MODULE 2: SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA (sALCL)

sALCL: INTRODUCTION

Anaplastic Large Cell Lymphoma (ALCL) is a subtype of mature T-cell and Natural Killer (NK)-cell neoplasms, which are a subset of non-Hodgkin's lymphomas (NHLs).[1,2] T-cell lymphomas, so-called by their post-thymic origin, are a biologically diverse and uncommon group of diseases.[1]

Routine immunophenotyping and molecular diagnostics, coupled with disease-specific clinical and pathologic features led to the recognition of the full spectrum of T-cell neoplasms, which include ALCL,[1] a cytotoxic T-cell or null phenotype that is lacking expression of both T- and B-cell markers.

ALCL was first described in 1985, as a Ki-1 (now commonly referred to as CD30) lymphoma, characterised by large pleomorphic cells expressing CD30, and with a tendency to invade lymph node sinuses.[3] The current designation for this neoplasm is ALCL, per the 2008 World Health Organization (WHO) classification of lymphoid neoplasms.[1,4]

There are three distinct forms/types of ALCL that have only recently been recognized.[1,2] They are: primary cutaneous ALCL, systemic ALK+ ALCL (sALCL), and systemic ALK- ALCL.

FREQUENCY OF T-CELL LYMPHOMA SUBTYPES: FROM THE INTERNATIONAL PTCL STUDY

A recent International Peripheral T-cell and Natural Killer/T-Cell Lymphoma Study, involving 22 institutions in North America, Europe and Asia, provided data on the distribution or frequency of different PTCL subtypes - based on 1,314 cases by a consensus diagnosis.[5]

Data from this study showed that the most common subtypes were: PTCL-Not Otherwise Specified (NOS) (26%) and angioimmunoblastic TCL (AITL) (19%), followed by NK/T-cell, Adult T-cell leukaemia/lymphoma (ATLL), and ALCL (all approximately 10%), as well as enteropathy-type PTCL (5%).1All of the other specific subtypes of PTCL represented less than 2% of the total.[5]

If you look at the left side of the pie chart, you'll notice that ALK+ and ALK- ALCL are listed separately.

sALCL: CLINICAL AND BIOLOGICAL FEATURES

ALCL is a clinically and biologically heterogeneous disease.[6] Systemic ALCL (sALCL) is a clinically aggressive, systemic lymphoma that primarily involves lymph nodes.[6,7] Virtually all ALCL characteristically displays strong, uniform, membranous and paranuclear staining for CD30.[4]

The recent WHO classification now recognises a sub-classification of sALCL—two subgroups, based on expression of the ALK protein: systemic ALK-1 expressing ALCL (ALK+), and systemic ALK-1 negative ALCL (ALK-) which is regarded as a provisional disease entity by the 2008 WHO classification.[2]

Of the two ALCL subgroups, neoplasms that aberrantly express ALK and others that do not, ALK+ ALCL represent approximately 50–80% of all ALCLs. The remaining cases are ALK- ALCL.[6]

ALK+ ALCL has become a relatively well-defined entity at the histologic, immunophenotypic, and molecular levels.[6]

There is currently no clear consensus regarding ALK- ALCL, although the predominant opinion expressed is that these neoplasms are not a distinct entity at the immunophenotypic or molecular level.[6]

Emerging data indicate that ALK- ALCL are more aggressive neoplasms with poorer outcomes compared to those in patients with ALK+ ALCL.[7]

sALCL: INCIDENCE AND EPIDEMIOLOGY

sALCL is an uncommon type of NHL. It accounts for 2-8% of all NHLs in adults, and 10-30% of all NHLs in children.[8-10]

The incidence and mortality of sALCL was estimated using latest available data from the WHO (numbers of cases of NHL in the WHO Europe region) and the median % of all NHLs in adults (5%) and children (20%).[6,8-10]

In the WHO Europe region, the estimated incidence of sALCL is approximately 5,000 adults/year and 20,000 children/year4 and the estimated mortality is approximately 2,000 adults/year and 8,000 children/year.[6]

In a cohort analysis of about 300 pts with PTCL, sALCL accounts for approximately 12% of all subtypes: ALK+ (6.6%), and ALK- (5.5%).[5]

In the International Peripheral T-cell Lymphoma Project, the distribution of sALCL differed by geographic region. sALCL appears to be relatively uncommon in the Asian population, and more common in Western countries. ALK+ ALCL is more common than ALK- ALCL in North America but appears to be slightly less common than ALK- ALCL in Europe, whereas the frequency of the two subgroups in Asia is similar.[5]

sALCL: DEMOGRAPHICS, AETIOLOGY AND POTENTIAL RISK FACTORS

sALCL occurs more frequently in children compared with adults.[7]

There is a bimodal age distribution by subgroup and sALCL is more common in men versus women. ALK+ is most common in children and young adults.[1,4,7,11] It occurs mainly in the first three decades of life with male predominance being particularly striking in the second and third decades of life.[7] ALK- is more common in older patients (>50 years).[1,11]

The aetiology of ALCL is unknown, but some potential risk factors for NHL include:

- Family history of haematopoietic malignancies[12]
  - NHL confers a consistently stronger familial association among men than women, and NHL risk was highest among individuals who reported a brother with NHL.[4]
- Immunosuppression, immunodeficiencies, autoimmune disease, and environmental factors[13]
  - Pathogens linked to the risk of lymphoma include the Epstein-Barr virus (EBV), however, EBV infection of the tumour cells in ALCL is rare or absent.[1,7]
  - Chemicals that have been implicated in lymphomagenesis include agricultural herbicides and insecticides and hair dyes.[1]

KNOWLEDGE CHECK

Potential risk factors for NHL include

A. Family history of haematopoietic malignancies
B. Autoimmune disease, immunosuppression and immunodeficiencies
C. Environmental factors
D. A and B
E. All of the above

sALCL: CLINICAL PRESENTATION AND SYMPTOMS

sALCL presents as an aggressive disease, primarily involving sinus areas of the lymph nodes.[7,10,14]

Extranodal involvement is frequent (60% of cases), with approximately 40% of patients with ALK+ sALCL showing two or more extranodal sites of the disease.[10] The most frequent extranodal sites in ALK+ patients include: bone, subcutaneous tissue, bone marrow, and spleen.[7] The most frequent extranodal sites in ALK- patients include: skin, lung, liver, bone, and bone marrow.[7]

The distribution of nodal disease is similar between ALK+ and ALK- patients, with 54% of ALK+ patients having nodal disease vs 49% of ALK- patients. The distribution is also similar among patients with extranodal disease : 20% of patients ALK+ 20% have extranodal disease vs 21% of ALK- patients. Involvement of the gut and central nervous system is rare.[10,14]

In children, extranodal disease includes visceral involvement in 43% of cases and skin lesions in 26% of cases.[14]

Approximately two-thirds of patients with sALCL are known to have advanced-stage disease.[14] B symptoms are common and experienced by 50-75% of patients.[2,11,15] B symptoms include fever, weight loss, night sweats, fatigue and swollen lymph nodes.

The clinical presentation in children is similar—54% of child patients experience B symptoms.[16] Lymph node involvement is very common, occurring in 92% of children,7 with extranodal disease in approximately 68% of cases.[16]

sALCL: DIAGNOSTIC TESTS AND PROCEDURES

ALCL is currently diagnosed according to the WHO classification system. The evaluations include[2,3]; a full history, physical examination, and complete blood count with differential, and a metabolic panel including lactate dehydrogenase (LDH).

The workup also includes excision resection of the lymph node, skin biopsy for histology, bone marrow biopsy and aspirate, T-cell immunophenotyping; immunostaining for CD30, and molecular genetic analysis to detect antigen receptor gene rearrangements; specifically translocation of genomic DNA from chromosomes 2 and 5 [t(2;5)] and variants.

Additionally, the evaluation includes immunostaining with anti-ALK monoclonal antibodies and/or reverse transcriptase polymerase chain reaction. These should be performed to detect the upregulation of ALK for diagnostic and prognostic purposes.[3]

Finally, full body imaging computed tomography and fluorodeoxyglucose positron emission tomography scans should be done for the presence/extent of systemic disease and detection of extranodal disease.[3]

All histopathologic and molecular results should be correlated with clinical findings and patients classified according to the WHO/European Organisation for Research and Treatment of Cancer consensus classification.[3]

sALCL: DIAGNOSTIC IMMUNOPHENOTYPIC AND MOLECULAR CHARACTERISTICS

Immunohistochemical screening of a large number of undifferentiated large cell malignancies has revealed that the tumour cells of nearly all ALCL cases show a strong expression of CD30 on the cell membrane and in the Golgi region. As a result, membrane-associated expression of CD30 has been included in the definition of ALCL.[10]

To make a diagnosis under the present system of classification, the WHO requires, in addition to the presence of 'hallmark' cells, immunopositivity for CD30,[2] immunopositivity for ALK protein, and immunopositivity for epithelial membrane antigen (EMA).

Demonstration of the ALK protein by immunohistochemistry is usually sufficient to establish the diagnosis of ALK+ ALCL in cases with typical morphology.[3]

sALCL also includes common chromosomal translocation characterised by t(2;5)(p23;q35) that results in production of nucleophosmin (NPM)-ALK chimeric protein (also referred to as p80).[3,6]

ALK fuses with nucleophosmin promoter in approximately 85% of cases of ALCL.[6,7]

CLINICAL AND PATHOLOGICAL FEATURES OF THE sALCL SUBGROUPS AND PRIMARY CUTANEOUS ALCL

This screen shows the clinical and pathological features of the sALCL subgroups and primary cutaneous ALCL.

Most cases of sALCL are CD4+.[1]

Epithelial membrane antigen and clusterin can be useful diagnostic markers to differentiate cutaneous ALCL from sALCL.[1]

Other features which help to differentiate the two sALCL subgroups are age, male predominance, and survival rates.

This is because ALK- ALCL occurs in older patients (with a peak of incidence in the sixth decade of life).

ALK- ALCL also has a lower male predominance and poorer survival when compared to ALK+ ALCL.[6]

Clinical and pathological features of the sALCL subgroups and primary cutaneous ALCL

Features	ALK+	ALK-	Primary cutaneous ALCL
CD30	+	+	+
T-cell phenotype	CD4+/CD8-	CD4+/-/CD8-	CD4+/CD8-
ALK protein	+	-	-
Clusterin	+	+	-
EMA	+	±	-
Cytotoxic proteins*	+ (80%)	+ (50%)	+ (70%)
Median age, years	<30	>50	>50
Male:Female	M > F	M = F	M > F
5-year survival	65–90%	30–40%	>90%

ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; EMA = epithelial membrane antigen;
*Cytotoxic proteins = granzyme B, perforin, TIA1 (T-cell intracytoplasmic antigen)

Savage K. Blood Reviews 2007;21:201–216.

sALCL: STAGING AND PROGNOSTIC TOOLS

Identifying high-risk groups is of particular importance when evaluating the suitability and the success of a therapeutic intervention.[14,17]

The disease staging for sALCL is similar to that of other NHLs and uses the Ann Arbor classification system.[14]

The International Prognostic Index (IPI)[17] is a standard prognostic model that predicts survival and is used to identify high-risk groups.[17] The IPI is widely used for adult lymphomas, but has not yet been studied/assessed in children with lymphomas.[16]

In the National Comprehensive Cancer Network (NCCN) guidelines for NHLs, patients are stratified into two groups based on an age-adjusted IPI.[14] The NCCN guidelines also recommend the use of the prognosis in T-cell lymphoma (PIT) scoring system.[14]

sALCL: SURVIVAL BY SUBGROUP

Outcomes are significantly better for patients with ALK+ versus ALK- ALCL.[11,14,18,19]

In a paper by Savage et al, the 5-year OS for ALK+ ALCL patients was 70-93% and the 5-year OS for ALK- ALCL patients was 37-49%.[11,14,18]

Outcomes in young people (median age 10 years) are similar to those in adults with ALK+ ALCL, with a 5-year OS of 81% (95% CI, 76-86%) and 5-year progression-free survival of 71% (95% CI, 65-77%).[20]

In the four studies reported here, patients with ALK+ ALCL had significantly better survival rates compared with ALK- ALCL patients, although the ALK+ patients in all four studies were much younger than the ALK- patients. That said, expression of ALK is closely correlated with age and IPI.

KNOWLEDGE CHECK

Features which help to differentiate the two sALCL subgroups are

A. Age
B. Male predominance
C. Immunopositivity for CD30
D. A and B
E. A, B and C

sALCL: TREATMENT OVERVIEW

CHOP-based chemotherapy is currently considered the standard first-line treatment for treatment of patients with systemic ALCL.[1] It is effective in approximately 80% of cases involving children and 60% of adults with ALK+ ALCL.[21]

Consolidation with high dose therapy (HDT) followed by autologous stem cell transplant (ASCT) support is not recommended if patients achieve complete remission.[1] Patients with ALK- ALCL have a poorer outcome.[14]

In fact, chemotherapy is effective in approximately 40% of cases3 and consolidation with HDT followed by ASCT is recommended.[1]

Allogeneic transplantation may be an effective procedure for relapsed or refractory ALK+ ALCL but its value in the treatment of ALK- ALCL remains to be defined.[1]

Generally treatment approaches to date have been similar among the PTCL subtypes; however, given the underlying biologic heterogeneity, subtype specific therapies may be more optimal.[1]

sALCL: INDUCTION THERAPY

There are currently no clinical practice or treatment guidelines for ALCL from the:

- American Society of Hematology
- American Society of Clinical Oncology
- European Hematology Association
- European Society for Medical Oncology
- International Conference on Malignant Lymphomas.

National Comprehensive Cancer Network (NCCN) treatment recommendations are available for ALK+ and ALK- ALCL for: induction therapy, follow-up therapy, and additional therapy for patients showing a poor response following induction therapy or for relapsed/refractory ALCL.[3]

sALCL: FOLLOW-UP AND ADDITIONAL THERAPY

For ALK+ ALCL patients who relapse following induction therapy, additional therapy is recommended.

For ALK- ALCL patients with IPI low/low- intermediate stage I,II disease, following induction therapy, interim restaging is recommended. If the PET-CT scan is positive, there should be a re-biopsy before changing course of treatment to follow-up therapy.[3]

For patients with complete response completion of the planned RT is recommended and in those with a partial response RT or high dose chemotherapy with stem cell rescue or clinical trial is recommended.

For those without a response or with progressive disease, treatment is similar to that recommended for relapsed or refractory sALCL.[3]

For ALK- ALCL patients with IPI high- intermediate/high stage I, II disease, and stage III, IV disease, following induction therapy if the PET-CT scan is positive, there should be a re-biopsy before changing treatment course.[3]

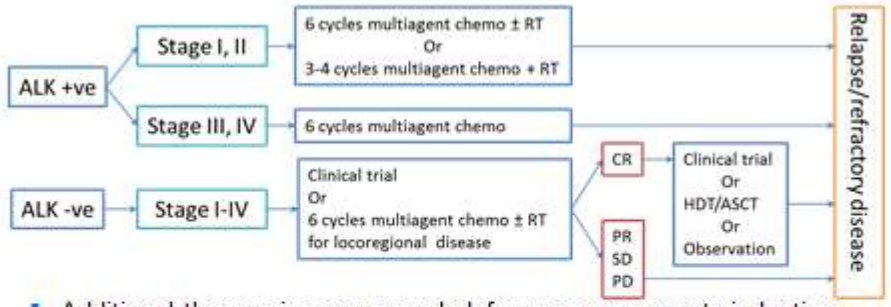
Those with a complete response in this category can be kept under observation. Alternatively, they can undergo a HDT/ASCT with local RT before or after the HDT.[3]

sALCL: CURRENT TREATMENT PARADIGM

Relapse or refractory disease in ALK positive disease despite multi-agent chemotherapy with or without RT requires additional therapy.[3]

Additional therapy is also recommended for poor response to induction therapy in ALK negative disease or following progression or relapse after an initial complete response to treatment.[3]

sALCL: current treatment paradigm



Additional therapy is recommended for poor response to induction therapy or relapsed/refractory ALCL

	Candidate for transplant	Non-candidate for transplant
Additional therapy	Clinical trial or second-line therapy before transplant	Clinical trial or second-line therapy or palliative RT

ALCL = anaplastic large cell lymphoma; RT = radiation therapy; IPI = International Prognostic Index

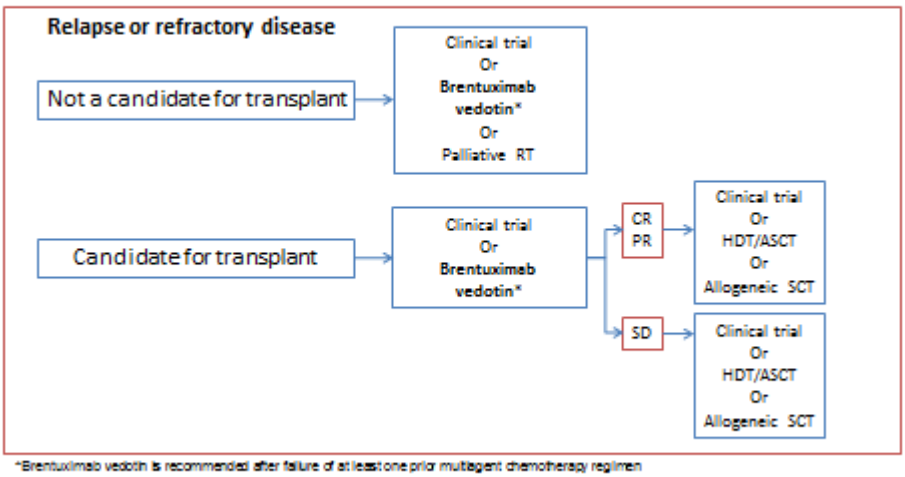
NCCN Non-Hodgkin's Lymphomas Version1.2014 http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

sALCL: TREATMENT OF RELAPSE OR RECURRENCE

Brentuximab vedotin is a treatment option recommended by NCCN for the treatment of recurrent or relapsed sALCL in patients who are not eligible for transplant.[3]

Brentuximab vedotin is also recommended for the treatment of relapse/refractory disease in patients who are eligible for transplant; a clinical trial or HDT/ASCT or an allogeneic SCT may be considered after treatment with brentuximab vedotin.[3]

sALCL: treatment of relapse or recurrence



*Brentuximab vedotin is recommended after failure of at least one prior multiagent chemotherapy regimen

NCCN Non-Hodgkin's Lymphomas Version1.2014 : http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

NCCN SUGGESTED CHEMOTHERAPY REGIMENS

NCCN has suggested treatment regimens for first-line therapy, second-line therapy in transplant candidates, and second-line therapy in patients who are not candidates for transplant.[3]

This screen shows a variety of first and second-line treatment regimens.

Additionally, standard induction for PTCL remains undefined with the exception of ALK+ ALCL, for which CHOP remains the standard. Clinical trials are preferred for all other subtypes of PTCL including ALK- ALCL.[3]

First-line consolidation is recommended for all patients except those with low risk IPI where consolidation with high dose therapy and stem cell rescue is recommended.[3]

ALK+ ALCL does not need consolidative transplant if the patient is in remission.[3]

Activity has been demonstrated with alemtuzumab in small clinical trials.[3]

The NCCN notes that there is a need for additional/larger trials to confirm the activity of alemtuzumab.

NCCN suggested chemotherapy regimens

First-line therapy	Second-line chemotherapy (transplant candidate)	Second-line chemotherapy (non-transplant candidate)
CHOP-21 for ALK+ ALCL	DHAP	Alemtuzumab
CHOEP-21 for ALK+ ALCL	ESHAP	Bortezomib
CHOP every 2 or 3 weeks	GDP	Dose adjusted EPOCH
CHOP followed by ICE	GemOx	Gemcitabine
CHOP followed by IVE	ICE	Pralatrexate
HyperCVAD alternating with high-dose methotrexate and cytarabine	MINE Pralatrexate	RT Romidepsin

ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; CVAD = cyclophosphamide, vincristine, doxorubicin, dexamethasone; DHAP = dexamethasone, cisplatin, cytarabine; ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin; GDP = gemcitabine, dexamethasone, cisplatin; GemOx = gemcitabine, oxaliplatin; ICE = ifosfamide, carboplatin, etoposide; IVE = ifosfamide, etoposide and epirubicin; MINE = mesna, ifosfamide, mitoxantrone, etoposide; RT = radiation therapy

NCCN Non-Hodgkin's Lymphomas Version1.2014 : http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

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