REVIEW SERIES

Few and far between: clinical management of rare extranodal subtypes of mature T-cell and NK-cell lymphomas

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Abstract

While all peripheral T-cell lymphomas are uncommon, certain subtypes are truly rare, with less than a few hundred cases per year in the USA. There are often no dedicated clinical trials in these rare subtypes, and data are generally limited to case reports and retrospective case series. Therefore, clinical management is often based on this limited literature and extrapolation of data from the more common, nodal T-cell lymphomas in conjunction with personal experience. Nevertheless, thanks to tremendous pre-clinical efforts to understand these rare diseases, an increasing appreciation of the biological changes that underlie these entities is forming. In this review, we attempt to summarize the relevant literature regarding the initial management of certain rare subtypes, specifically subcutaneous panniculitis-like T-cell lymphoma, hepatosplenic T-cell lymphoma, intestinal T-cell lymphomas, and extranodal NK/T-cell lymphoma. While unequivocally established approaches in these diseases do not exist, we make cautious efforts to provide our approaches to clinical management when possible.

Introduction

The mature T-cell and NK-cell lymphomas are a broad class of heterogeneous clinicopathological entities. The list of unique disease subtypes encompassed in this group is seemingly ever-growing, now numbering 34 distinct subtypes in the recently updated fifth edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours.[1] Similarly, in the first edition of the International Consensus Classification (ICC) of Mature Lymphoid Neoplasms, over 30 entities are named.[2] Despite the breadth of pathology, T-cell and NK-cell lymphomas are exceptionally rare diseases, with an annual incidence in the USA of under 2 cases per 100,000 persons.[3] Individual disease incidence rates vary from 0.4-0.5 per 100,000 for the most common subtypes, such as peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), to ≤0.1 per 100,000 for rarer subtypes, such as hepatosplenic T-cell lymphoma (HSTCL) and extranodal NK/T-cell lymphoma (ENKL).[3] This rarity has made dedicated study and clinical management of T-cell lymphomas particularly challenging, as clinicians are often forced to rely on case series and anecdotal reports in the face of relatively few clinical trials, especially for the rarest subtypes. Acknowledging this challenge, our goal herein is to summarize relevant literature on the clinical management for certain rare subtypes of mature T-cell and NK-cell lymphomas (Figure 1).

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) falls under the category of primary cutaneous T-cell lymphomas, including mycosis fungoides, which are reviewed elsewhere.[4] SPTCL was first recognized as a distinct WHO entity in 2001, although until reliable immunohistochemistry markers became readily available in the early 2000s, SPTCL was often grouped with the related but distinct primary cutaneous γδ T-cell lymphoma (PCGDTCL), which demands a different therapeutic approach.[5] However, it is now realized that SPTCL evolves from a mature cytotoxic αβ T cell, and cases expressing the γδ T-cell receptor are considered PCGDTCL.

SPTCL classically presents in middle-aged females as multiple subcutaneous, non-ulcerated nodules or plaques.[6,7] A personal or family history of autoimmunity, especially lupus erythematosus, may be present in up to one-third of patients, and the distinction between SPTCL

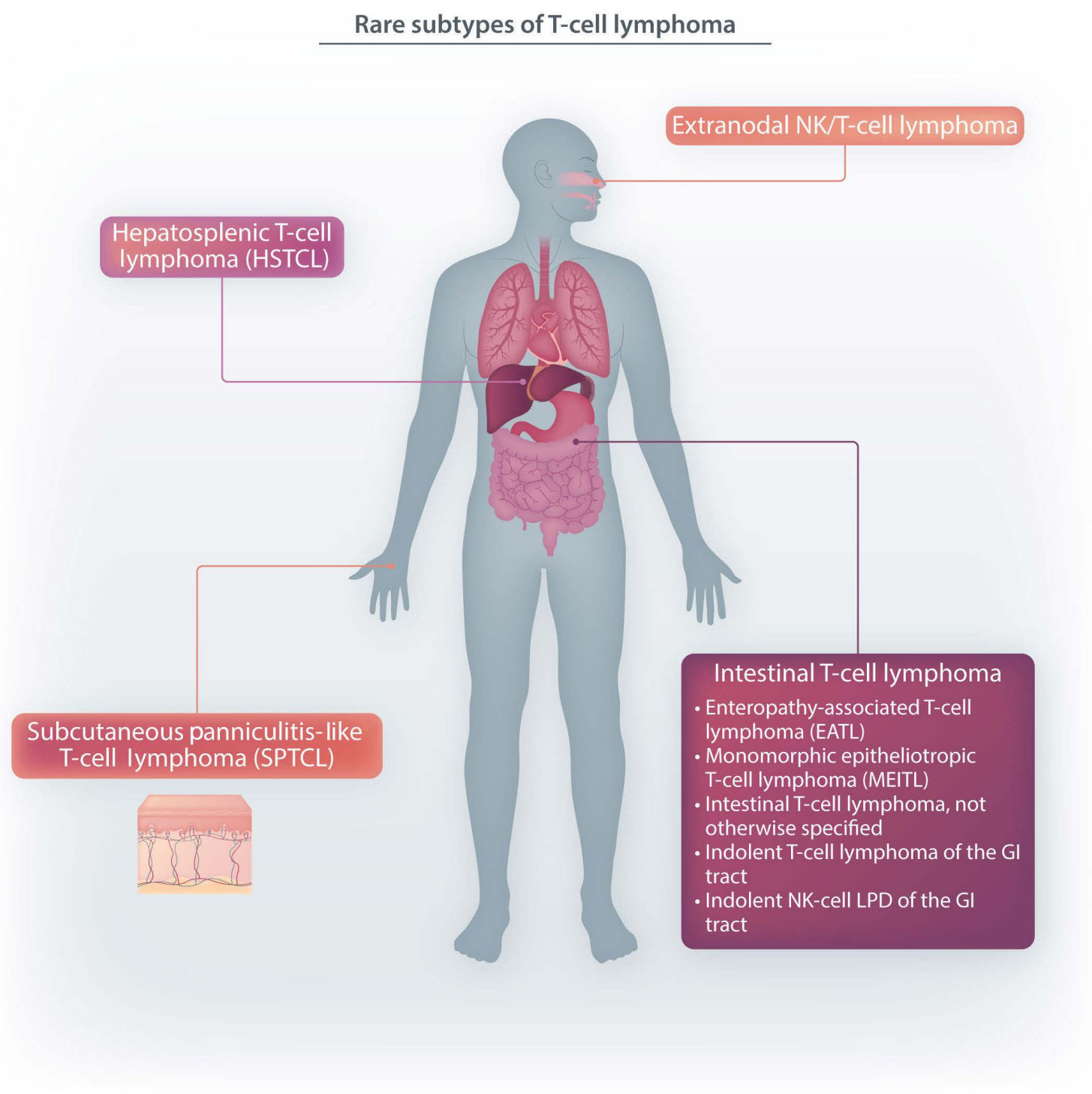

Figure 1. Overview of the rare subtypes of T-cell lymphoma covered in this review. Figure created at BioRender.com. GI: gastrointestinal; LPD: lymphoproliferative disorder.

and lupus panniculitis is often challenging.[8] Involvement of the legs seems to be slightly more common, but involvement of the head/neck and trunk has been documented.[6,7] Extracutaneous involvement, including nodal, bone marrow, and/or visceral disease, appears to be very uncommon and should be confirmed with biopsy. Many patients have constitutional symptoms, such as fevers and night sweats.[6,7] In roughly one-fifth of patients, hemophagocytic lymphohistiocytosis (HLH) is present.[7] HLH appears to be more common and more severe in individuals harboring germline mutations in *HAVCR2*.[9-12]

A suggested management approach for SPTCL in shown in Figure 2. The clinical evaluation is rooted in a proper pathological confirmation showing a lymphoid infiltrate involving fat lobules, with neoplastic cells having a mature αβ T-cell phenotype, usually $CD8^+$ and negative for Epstein-Barr virus (EBV), with expression of cytotoxic markers. We perform staging evaluation with positron emission tomography/computed tomography (PET/CT), as most lesions are avid with a median SUV near 9.0.[7] In addition, we undertake routine laboratory studies, including serology for human T-cell lymphotropic virus-1 to exclude cutaneous manifestations of adult T-cell leukemia/lymphoma. Diagnostic evaluation for HLH, such as measurement of ferritin, fibrinogen, triglycerides, and soluble IL-2 receptor, can be performed (we consider such evaluation in all patients as a baseline and always evaluate patients with high clinical suspicion). We often perform a rudimentary investigation for autoimmune disorders, particularly in patients in whom lupus panniculitis is entertained, by determining whether antinuclear antibodies and other serological markers are present. Positive or ambiguous results should prompt a formal rheumatology evaluation. Finally, we consider referring patients with a suspected or

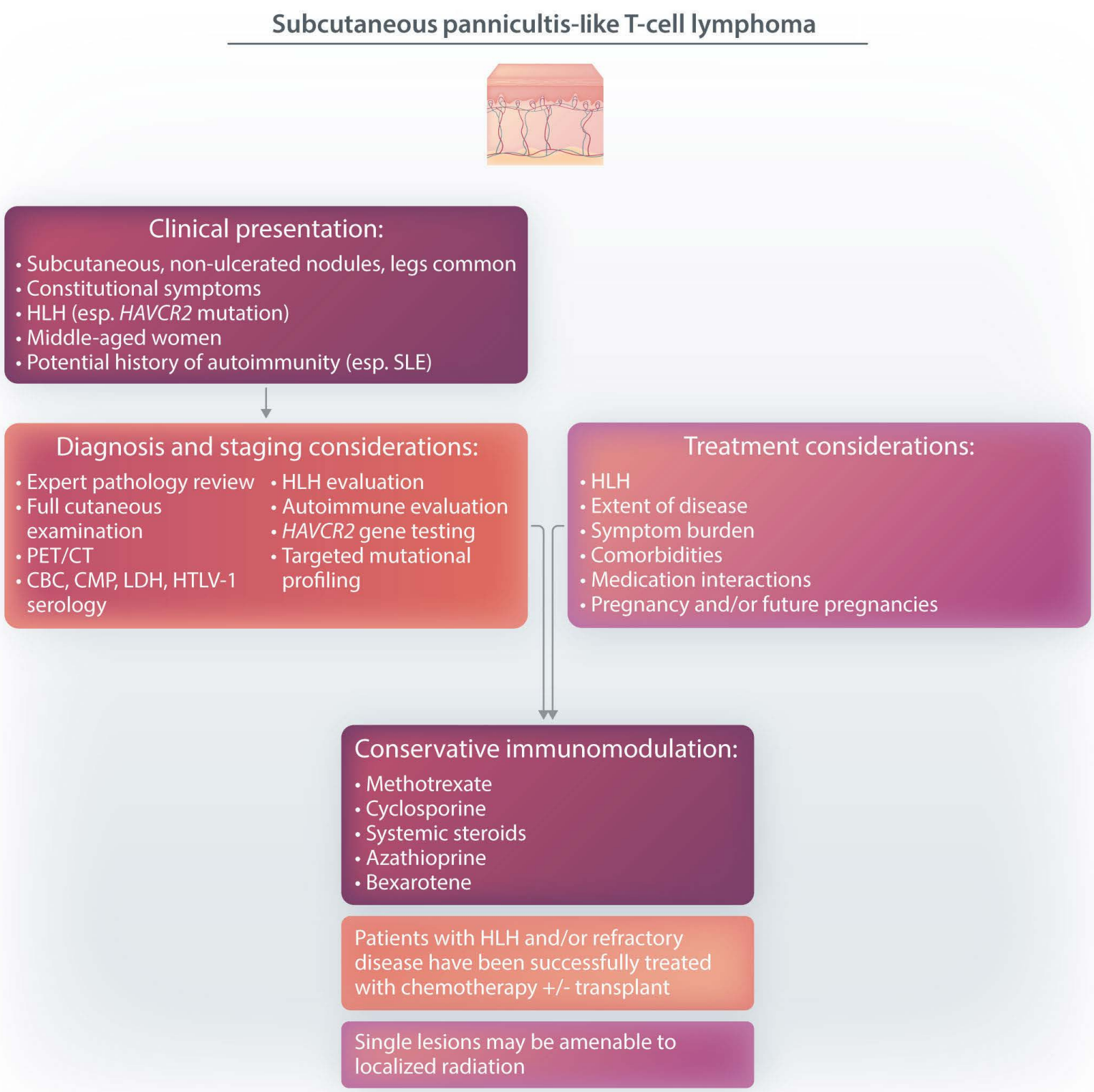

Figure 2. Suggested clinical management schema for subcutaneous panniculitis-like T-cell lymphoma. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) usually presents as multifocal subcutaneous, non-ulcerated nodules, commonly involving the legs. Constitutional symptoms can be present, and rarely patients present with evidence of hemophagocytic lymphohistiocytosis (HLH). HLH appears to be more common in those with germline *HAVCR2* mutations. Considerations in diagnostic and staging procedures are shown. In the absence of HLH and/or clinical deterioration, SPTCL can be managed with conservative immunomodulatory strategies. Figure created at BioRender.com. SLE: systemic lupus erythematosus; PET/CT: positron electron tomography/computed tomography; CBC: complete blood count; CMP: chemistry panel; LDH: lactate dehydrogenase; HTLV-1: human T-cell lymphotropic virus-1.

confirmed diagnosis to clinical genetics for *HAVCR2* single-gene testing as a risk-stratification tool, although this testing is not widely available and not required for optimal management. No specific recommendations for additional testing of family members exist for patients with detected *HAVCR2* aberrations, and we rely on genetic counseling for formal advice.

The management of SPTCL should be framed by the understanding that this is most often an indolent disorder for which immunomodulatory approaches are often effective.[6,7] As noted previously, prior grouping of SPTCL with PCGDTCL – a generally very aggressive primary cutaneous lymphoma – initially led to concern that SPTCL was a similarly aggressive subtype. However, in 2008, the European Organization for Research and Treatment of Cancer compared clinical outcomes of 63 cases of SPTCL (at that time, referred to as αβ SPTCL) *versus* 20 cases of PCGDTCL (at that time, referred to as γδ SPTCL).[6] Most patients in

this series were treated with anthracycline-based combination chemotherapy, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Five-year overall survival (OS) was markedly different between the two groups, at 82% for SPTCL *versus* 11% for PCGDTCL (P<0.001). A more recent, multi-institutional cohort of 95 cases of SPTCL and related adipotropic lymphoproliferative disorders between 1998 and 2018 confirmed the generally indolent behavior of SPTCL.[7] With a median follow-up of 56 months, 67% of patients achieved a complete response (CR) to a median of three cumulative therapies. While relapses were common, no patients died of disease or HLH. Immunomodulatory agents included systemic steroids, cyclosporine, methotrexate, and others, with an objective response rate (ORR) of 52%. In particular, most patients treated with cyclosporine had a response (94%), and methotrexate as a first-line agent in seven patients produced a response in all seven. Therefore, for most patients, our approach is conservative immunosuppression with any of the agents above (in particular, cyclosporine or methotrexate), taking into consideration current symptoms, coexisting conditions, and concurrent medications. Other, smaller series show equally high response rates to immunosuppression.[13-15] We assess response with PET/CT, and in those with evidence of HLH, with continued assessment of abnormal clinical and laboratory parameters.

For those with relapsed/refractory (R/R) disease, we sequence immunosuppressive agents in efforts to avoid combination chemotherapy. In clinically aggressive or multiply relapsed disease, combination chemotherapy, often with consolidative transplant (autologous and allogeneic) has efficacy, similar to paradigms for PCGDTL or nodal peripheral T-cell lymphomas.[6,7,16] The optimal management of frank HLH is unclear, and treatment of the underlying SPTCL is logical, with consideration for steroids and etoposide.[17] Emerging data on ruxolitinib in the treatment of HLH, predominantly in the pediatric population, are encouraging,[18] and we consider this agent in persistent HLH. At least one case report describes this approach in a patient with underlying SPTCL.[19] Finally, CD30 expression is rare and, if detected, usually weak in intensity.[6,7,20] Therefore, while we could consider brentuximab vedotin in multiply R/R disease, we acknowledge the absence of data.

Hepatosplenic T-cell lymphoma

HSTCL classically presents in males in the setting of chronic immune suppression or dysregulation, specifically inflammatory bowel disease (IBD) or after solid organ transplantation.[21-23] In three representative case series, up to 20% of patients had IBD, an autoimmune disorder other than IBD, or had received a solid organ transplant.[21-23] The association with IBD and IBD-directed therapy, in particular, has been reviewed in detail, stemming from a 2006 report of eight cases (six fatal) in seven males and one female with IBD who were treated with the tumor necrosis factor-α inhibitor, infliximab, in combination with additional immunosuppressant therapy.[24] This led to a Food and Drug Administration boxed warning for infliximab in 2006. An epidemiological survey of over three million reports to the Food and Drug Administration Adverse Event Reporting System identified 30 unique cases of incident HSTCL in patients under chronic immunosuppression.[25] Available evidence seems to suggest that the greatest risk for HSTCL is in those receiving concomitant tumor necrosis factor-α blockade and thiopurines. A study from the International T-cell Lymphoma Project (ITCP) shows that HSTCL can present in older individuals as well.[26]

HSTCL generally presents aggressively with hepatosplenomegaly and cytopenias. Bone marrow is nearly always involved, but lymphadenopathy is uncommon and should prompt consideration of a biopsy.[22-24] Bone marrow or liver biopsy is mandatory to demonstrate a predominantly intrasinusoidal infiltrate of mature γδ (rarely αβ) cytotoxic T cells, commonly with isochrome 7q and trisomy 8 chromosomal abnormalities (detectable by fluorescence *in situ* hybridization)[27-31] and mutational signatures with enrichment in genes of the *JAK/STAT* pathway and chromatin modification, such as *SETD2*.[32-35] The diagnosis *must* be distinguished from other γδ T-cell lymphomas, particularly γδ T-cell large granular lymphocytic leukemia, through careful clinical and pathological review, focusing on histology, cytogenetics, and molecular findings if available.[36]

Therapy of curative intent for HSTCL entails combination chemotherapy induction followed by allogeneic hematopoietic stem cell transplant (alloHCT) in first remission. The optimal induction regimen is unclear (Table 1), although available evidence appears to suggest that CHOP is inadequate with refractory disease being common. In an early evaluation of 21 cases, all except two of whom were treated with CHOP/CHOP-like therapy, the median OS was 16 months; all patients died except the two patients who received non-CHOP induction.[21] A second report of 15 cases from the MD Anderson Cancer Center similarly found that of six patients treated with CHOP/CHOP-like induction, all died within 2 years.[22] In this series, all four surviving patients were treated with non-CHOP induction. An analysis of 166 cases of HSTCL between 1990 and 2018 showed a significantly increased ORR in patients receiving cytarabine/etoposide/platinum-containing regimens (ORR: 82%; CR: 56%) *versus* CHOP/CHOP-like regimens (ORR: 52%; CR: 38%).[37] The median OS was significantly prolonged in the non-CHOP induction group at 36.5 *versus* 18 months (hazard ratio [HR]=0.33, 95% confidence interval [95% CI]: 0.19-0.58). In the absence of prospective or randomized data, this

Table 1. Selected series detailing outcomes in hepatosplenic T-cell lymphoma.

Series	Induction	ORR, CR	Transplant	PFS^ mths	OS^ mths	Notes
Falchook[22] N=15	CHOP-like: 5 hyperCVAD: 4 other: 6	CHOP/CHOP-like: 40%, 40% hyperCVAD: 100%, 75%	Auto: 2 Allo: 2	NR	11	No patients receiving CHOP/CHOP-like induction survived.
Belhadj[21] N=21	CHOP/CHOP-like: 19 platinum-cytarabine-based: 2	CHOP/CHOP-like: 61%, 47% platinum-cytarabine-based: 100%, 0%	Auto: 2 Allo: 1	NR	16	Only 2 patients survived, both treated with platinum-cytarabine (alive at 42 and 52 mths). All other patients died.
Voss[38] N=15	CHOP/CHOP-like: 4 ICE/IVAC: 8 other: 2	CHOP/CHOP-like: 75%, 50% ICE/IVAC: 75%, 38%	Auto: 4 Allo: 5	13.3	59	6 of 7 surviving patients received non-CHOP induction and 5 of 7 surviving patients received allo.
Yabe[23] N=28	CHOP/CHOP-like: 9 hyperCVAD: 15 other: 19*	NR	Auto: 7 Allo: 5	28.3	28.3	Transplant (auto or allo) associated with longer OS (HR=0.3, 95% CI: 0.1-1.3) and EFS (HR=0.2, 95% CI: 0.1-0.9)
Tanase†[42] N=25	CHOP: 8 cytarabine/etoposide/ platinum-containing: 14 other: 3	NR	Auto: 7 Allo: 18	3-yr: 48%	3-yr: 54%	5 of 7 patients receiving auto relapsed and died.
Foss[26] N=31	Anthracycline: 60% non-anthracycline: 40%	40% CR (response by regimen not specified)	8 (auto *vs.* allo not specified)	11	13	3-yr PFS and OS of 40%.
Klebaner‡[37] N=84	CHOP/CHOP-like: 50 cytarabine/etoposide/ platinum-containing: 34	CHOP/CHOP-like: 52%, 38% cytarabine/etoposide/ platinum-containing: 82%, 56%	Auto: 20 Allo: 15	NR	see notes	CHOP/CHOP-like: 18 mths. Cytarabine/etoposide/platinum-containing: 36.5 mths.

^Median unless specified. *First-line regimens not specified. Therefore, the total number of regimens reported is greater than the total number of patients. †European Society for Bone and Marrow Transplantation (EBMT) transplant database series (all patients received transplant). ‡Meta-analysis of published cases. Allo: allogeneic hematopoietic stem cell transplant; Auto: autologous hematopoietic stem cell transplant; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CI: confidence interval; CR: complete response; EFS: event-free survival; HR: hazard ratio; hyperCVAD: cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine; ICE: ifosphamide, carboplatin, etoposide; IVAC: ifosphamide, etoposide, cytarabine; mths: months; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; yr: year.

analysis suggests that cytarabine/etoposide/platinum-containing induction regimens are potentially superior to CHOP-based approaches and should be prioritized in curative intent strategies. Our institutional preference is ifosfamide-containing regimens, such as ICE (ifosfamide, carboplatin, etoposide), usually for two or three cycles followed by response assessment with PET/CT evaluation and bone marrow biopsy. In patients who achieve CR or near CR, we proceed quickly to alloHCT, usually with an additional cycle of therapy to minimize any break in therapy. In our published experience of 14 patients with HSTCL, most of whom were treated with ICE or IVAC (ifosfamide, etoposide, cytarabine), we observed a median OS of 59 months, with six of seven surviving patients receiving non-CHOP induction, and five of seven surviving patients receiving alloHCT.[38] Most National Comprehensive Cancer Network (NCCN) centers use ICE as their initial approach although the guidelines[39] also list DHAP(X) (dexamethasone, cytarabine, and a platinum), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, cytarabine),[22,23] and IVAC (ifosfamide etoposide, cytarabine) as other recommended regimens. European guidelines from the European Society of Medical Oncology propose ICE, IVAC, and CHOEP (CHOP plus etoposide) as induction regimens for HSTCL.[40]

A graft-*versus*-lymphoma effect is likely a critical factor in long-term survival, as most patients will relapse in the absence of alloHCT. In the analysis of 166 published cases, 2-year OS was 12% for those who did not receive any transplant *versus* 56% for those receiving alloHCT (although the non-transplant group likely included non-re-

sponders to therapy).[37] In the largest report of alloHCT in HSTCL, estimated 3-year relapse-free survival and OS in 54 patients was 42% and 56%, respectively.[41] The European Society for Bone and Marrow Transplantation made similar findings.[42] While consolidation with autologous hematopoietic stem cell transplantation (autoHCT) can be considered,[38] our preference, based on limited available data, is early transplant evaluation and alloHCT in eligible patients. In patients with R/R disease, we treat with alternative regimens in the absence of a clinical trial. Donor lymphocyte infusion in those who relapse after alloHCT may have effect.[38]

Intestinal T/NK-cell lymphomas

Enteropathy-associated T-cell lymphoma

The intestinal T-cell and NK-cell lymphomas are unified by their primary involvement of the gastrointestinal tract (Figure 3). The two most recognized entities, enteropathy-associated T-cell lymphoma (EATL, formerly referred to as type 1 EATL) and monomorphic epitheliotropic T-cell lymphoma (MEITL, formerly referred to as type II EATL) are now recognized as genomically distinct diseases.[43-58]

EATL is the most common intestinal T-cell lymphoma in Western countries, presenting with abdominal symptoms in individuals with a preceding or concomitant diagnosis of celiac disease. Direct visualization reveals destructive ulcerating lesions, or at times a frank mass, most commonly in the small bowel, although multifocal lesions involving other intestinal or extraintestinal sites are not uncommon.[43-58] Biopsies show a pleomorphic population of medium/large-sized cells in an inflammatory background, with the neoplastic cells being most often $CD4^-$/$CD8^-$ mature T cells, although CD4/CD8 expression is seen, frequently with 9q34 gains, 16q12 deletions, and *JAK/STAT* mutations.[50,59-61] EATL is a recognized complication of celiac disease, although the pathogenesis is complex. EATL may be preceded by a condition known as refractory celiac disease, defined as persistent gastrointestinal symptoms and abnormal histological findings despite a strict gluten-free diet for ≥6–12 months. This etiological relationship has been reviewed by Dogan and colleagues and elsewhere (see excellent reviews and guidelines,[62] recent genomic analysis and commentary,[63,64] and clinical practice guidelines for refractory celiac disease from the American Gastroenterological Association[65]). The optimal management of EATL is undefined, and interpretation of primary literature is challenging due to the rarity of the condition, evolving classifications (previously EATL could refer to EATL, MEITL or other intestinal T-cell lymphomas), and sub-analyses of larger trials that include various histologies (Table 2). Still, essentially all reports describe an aggressive natural history with generally unsatisfactory long-term outcomes. For example, in the ITCP, 3-year progression-free survival (PFS) and OS for EATL was 28% and 30%, respectively, with a median OS of 11 months.[26] The best outcomes have been observed with combination chemotherapy followed by consolidative transplantation, although the optimal induction is unclear. In the ITCP, in which nearly all patients with EATL received upfront anthracycline-based therapy, the CR rate to first-line therapy was 30%.[26] Intensified efforts have varied results. In a small series of ten patients treated with six cycles of CHOEP, the response rate was again 30%.[48] However, in the Nordic NLG-T-01 trial, one of the largest prospective trials in T-cell lymphoma, CHOEP-14 for six cycles (CHOP-14 in patients >60 years) followed by autoHCT in 21 patients with EATL resulted in a 5-year PFS and OS of 38% and 48%, respectively, and updated results showed a 10-year PFS and OS of 29%, highlighting potential for long-term survival with this program.[66]

Other studied options include a novel regimen consisting of two cycles of IVE (ifosfamide, etoposide, epirubicin) followed by two cycles of high-dose methotrexate and autoHCT.[51] In a preliminary evaluation of this regimen in six patients, four achieved a CR and remained free of disease at over 1.5 years. A larger, retrospective analysis of a modified version of this regimen (later referred to as the Newcastle Regimen) tested one cycle of CHOP followed by three courses of IVE alternating with intermediate-dose methotrexate and autoHCT in 26 patients.[55] Five-year PFS and OS rates were both 68%. In comparison to a historical control of 31 patients treated with anthracycline-base therapy, there was a trend to improved CR rate with IVE/methotrexate (65% *vs.* 42%; P=0.06) and death was less frequent (39% *vs.* 81%, P=0.001). A phase II trial of this approach in T-cell lymphomas (including 11 patients with EATL) reported comparatively shorter but still encouraging survival in patients with EATL, with a 1-year PFS and OS of 45%.[67]

Given the frequent expression of CD30, EATL was included in the ECHELON 2 study, but only three patients were enrolled. A separate phase II study, the EATL-001 trial, evaluated BV-CHP (brentuximab vedotin, cyclophosphamide, doxorubicin and prednisolone) followed by autoHCT in 14 patients with EATL.[68] A CR was observed in 64%. Three patients had primary progressive disease, but in all others, no relapses occurred, with a 2-year PFS and OS of 63% and 68%, respectively. Taken together, intensified approaches with CHOEP or BV-CHP in $CD30^+$ tumors followed by autoHCT would be our preferred upfront approaches. Treatment of R/R disease is empiric. Second-line chemotherapy can be attempted.[57] A durable response to CD30-directed chimeric antigen receptor T-cell therapy has been described.[69] We assess disease response in EATL (and MEITL, see below) with PET/CT, and we consult closely with colleagues in Radiology and Gastroenterology to determine the most appropriate imaging and surveillance modality if there is difficulty in fully visualizing involved bowel regions.

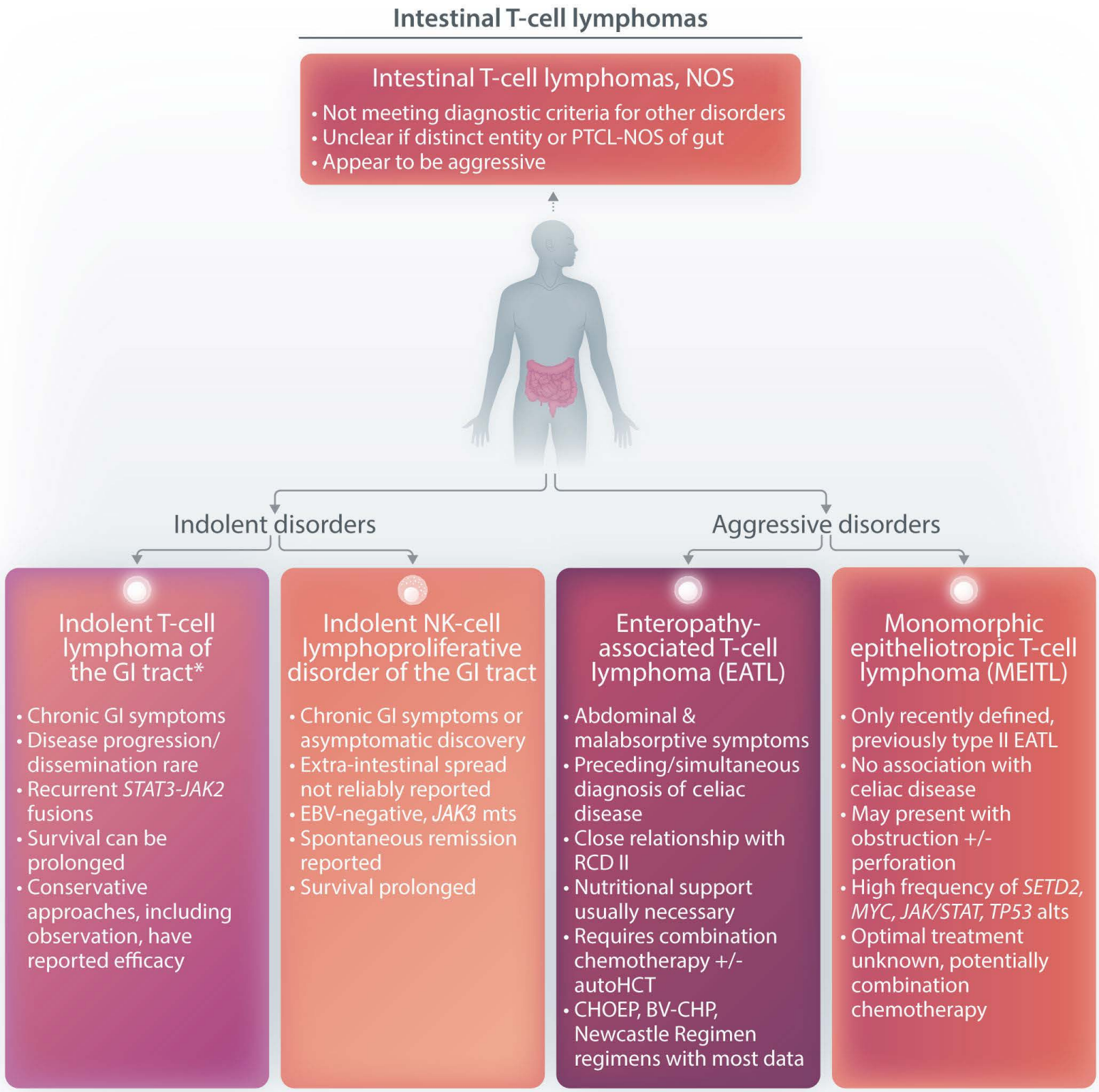

Figure 3. Intestinal T-cell lymphomas. Five subtypes of intestinal T-cell lymphomas are recognized in current classification schemas. Indolent disorders consist of indolent T-cell lymphoma of the gastrointestinal (GI) tract and indolent NK-cell lymphoproliferative disorder of the GI tract, and aggressive disorders consist of enteropathy-associated T-cell lymphoma and monomorphic epitheliotropic T-cell lymphoma. A fifth subtype, intestinal T-cell lymphoma, is undefined and used for intestinal T-cell lymphomas not meeting diagnostic criteria for the other subtypes. *Indolent T-cell lymphoma of the GI tract is named as such in the World Health Organization schema[1] but referred to as indolent T-cell lymphoproliferative disorder of the GI tract in the International Consensus Classification.[2] Figure created at BioRender.com. NOS: not otherwise specified; PTCL: peripheral T-cell lymphoma; EBV: Epstein-Barr virus; mts: mutations; RCD: refractory celiac disease; autoHCT: autologous hematopoietic stem cell transplantation; CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; BV-CHP: brentuximab vedotin, cyclophosphamide, doxorubicin, prednisolone; alts: alterations.

Monomorphic epitheliotropic T-cell lymphoma

Like EATL, MEITL is a primary intestinal T-cell lymphoma, although there is no clear association with celiac disease and there may be a predilection in those of Asian descent.[70-73] As MEITL was previously referred to as type II EATL (and before that, often grouped with intestinal T-cell lymphomas), dedicated literature is very sparse. Still, genomic studies increasingly demonstrate that MEITL is distinct from EATL.[59] As the name implies, MEITL is monomorphic, usually positive for CD8 and CD56, and most commonly derived from intraepithelial γδ T cells. Cytogenetic analyses and mutational profiling are increasingly defining the genomic landscape of this disease.[59,74,75]

MEITL is aggressive, and while sporadic patients are included in clinical trials of patients with other peripheral T-cell lymphomas, there have been no dedicated treatment

Table 2. Selected series detailing outcomes in enteropathy-associated T-cell lymphoma.

Series	Induction	ORR, CR	Transplant	PFS	OS	Notes
Bishton[51] N=6	IVE/HD MTX + BEAM auto	100%, 83%	Auto: 6 Allo: 0	Not reported, 2 relapses at 0.2 and 1.7 yr	2 relapsed and died, all others alive (1.8-4.3 yr post-transplant)	All patients with CD. Prior to induction, 24-h NPO with oral antibiotics for "gut sterilization." All patients received enteral feeding.
Sieniawski[55] N=26	Newcastle (CHOP x 1, IVE/MTX + BEAM auto)	69%, 65%	Auto: 14 Allo: 0	5-yr: 52%	5-yr: 60%	Retrospective analysis. Significantly improved outcomes compared to historical controls receiving anthracycline-based therapy.
Foss[26] N=65	Anthracycline: 97% non-anthracycl.: 3%	30% CR	10 (auto *vs.* allo not specified)	7 mths; 3-yr: 28%	11 mths; 3-yr: 30%	Not specified whether EATL included other intestinal T-cell lymphomas.
Phillips[67] N=11	Newcastle (CHOP x 1, IVE/MTX + BEAM auto)	55%, 55%	Auto: 13 Allo: 0	1-yr: 45%	1-yr: 45%	Prospective phase II trial. Included other histologies, including suspected MEITL.
Sibon[68] N=14	BV+CHP/etoposide/ HD MTX + BEAM auto	79%, 64%	Auto: 11 Allo: 0	2-yr: 63%	2-yr: 68%	Prospective phase II trial in only EATL. All patients CD30$^+$ (≥10%). Aside from 3 primary refractory patients, no relapses occurred.
Relander[66] N=21	CHOEP-14 (CHOP-14 >60 yr) + auto	82%, 51% (overall trial population)	Not reported by histology	10-yr: 29%	10-yr: 29%	Prospective evaluation. Not specified whether EATL included other intestinal T-cell lymphomas.

Allo: allogeneic hematopoietic stem cell transplant; anthracycl.: anthracycline; Auto: autologous hematopoietic stem cell transplant; BEAM: carmustine, etoposide, cytarabine, melphalan; BV-CHP: brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CD: celiac disease; CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CR: complete response; EATL: enteropathy-associated T-cell lymphoma h: hours; HD: high dose; IVE/MTX: ifosphamide, etoposide, epirubicin, methotrexate; MEITL: monomorphic epitheliotropic T-cell lymphoma; mths: months; NPO: nothing by mouth; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; yr: year.

studies and the optimal approach is unclear. Patients often present with abdominal symptoms secondary to intestinal lesions, including perforation requiring upfront emergency resection.[71,72] Many patients may be unable to tolerate further therapy due to debilitation. For example, in a multinational report from Asia of 38 patients, 26% did not receive any systemic therapy (all died). In this series, the median OS was 7 months, with most patients receiving anthracycline-based therapy.[70] In a slightly larger series of 42 patients there was an improved median OS of 14.8 months.[71] More patients in this series received chemotherapy (88%), which was predominantly CHOP (71%), with a CR rate to first-line therapy of 38%. Ability to receive chemotherapy, response to first-line therapy, and receipt of autoHCT were all significantly associated with improved OS in univariate analyses. A non-significant increase in OS was seen in seven patients who received non-CHOP induction including CHOEP, EPOCH and non-anthracycline based regimens. In the largest series to date of 71 patients, the median OS was 7.8 months and 2-year OS was only 15%.[75] High frequencies of alterations and mutations in *MYC*, *SETD2*, *STAT5B*, and *JAK3* were observed, as well as *TP53* mutations in over one-third of patients. Eight patients survived beyond 2 years; all underwent surgery and six subsequently received chemotherapy. We would prioritize clinical trial enrollment in all eligible patients. In the absence of a clinical trial, we most often treat MEITL as nodal PTCL with CHOEP and plan consolidation of CR with autoHCT. However, due to the scarcity of data and the apparent higher rates of chemorefractory disease, we often restage early and change course with alternate therapy and planned alloHCT if the response is inadequate. Efforts to capitalize on aberrancies in the *JAK/STAT* pathway are worth considering in this aggressive disease and warrant further study.

Intestinal T-cell lymphoma, not otherwise specified

Intestinal T-cell lymphoma, NOS, introduced in the WHO-HAEM4R and listed in both the WHO[1] and ICC[2] classification systems, is a non-descript category for T-cell lymphomas of the intestines that do not conform to diagnostic criteria

for EATL or MEITL. Whether this is a unique entity or simply represents PTCL-NOS with intestinal involvement is unclear.[76] Comprehensive immunophenotyping and mutational profiling, if available, are recommended. We would most likely treat intestinal T-cell lymphoma, NOS, similarly to EATL or PTCL-NOS once confidently distinguished from the indolent processes described below.

Indolent T-cell and NK-cell disorders of the gastrointestinal tract

Indolent T-cell lymphoma of the gastrointestinal tract (referred to as indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract in the ICC) is a clonal process marked by a chronic natural history generally without progressive, disseminated disease. Only case reports and cases series exist.[77-88] Presenting symptoms include dyspepsia, vomiting, and diarrhea.[86] Disease has mostly been documented in the small intestine, but involvement of the oral cavity, esophagus, and large bowel has also been reported.[86] While mesenteric adenopathy can be seen, frank peripheral adenopathy or extraintestinal involvement is uncommon.[86] Macroscopically, intestinal polyps may be seen, and microscopically, a non-destructive, superficial lymphoid infiltrate of mature, αβ T cells with a low proliferation rate is observed.[86] Recently, recurrent *STAT3-JAK2* fusions and additional mutational events resulting in JAK-STAT activation have been identified.[87,88] The optimal management of indolent T-cell lymphoma of the gastrointestinal tract is unknown and has been non-uniform in the literature, but options include observation, resection, budesonide, mesalamine, interferon, and combination chemotherapy.[86,88] Three tentative conclusions can be made: (i) OS is long regardless of management, including with observation, with most patients in available reports being alive, some beyond 20 years; (ii) the natural history appears to be a locally chronic disease without high risk of aggressive transformation or spread; and (iii) no therapy appears reliably curative. Based on all available literature, if symptoms need treatment, we would favor conservative therapies at first and avoid the use of chemotherapy.

The related indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract is a new entry in the WHO classification and also designated in the ICC, and was previously referred to as lymphomatoid gastropathy[89] or NK-cell enteropathy.[90] This entity was first documented in a Japanese case series in 2010, describing ten cases of a self-limited, EBV-negative NK-cell proliferation in the stomach.[89] Patients were middle-aged with an equal sex distribution. Three cases were discovered upon follow-up of prior gastric malignancy, and the others were discovered via gastric cancer screening. No patients had extragastric disease, and all patients were observed and alive at the time of publication. Only three patients had recurrent disease after initial resection, and in each case recurrent lesions self-resolved without intervention. Soon after this report, an additional eight cases from the USA were published, again describing an EBV-negative NK-cell proliferation confined to the gastrointestinal tract.[90] In this series, most patients presented with vague abdominal complaints. Again, no extraintestinal involvement was detected. All patients were observed endoscopically and none developed progression. No patients died. Recurrent somatic *JAK3* mutations were recently identified in some cases in a series led by our center.[91] This series and others[92-94] all reiterate that the condition has a chronic, at times spontaneously remitting natural history for which observation may be appropriate. As in indolent T-cell lymphoma of the gastrointestinal tract, we perform full staging, including endoscopic bowel evaluation, peripheral blood flow cytometry, bone marrow assessment, and mutational profiling, with a dedicated effort to rule out PTCL or ENKL, which require treatment (see below). Close observation is recommended with endoscopic follow-up in the absence of concerning clinical or pathological features.

Extranodal NK/T-cell lymphoma

ENKL are predominantly extranodal diseases with a predilection for the upper aerodigestive tract, as first noted by Ng and colleagues over 30 years ago, recognizing a pattern of cases of sino-nasal lymphoma showing NK-cell markers.[95] ENKL involving the upper aerodigestive tract has traditionally been called nasal type ENKL, whereas non-nasal ENKL or more disseminated disease with an unknown site of origin is sometimes called extranasal ENKL. The qualifier ‘nasal type’ has been retained by the ICC[2] but not the WHO.[1] The frequency of this disease is higher in Asian populations.[96] A common presentation for nasal type ENKL is a rapidly growing, destructive mass involving any number of facial structures, including the nasopharynx or palate, with frequent invasion of local structures such as skin, sinuses, or orbits. Systemic symptoms and hemophagocytosis may be present at diagnosis. Key histopathological findings include a diffuse, aggressive lymphocytic infiltrate displaying NK-cell or T-cell markers along with universal EBER positivity. We evaluate patients with newly diagnosed, nasal type ENKL with direct visualization of the nasopharynx, CT or magnetic resonance imaging of nasal structures, PET/CT, laboratory studies including quantitative assessment of EBV DNA by polymerase chain reaction,[97] and bone marrow biopsy to confirm stage. Given our nearly universal use of radiation therapy (RT) as an adjuvant or consolidation for patients with early-stage disease, we routinely consult Radiation Oncology colleagues during the initial workup

for assessment of pretreatment disease volumes to facilitate planning of post-chemotherapy radiation. While we evaluate prognosis with the prognostic index of NK lymphoma plus EBV DNA scoring system (PINK-E; risk factors: age >60 years, stage III/IV, distant [non-regional] lymph node involvement, non-nasal subtype, detectable plasma EBV-DNA at diagnosis),[98] our treatment decisions are primarily driven by stage of disease and the patient's fitness, as described below.

Our treatment approach is broadly based on the stage and extent of disease, the patient's comorbidities, candidacy for HCT, and goals of care. A number of overarching principles shape our management, including recognition of: (i) the importance of RT for local disease control; (ii) the additive benefits of systemic therapy in addition to RT, primarily with pegaspargase-based combination chemotherapy regimens to overcome inherent chemoresistance and address micrometastatic disease; (iii) the ability to consolidate response with either autoHCT or alloHCT; and (iv) the promising activity of PD-1 and PD-L1 targeting monoclonal antibodies in R/R ENKL.

For fit patients with stage I/II nasal ENKL, we typically use combined modality therapy that incorporates local RT directed at the main sites of disease plus systemic therapy. While early retrospective analyses were conflicting regarding the benefit of systemic therapy in addition to RT,[99,100] later population-level data from both the International Peripheral T-Cell Lymphoma Project and the China Lymphoma Collaborative Group showed a clear survival benefit when systemic therapy is added to RT.[96,101] The conflicting data from earlier reports may stem from the use of CHOP or CHOP-like chemotherapy regimens that are now recognized as suboptimal for treating ENKL. The benefits of systemic therapy in addition to RT in stage I/II ENKL were recently documented in a small, multicenter randomized control trial in China, in which 65 patients with stage I/II ENKL were randomized to RT alone *versus* sequential asparaginase-based chemotherapy followed by RT.[102] The response rate (83.3% *vs*. 60.0%), 5-year PFS (82.9% *vs*. 56.5%), and 5-year OS (85.7% *vs*. 60.4%) were significantly improved with the addition of chemotherapy to RT. As expected, combined modality therapy resulted in statistically significantly increased myelosuppression, although grade III/IV events were uncommon overall. For patients ineligible for multiagent chemotherapy with stage I/II nasal ENKL, we typically use RT alone (generally at doses of 50 to 55 Gy) or combine RT with less intensive chemotherapy.

There is uncertainty regarding the optimal sequencing and type of therapy in this paradigm, and supportive data exist for sequential chemoradiation,[102-104] sandwich chemoradiation,[105-107] and concurrent chemoradiation (typically followed by additional chemotherapy alone).[108-113] As RT alone is highly effective (especially for stage I disease)[114] and concurrent chemotherapy generally compromises the choice and intensity of chemotherapy as well as adding toxicity, we typically favor sequential approaches instead, which can avoid the additive toxicity of concurrent chemoradiation and still enable early incorporation of effective systemic therapy. In our institutional practice, for fit patients, we favor one to two cycles of the modified SMILE regimen (dexamethasone, methotrexate, ifosphamide, pegaspargase, etoposide) (see full regimen descriptions in Table 3) for systemic therapy followed by RT.[103] In patients with early-stage and localized nasal ENKL who attain a CR after combined modality therapy, we generally observe rather than consolidate with transplantation. Table 3 details key studies and results for different therapeutic strategies in early-stage ENKL. Dosing, radiation strategies, and even staging vary between published reports, and clinicians should consult the primary literature for specific treatment details of any particular treatment program.

For patients with advanced-stage ENKL, we use combination chemotherapy and often consider combined modality therapy in those with a symptomatic, invasive mass in the upper aerodigestive tract given the effectiveness of RT and the morbidity associated with local treatment failure. In advanced-stage disease, systemic therapy regimens all integrate L-asparaginase or pegaspargase (Table 3) and include modified SMILE,[103,115,116] P-GemOx (pegaspargase, gemcitabine, oxaliplatin),[117] DDGP (cisplatin, dexamethasone, gemcitabine, pegaspargase),[118] and AspaMetDex (L-asparaginase, methotrexate, dexamethasone).[119] At our institution, we use modified SMILE in most fit patients due to institutional experience with the regimen and its known long-term efficacy.[101] Still, we acknowledge the efficacy of other asparaginase-containing regimens listed above, in particular those containing gemcitabine, which show largely comparable results with potentially less toxicity, but for which there are noticeably fewer data and less long-term follow-up in comparison to those for the SMILE regimen. Outside of China, these regimens have not been compared directly, and the most critical principle in practice is to use asparaginase-based induction and not an anthracycline-containing regimen.

Of note, a randomized trial of SMILE *versus* DDGP was conducted in China in patients with newly diagnosed, stage III/IV ENKL.[120] Patients treated with DDGP achieved improved PFS (median not reached *vs*. 6.8 months, HR=0.42, 95% CI: 0.23-0.77) and OS (median not reached *vs*. 75.2 months, HR=0.41, 95% CI: 0.19-0.89) compared to those treated with SMILE. The ORR favored the DDGP arm (90.0% *vs*. 60.0%, *P*=0.067). However, there are important caveats regarding this trial that limit its routine use in clinical practice. First, the trial applied an alternative staging system that is not routinely used in North America (called the Chinese Southwest Oncology Group and Asia

Lymphoma Study Group system).[121] In this system, stage III disease is any lesion with regional lymph node involvement, which would typically be considered stage II disease in the Lugano Modification of the Ann Arbor Staging System. More patients with stage III disease in this system (*vs.* stage IV) were in the DDGP arm, which may indicate that the DDGP arm was enriched with patients who would otherwise be considered to have early-stage disease (and likely more favorable prognoses). In addition, the SMILE regimen was significantly modified and resulted in exces-

Table 3. Selected series in untreated extranodal NK/T-cell lymphoma.

Setting	Regimen	Administration	Transplant information†	Survival	Notes
Early stage: concurrent chemo-radiation	Cisplatin-RT followed by VIPD[108]	Weekly cisplatin x 4 with RT followed by VIPD x 3	Not stated	3-yr PFS: 86% 3-yr OS: 85%	Cisplatin-RT has been followed by other regimens (see reference 114).
	DEP-RT followed by DVIP[112]	DEP x 2 with RT followed by DVIP x 2	Not stated	5-yr PFS: 60% 5-yr OS: 66%	DVIP dosing differs from VIPD, (consult reference 112).
	DeVIC-RT[110]	DeVIC x 3 with RT	Auto: 0 (0%) Allo: 0 (0%)	5-yr PFS: 67% 5-yr OS: 73%	2/3 dosing of DeVIC (2/3DeVIC) was primarily used due to toxicity.
Early stage: sequential chemo-radiation	mSMILE followed by RT[103]	mSMILE x 1-2 cycles followed by RT	Auto: 1 (6%) Allo: 0 (0%)	median PFS/OS: not reached	94% ORR (89% CR) in stage I-II disease.
	DDGP followed by RT[102]	DDGP x 3 cycles followed by RT	Not stated	5-yr PFS: 83% 5-yr OS: 86%%	Randomized trial comparing DDGP-RT *versus* RT alone.
	P-GemOx followed by RT[104]	P-GemOx x 2-6 cycles (not defined) followed by RT	Auto: 0 (0%) Allo: 0 (0%)	5-yr PFS: 66% 5-y OS: 81%	-
Early stage: sandwich chemo-radiation	GeLOx-RT-GeLOx[105]	GeLOx x ≥ 2 cycles followed by RT followed by GeLOx x 2-4 cycles (6 total cycles)	Not stated	5-yr PFS: 74% 5-yr OS: 85%	-
	LVP-RT-LVP[106]	LVP x 2 cycles followed by RT followed by LVP x 2-4 cycles	Not stated	5-yr PFS: 64% 5-yr OS: 64%	-
Advanced stage: combination chemo-therapy^	mSMILE[103]	mSMILE x 3-4 cycles ± RT	Auto: 3 (30%) Allo: 4 (40%)	median PFS: 8 mths median OS: 11 mths	Key differences in mSMILE and SMILE[116,117] are summarized in reference 104.
	DDGP[118]	DDGP x 4-6 cycles	Not stated	3-yr PFS: 62% 3-yr OS: 75%	See text for DDGP *versus* SMILE comments.
	P-GemOx[117]	P-GemOx x 6-8 cycles (usually followed by RT)	Auto: 7 (20%)* Allo: 0 (0%)	3-yr PFS: 39% 3-yr OS: 65%	Reference includes newly-diagnosed advanced and R/R.
	AspaMetDex[119]	AspaMetDex x 3 cycles	Auto: 5 (26%) Allo: 0 (0%)	See notes	Trial in R/R ENKL regardless of stage, consult reference for detailed outcomes.

†This column refers to the number (and percentage) of patients in each series who underwent transplant consolidation in remission following the stated regimen listed under the Administration column. *Publication does not state whether these 7 patients had newly diagnosed or R/R disease. allo: allogeneic hematopoietic stem cell transplant; AspaMetDex: L-asparaginase, methotrexate, dexamethasone; auto: autologous stem cell transplantation (or high-dose therapy with autologous stem cell rescue); DDGP: cisplatin, dexamethasone, gemcitabine, pegaspargase; DEP: dexamethasone, etoposide, cisplatin; DeVIC, dexamethasone, etoposide, ifosphamide, carboplatin; DVIP: dexamethasone, etoposide, ifosphamide, cisplatin; ENKL: extranodal NK/T-cell lymphoma; GeLOx: gemcitabine, L-asparaginase, oxaliplatin; LVP: L-asparaginase, vincristine, prednisone; mths: months; mSMILE: dexamethasone, methotrexate, ifosphamide, pegaspargase, etoposide; P-GemOx: pegaspargase, gemcitabine, oxaliplatin; R/R: relapsed/refractory; RT: radiation therapy; SMILE: dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide; VIPD: etoposide, ifosphamide, cisplatin, dexamethasone; yr: year.

sive toxicity including seven treatment-related deaths (17.5% of patients treated with SMILE) and lower efficacy than in other published studies. In our own institutional experience of using the modified SMILE regimen, we did not document any treatment-related deaths,[103] and we are hesitant to extrapolate the results of this Chinese trial given the non-conventional staging system used and the unusually high treatment-related mortality in the SMILE arm.

We strongly consider consolidative HCT in patients with advanced-stage disease who attain complete remission, although the decision whether to perform autoHCT or alloHCT is highly individualized based on disease presentation, chemosensitivity, treatment tolerability, patients' fitness, and donor availability. Our practice is to consider alloHCT when possible, especially for patients with advanced-stage disease involving multiple extranodal sites, although there is no clear consensus. If the goal is alloHCT, there is no minimum number of cycles of therapy that must be performed (we proceed as fast as possible once remission has been obtained). In terms of autoHCT, a recently reported retrospective study of 20 patients who underwent upfront autoHCT who were compared to a matched, 60-patient control group who were observed suggested improved PFS and OS with autoHCT.[123] There are other reports documenting the efficacy of autoHCT.[123,124] In terms of alloHCT, the Center for International Blood and Marrow Transplant Research used pooled data to evaluate 82 patients with ENKL who underwent alloHCT (30 patients in first CR).[125] Of note, 22% in this series were refractory to frontline therapy and only 38% received pegaspargase prior to alloHCT. With a median follow-up of 36 months, the 3-year PFS and OS was 28% and 34%, respectively. Non-relapse mortality at 3 years was 30%. The Asia Lymphoma Study Group reported outcomes for 18 patients undergoing alloHCT (9 patients in first CR), demonstrating 5-year event-free survival and OS of 51% and 57%, respectively.[126] For patients with prolonged follow-up in both series, survival plateaus suggest curative potential.

Driven by EBV, PD-L1 is frequently expressed on NK/T cells as a mechanism to avert immune surveillance. For R/R ENKL, recent results on the use of anti-PD-1 and anti-PD-L1 monoclonal antibodies are encouraging (Table 4).[127-133] These agents are the preferred therapies in the R/R setting, if accessible.[39] Table 4 details outcomes of the various agents. None is approved in the USA and Europe, and only pembrolizumab and nivolumab are compendium-listed by the NCCN guidelines (to the best of our knowledge, none of these agents is approved globally at the time of publication).[39] While pseudo-progression has been reported with these agents, hyperprogression akin to that reported in adult T-cell leukemia-lymphoma[134] has not been consistently observed in ENKL. We await final results from larger series with longer follow-up in the R/R setting to assess response durability as well as the use of checkpoint blockade prior to alloHCT, given concerns regarding graft-*versus*-host disease. Ongoing studies are evaluating the incorporation of checkpoint blockade in first-line regimens (NCT03728972). Finally, additional EBV-directed therapies for R/R ENKL are under investigation, including nanatinostat, a selective histone deacetylase inhibitor, in combination with valganciclovir,[135] and autologous EBV-specific T cells.[136]

A word on non-cytotoxic therapies

The last decade has witnessed numerous attempts to utilize non-cytotoxic therapies in T-cell lymphomas, primarily in the R/R setting. These agents include brentuximab vedotin,[137,138] belinostat,[139] romidepsin,[140,141] pralatrexate,[142] bortezomib,[143,144] lenalidomide,[145-147] duvelisib,[148] and ruxolitinib,[149] some of which are approved for use in the

Table 4. Anti-PD-1 and PD-L1 therapies in relapsed/refractory extranodal NK/T-cell lymphoma.

Agent	ORR (CR)	Median PFS	Median OS	DOR
Nivolumab[128] N=3, case series	Of 3 patients with R/R disease, 1 achieved CR and remained free of disease at publication. The other 2 patients exhibited clinical response in observable lesions but died of infection within 3 mths.			
Pembrolizumab[127] N=7, case series	Of 7 patients with R/R disease, 4 achieved a response (ORR 57%) with 2 CR (29%). No survival data provided.			
Avelumab[131] N=21	38% (24%)	2.7 mths	Not reached	Not reported, 5 of 21 patients with ongoing treatment beyond 12 mths
Sintilimab[133] N=28	75% (21%)	Not reported	Not reached (2-yr OS: 79%)	4.1 mths
Tislelizumab[132] N=22	32% (18%)	2.7 mths	9 mths	Not reached
Sugemalimab[129] N=80	45% (36%)	Not reported	Not reached (18-mth OS: 58%)	Not reached (18-mth DOR rate: 83%)

CR: complete response; DOR: duration of response; mths: months; ORR: objective response rate; OS: overall survival; PFS: progression free survival; R/R: relapsed/refractory; yr: year.

USA and Europe, and others which can be variably used off-label. The referenced clinical trials of these agents are dominated by the more common nodal T-cell lymphomas (PTCL-NOS, angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma), and only a handful of patients with the rare subtypes discussed in this review were included in these trials. Therefore, when referencing response rates and survival times following the use of these agents, it is imperative to realize that the true efficacy of many novel therapies remains largely unclear in the rare subtypes. An increasing reliance on molecular drivers of response and resistance may allow for a more nuanced application of therapies, as histology-specific clinical trials are challenging to conduct (although not insurmountable[68]) given the sheer rarity of these entities.

Conclusions

Treating rare diseases is a challenging endeavor. Informative clinical trials are lacking, and management decisions are consequently derived from imperfect data. Still, patients with rare diseases need treatment, and as clinicians we must therefore thoughtfully review prior literature, searching for themes and guiding principles that, when coupled with knowledge on underlying biology and our own personal experiences, can allow for reasonable management decisions. Thanks to tremendous basic science and translational reaearch, as well as multicenter, often international clinical efforts in the dedicated study of T-cell lymphomas, we are hopeful that the next decade can provide further insights into these rare entities and refine treatment paradigms based on greater degrees of evidence.

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Contributions

All authors wrote the paper and approved the final version of the manuscript.

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