0]
CCRT-ESHAP	13	12 CR 1 PR	2-year 72% (35, 90%)					
CCRT-DEP ± DVIP	33	20 CR 6 PR	5-year 66% (50, 83%)					
CCRT-VIPD	30	24 CR 1 PR	3-year 86% (NA)					
CCRT-VIDL	30	26 CR 1 PR	5-year 73% (NA)					
SCRT-DDGP	30	22 CR 3 PR	5-year 86% (NA)					
SCRT/Sandwich-SMILE	17	14 CR	NA					
Sandwich-MESA	40	34 CR 1 PR	2-year 92% (NA)	53%	13%	0	NA	[76]
Sandwich-GELOX/PGEMOX	27	20 CR 6 PR	5-year 85% (NA)	33%	7%	30%	4% ↑ transaminases	[77, 78]
SMILE	38	17 CR 13 PR	1-year 55% (38, 69%)	100%				[79]
PEMD	32	15 CR 9 PR	4-year 51% (32, 70%)					
AspaMetDex	19	11 CR 3 PR	NA[a]					
PGEMOX ± RT/ Autotrasplant	35	18 CR 10 PR	3-year 65% (NA)					
GDP	41	17 CR 17PR	2-year 55% (NA)	34%[b]				[83]
DDGP	21	15 CR 5 PR	2-year 74% (NA)	62%	52%			[84]

CI 95% confidence interval, *CCRT* concurrent chemotherapy and radiation therapy, *SCRT* sequential chemotherapy and radiation therapy, *CR* complete remission, *PR* partial remission, *Pe* pegaspargase, *NA* not applicable, *AST* aspartate transaminase, *ALT* alanine transaminase.
[a]Median survival time of 12 months.
[b]Neutropenia.

No specific intensive asparaginase-based chemotherapy regimen provides clearly superior outcomes for advanced-stage ENKL, and all are associated with substantial adverse effects.

Due to poor survival rates, additional treatment should be considered for stage III/IV nasal or any stage non-nasal disease, even if remission is achieved.

HEMATOPOIETIC CELL TRANSPLANTATION

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Extranodal NK/T-Cell Lymphomas

NCCN Guidelines Index
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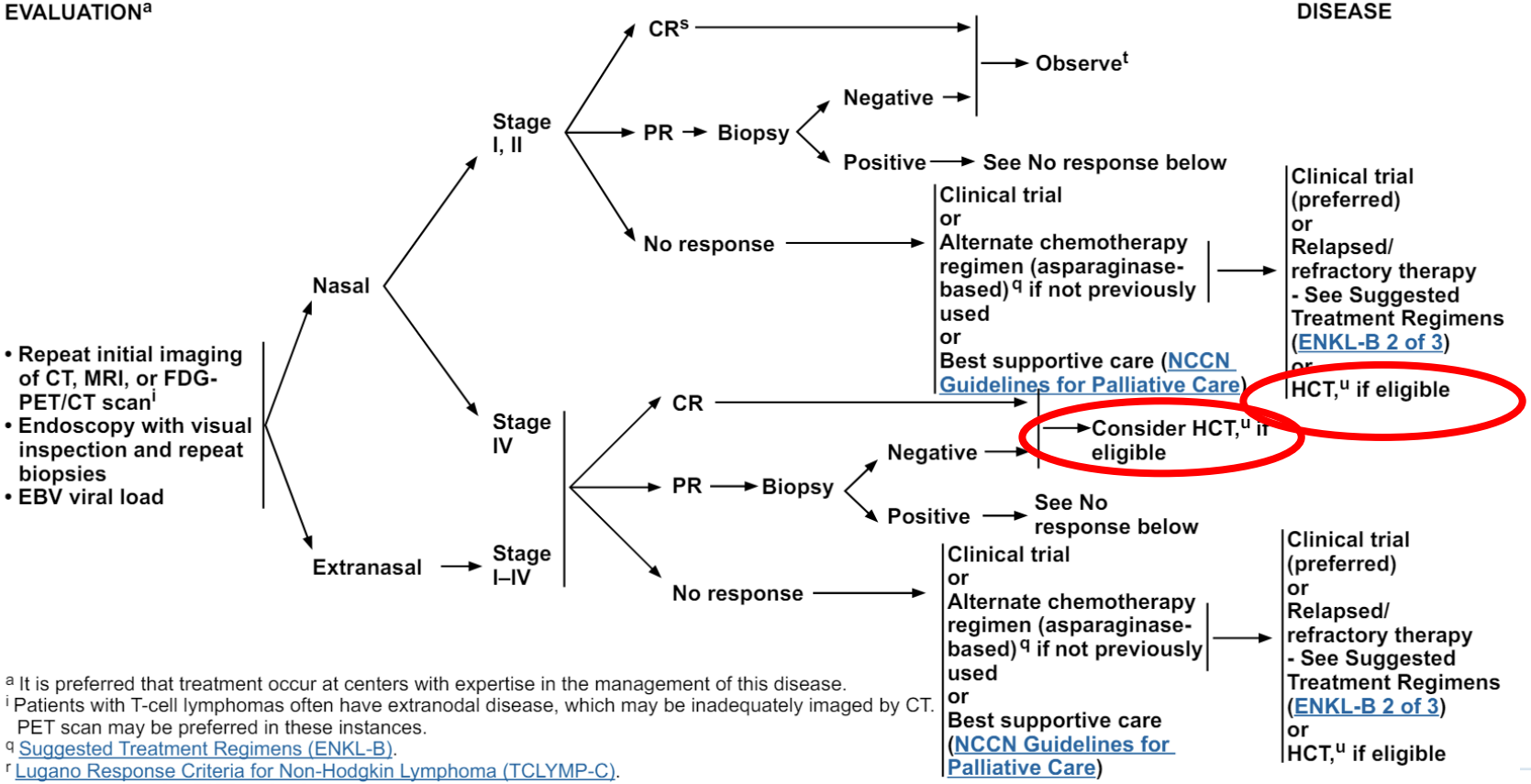
Discussion



[a] It is preferred that treatment occur at centers with expertise in the management of this disease.
[i] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[q] Suggested Treatment Regimens (ENKL-B).
[r] Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYMP-C).
[s] Includes a negative ENT evaluation.
[t] May include H&P, ENT evaluation, FDG-PET/CT scan, and EBV viral load by quantitative PCR.
[u] There are no clear data to suggest whether allogeneic or autologous HCT is preferred and treatment should be individualized.

There is no firm consensus regarding optimal post-induction management of ENKL and no well-controlled prospective studies or randomized trials to guide decision-making.

Autologous Transplantation

Table 4. Haematopoietic cell autotransplants in NKTL.

N subjects	Pre-transplant Response	Post-transplant Response	PFS (95% CI)	OS (95% CI)	Ref.
31	16 CR 15 PR	19 CR 4 PR 6 PD 2 NA	3-year 40% (22, 58%)	3-year 52% (34, 71%)	[87]
10	6 CR 2 PR 2 PD	NA	2-year 33% (13, 84%)	2-year 40% (19, 86%)	[15]
17	17 CR/PR	8 CR 9 PD	NA	NA	[88]

PFS progression-free survival, *OS* overall survival, *CI* confidence interval, *CR* complete remission, *PR* partial remission, *PD* progressive disease, *NA* not applicable.

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Relapsed/Refractory Disease

- The outcome of R/R patients is dismal, with a reported median PFS of 4.1 months and OS of 6.4 months
- Chemotherapy-based treatment is mostly ineffective, so these patients should be considered candidates **for clinical trials with novel therapies**
- In the absence of a clinical trial, **pembrolizumab or nivolumab** are appropriate options.
- Patients previously treated with SMILE or refractory to SMILE can be treated with gemcitabine and platinum-based regimens

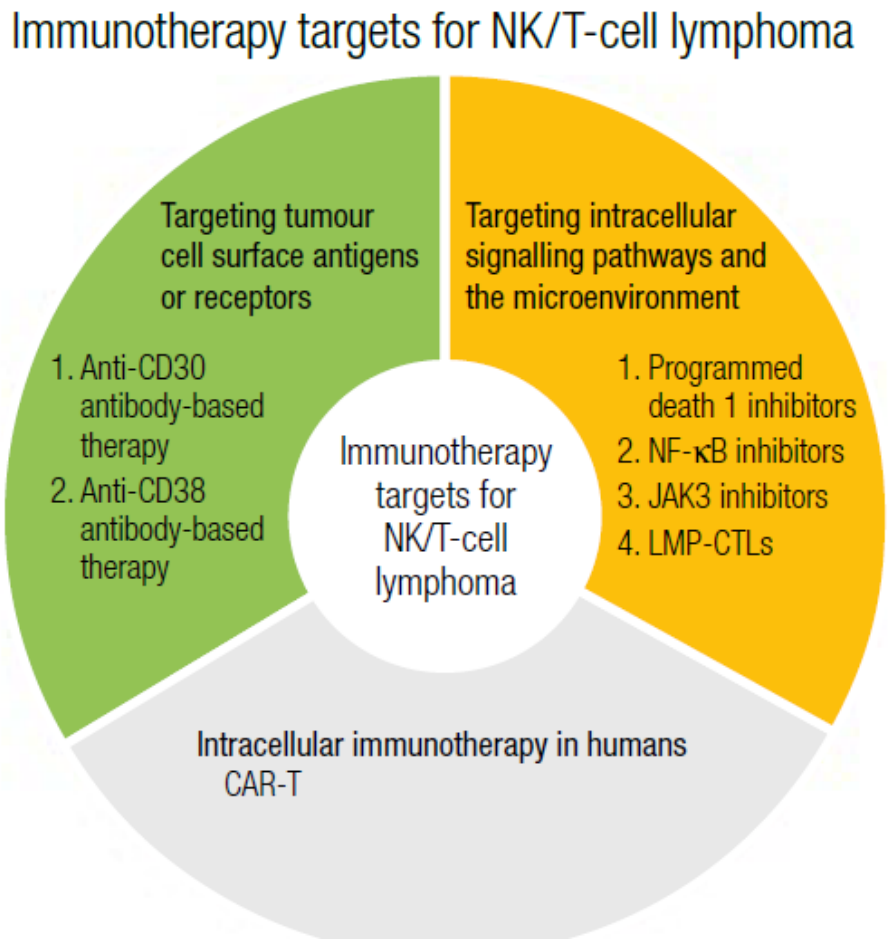
- Also, **PD-L1 antibody (avelumab), anti-CD30 and anti-CD38 antibodies** are increasingly used.
- **Histon deacetylase (HDAC) inhibitors** are other options
- Other drugs approved in T cell lymphomas, including **pralatrexate and romidepsin**

NCCN Guidelines Version 4.2024
Extranodal NK/T-Cell Lymphomas

SUGGESTED TREATMENT REGIMENS[a,b]

RELAPSED/REFRACTORY THERAPY
Preferred regimens[h,i] • Clinical trial • Pembrolizumab • Nivolumab
Other recommended regimens (alphabetical order) • Single agents ▸ Brentuximab vedotin for CD30+ disease ▸ Pralatrexate • Combination regimens (alphabetical order) ▸ Asparaginase-based combination chemotherapy regimen (ENKL-B 1 of 3) not used in first-line therapy ▸ DHA (dexamethasone and cytarabine) + platinum (cisplatin or oxaliplatin) ▸ DHA (dexamethasone and cytarabine) + carboplatin (category 2B) ▸ ESHA (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin) ▸ GDP (gemcitabine, dexamethasone, and cisplatin) ▸ GemOx (gemcitabine and oxaliplatin) ▸ ICE (ifosfamide, carboplatin, and etoposide)
Useful in certain circumstances • RT[g] • Belinostat[j] • Romidepsin[j]

Discussion



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References

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