

Anaplastic large cell lymphoma, ALK-negative

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Abstract

Anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-negative (ALCL-ALK–) is a provisional entity in the WHO 2008 Classification that represents 2–3% of NHL and 12% of T-cell NHL. No particular risk factor has been clearly identified for ALCL, but a recent study showed an odds ratio of 18 for ALCL associated with breast implants. Usually, the architecture of involved organs is eroded by solid, cohesive sheets of neoplastic cells, with peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) and classical Hodgkin lymphoma being the main differential diagnoses. In this regard, staining for PAX5 and CD30 is useful. Translocations involving ALK are

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absent, *TCR* genes are clonally rearranged. CGH and GEP studies suggest a tendency of ALCL-ALK⁻ to differ both from PTCL-NOS and from ALCL-ALK⁺.

Patients with ALCL-ALK⁻ are usually adults with a median age of 54–61 years, and a male-to-female ratio of 0.9. At presentation, ALCL-ALK⁻ is often in III–IV stage, with B symptoms, high International Prognostic Index score, high lactate dehydrogenase serum levels, and an aggressive course. ALCL-ALK⁻ presents with lymph node involvement in ~50% of cases; extranodal spread (20%) is less common. Staging work-up for ALCL-ALK⁻ is similar to that routinely used for nodal NHL. Overall prognosis is poor, with a 5-year OS of 30–49%, which is significantly worse when compared to OS reported in patients with ALCL-ALK⁺ (5-year: 70–86%). Patients with systemic ALCL exhibit a significantly better survival compared with patients with PTCL-NOS, with a 5-year OS of 51% and 32%, respectively. Age, PIT scoring system, β 2-microglobulin, and bone marrow infiltration are the main prognostic factors. The expression of proteins involved in the regulation of apoptosis (caspase 3, Bcl-2, PI9) and of CD56 is related to clinical outcome.

ALCL-ALK⁻ is generally responsive to doxorubicin-containing chemotherapy, but relapses are frequent. CHOP is the most commonly used regimen to treat systemic ALCL with complete remission rates of 56%, and a 10-year DFS of 28%. Encouraging results have been reported with more intensive chemotherapy regimens. The addition of etoposide improved outcome. Alemtumumab-CHOP regimen was associated with excellent remission rate but increased toxicity. The role of high-dose chemotherapy supported by ASCT has not been investigated in a trial of exclusively ALCL patients. When used in first remission, it was associated with a 5-year PFS of 64%. High-dose chemotherapy with ASCT is the standard therapeutic option for patients with relapsed or refractory disease. The role of allogeneic transplantation in patients with relapsed/refractory ALCL remains to be defined but there are data to support the contention that a graft-versus-lymphoma effect does exist. Myeloablative conditioning has been associated with 5-year PFS and OS of 40% and 41%, respectively, but a 5-year TRM of 33% was reported. Allo-SCT can be an option for relapsed/refractory ALCL in younger patients, preferably in the setting of a clinical trial.

Pralatrexate, anti-CD30 monoclonal antibodies, brentuximab vedotin (SGN-35) in particular, ¹³¹I-anti-CD45 radioantibody, yttrium-anti-CD25 radioimmunoconjugates, histone deacetylase inhibitors, bortezomib, gemcitabine, vorinostat, lenalidomide, and their combinations represent the most appealing chemotherapy and/or targeted agents to be investigated in future trials.

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1. General information

1.1. Definition and incidence

In the new WHO Classification, anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-negative (ALCL-ALK⁻) is included as a provisional entity. It is defined as a CD30⁺ peripheral T-cell neoplasm that is not reproducibly distinguishable on morphological grounds from ALCL-ALK⁺, but lacks the ALK protein. Most cases express T-cell-associated markers and cytotoxic markers. ALCL-ALK⁻ must be distinguished from primary cutaneous ALCL, other subtypes of CD30⁺ T or B-cell lymphoma with anaplastic features, and classical Hodgkin lymphoma.

ALCL, systemic type, represents 2–3% of NHL and 12% of T-cell NHL. Among all systemic ALCLs, those that are ALK-negative constitute 15–50% of cases. It affects adults with a slight predominance in males. The median age at diagnosis is approximately 55–60 years [1–3]. It usually involves lymph nodes at diagnosis (49% of cases) and, less frequently, extranodal sites (20% of cases). Two-third of patients present with stage III–IV of disease and B symptoms.

1.2. Risk factors

No particular risk factor has been clearly identified for ALCL. Presently, there is no convincing evidence that viruses causing NHL in humans, such as Epstein–Barr virus (EBV), the human T-cell leukaemia/lymphoma virus family, or others, could be involved in the origin of ALCL. A recent series of 64 ALCL cases revealed no EBV-encoded RNA

(EBER) or immunohistochemical evidence of EBV-latent membrane protein type 1 [4]. Correlation between ALCL and inherited immunological deficiency disease, or other immunological disorders, has not been well documented. Recent studies showed that autoimmune disorders may contribute to the risk of T-cell ALCL development [5]. Coeliac disease (odds ratio, 24.0; 95% CI, 8.8–65) and psoriasis (odds ratio, 2.25; 95% CI, 1.00–5.06) have been associated with increased risk of systemic T-cell ALCL, suggesting a possible pathogenic mechanism of chronic antigenic stimulation with local antigenic drive, ultimately leading to the development of lymphoma.

Although specific studies have not been undertaken in ALCL patients, all histotypes of NHL have been described as occurring in people whose work involves application of solvents, pesticides and fertilizers [6–9]. Association of ALCL-ALK⁻ with other malignancies has been anecdotally reported. Recently, a case of lymphomatoid papulosis followed by ALCL-ALK⁺ which then evolved to secondary ALCL-ALK⁻ was reported [10].

A recent study showed an odds ratio of 18.2 (95% CI: 2.1–156.8) for ALCL associated with breast implants [11]. An immunologic response (direct or indirect) related to the prosthesis, direct toxic damage from the silicone components, or both mechanisms have been hypothesized, but these observations have not been confirmed in formal epidemiological studies [12]. Although this association remains rare, 900 incidental cases have been reported [13]. Forty cases of breast implant-associated primary breast anaplastic T-cell lymphomas have been identified in relation to a specific type of textured breast prosthesis [14]. A model cell line, T-cell

lymphoma breast 1 (TLBR-1) was established from a primary tumour tissue to characterize the phenotype and cytogenetics of this entity. Staining for CD4, CD8, CD30, EMA were positive, while ALK-1, keratin, CD2, CD3, CD5CD20, CD56 and HHV-8 was negative. TLBR-1 expressed CD25 and CD122, IL-2 receptors that made the neoplastic growth IL-2 dependent. This cell line represents an important model for further studies of this disease and distinguishes this disease entity of ALCL-ALK⁻, which appears to have better prognosis, from other clinical forms.

2. Pathology and biology

2.1. Morphology

Usually, the organ architecture is eroded by solid, cohesive sheets of neoplastic cells. In the lymph node, the neoplastic cells tend to be diffuse through sinuses, mimicking metastatic involvement from carcinoma. Features such as sclerosis or eosinophilia may occur, but when present should raise the suspicion of classical Hodgkin lymphoma. The neoplastic cells show a similar morphological spectrum to ALCL-ALK⁺, although a “small cell variant” is not recognized. The main differential diagnoses of ALCL-ALK⁻ are peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) and classical Hodgkin lymphoma.

2.2. Immunophenotype

With complete immunophenotypic and molecular studies, ALCL-ALK⁻ can be distinguished from classical Hodgkin lymphoma in virtually all cases. In this regard, staining for PAX5 is useful: classical Hodgkin lymphoma will show weak expression of PAX5 in the majority of cases – a finding never observed in ALCL-ALK⁻. By contrast, the distinction between PTCL-NOS and ALCL-ALK⁻ is not always clear-cut. In ALCL-ALK⁻, all tumour cells are strongly positive for CD30, usually at the cell membrane and in the Golgi region. Staining should be strong and of equal intensity in all cells, a feature that is important in distinguishing ALCL-ALK⁻ from other PTCLs. By contrast, CD30 staining is usually more heterogeneous and weak. Loss of T-cell markers can occur, with greater frequency than typically seen in PTCL-NOS. A substantial minority of cases is positive for EMA.

2.3. Genetics

The genetics of T-cell lymphomas are poorly understood. The only well characterized abnormality is the translocation involving ALK, absent in ALK-negative lymphomas. The majority of cases (74–90%) show clonal rearrangement of *TCR* genes [15,16].

CGH studies indicate a tendency of ALCL-ALK⁻ to differ both from PTCL-NOS and from ALCL-ALK⁺ [17].

Table 1
Clinical features of ALK⁺ and ALK⁻ ALCL.

	ALK-positive	ALK-negative
Age at diagnosis	25–35 y	55–60 y
Sex	Male predominance	Male predominance
Stage at diagnosis	III–IV	III–IV
B-symptoms	Present	Present
IPI score	High	High
Lymph nodes involvement	Yes	Yes
Extranodal involvement	60%	20%
Extranodal sites	Bone, soft tissue, bone marrow, spleen	Skin, liver, GI tract
Leukaemic phase	Rare	Rare
CNS involvement	Rare	Rare

Similarly, gene expression profiling studies suggest that ALCL-ALK⁻ has a distinct profile.

Recurrent *IRF4* (*interferon regulatory factor-4*) translocations were recently found in PTCL-NOS and cutaneous ALCL and may represent a diagnostic tool to distinguish these entities from ALK-negative lymphomas which that lacked this translocation [18].

Recently, the translocation t(6;7)(p25.3;q32.3) was demonstrated in ALK-negative ALCL [18]. The 6p25.3 disrupted *DUSP22*, a dual specificity phosphatase that inhibits T-cell antigen receptor signalling in reactive T-cells by inactivating the MAPK, ERK2 [19]. *DUSP22* expression has a tumour suppressor function and the translocation resulted in *DUSP22* deregulation.

3. Diagnosis

3.1. Clinical presentations

Patients with ALCL-ALK⁻ are usually older than those affected by ALK-positive ALCL, with a median age at diagnosis of 54–61 years, compared with 27 years for the latter group; the male-to-female ratio is 0.9, being similar between ALK groups [1–3,20]. The main differences in clinical presentation between ALK-negative and ALK-positive ALCLs are given in Table 1. At presentation, ALCL-ALK⁻ is often in III–IV stage, with B symptoms, high International Prognostic Index (IPI) score, high lactate dehydrogenase (LDH) serum levels, and an aggressive course [20,21].

ALCL-ALK⁻ presents with lymph node involvement in ~50% of cases; extranodal spread (20% of cases) is less common than in the ALK-positive form [1,22,23]. The most frequent extranodal sites in ALCL-ALK⁻ are skin, liver and lung involvement compared with bone and soft tissue in ALCL-ALK⁺ [2]. Few cases of primary pancreatic localization have been reported [24]. Breast lymphomas are mainly ALCL-ALK⁻ [25]. Bone marrow has been reported as a site, although at a lower frequency than PTCL-NOS (7% vs. 21%) [2]; peripheral blood dissemination (as leukaemic phase) is rare. There are rare reports of ALCL presenting as a

Table 2
Ann Arbor staging system.

Stage I	Involvement of a single lymph node region or single lymphoid structure, such as spleen, thymus or Waldeyer ring (I), or a single extranodal site (IE).
Stage II	Involvement of two or more lymph node regions or lymphoid structures on the same side of the diaphragm (II) or localized involvement of an extralymphatic site (IIE). The number of anatomical regions involved should be indicated by a subscript (e.g., II ₃). Mediastinal nodes are a single lymph node region.
Stage III	Involvement of lymph nodes regions or lymphoid structures on both sides of the diaphragm (III), or localized involvement of an extralymphatic site (IIIE), or spleen (IIIs) or both (IIIEs). Moreover, stage III ₁ – characterized by splenic, hilar, coeliac or portal node involvement – can be distinguished from stage III ₂ which presents para-aortic, iliac and/or mesenteric node involvement.
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Localized involvement of liver or bone marrow is also considered stage IV.
Extranodal disease	Extranodal categorization in stages I–III includes a single extralymphatic involvement by limited direct extension from an adjacent nodal site. Extranodal involvement should be identified by a symbol (M: marrow, L: lung, D: skin, H: liver, P: pleura, O: bone).
Systemic symptoms	Fever > 38 °C of no evident cause for 3 consecutive days, night sweats and unexplained weight loss > 10% of body weight. Patients are divided according to the presence (B) or not (A) of these symptoms.
Bulky disease	Palpable masses and abdominal masses (CT scan or MRI) are defined as “bulky” when its largest dimension is ≥ 10 cm. Mediastinal mass is defined as “bulky” on a posteroanterior chest radiograph, when the maximum width is ≥ one-third of the internal transverse diameter of the thorax at the level of T ₅ –T ₆ vertebrae.

leukaemic disease, typically in children, when it is associated with a worse prognosis [26].

ALCL involvement of the central nervous system (CNS) is uncommon. Primary CNS ALCL has been reported in 14 cases, similarly distributed between ALK+ and ALK– [27]. In these patients, clinical outcome was worse than in other systemic extra-nodal ALCL and mortality was greater than in other CNS lymphomas. The course was generally rapid and fatal due to progressive neurological deterioration.

4. Staging

4.1. Staging procedures

Complete staging and work-up for ALCL is similar to that routinely used for nodal NHL. It includes an accurate physical examination, complete haematological and biochemical exams, total-body computerized tomography, and bone marrow aspirate and biopsy. Under certain circumstances, special procedures are required. CNS MRI or CT scan and CSF cytology examination is indicated in patients with neurological symptoms. Although extremely rare, bone lesions should be confirmed by routine X-ray studies, and biopsied if possible. Some particular sites of disease frequently involved by ALCL require special diagnostic procedures, such as gastrointestinal tract radiologic and endoscopic assessment. The staging of stomach and colon-rectum disease requires gastroscopy with several biopsy samples of macroscopically evident lesions, while the small intestine should be studied with contrasted radiological techniques. Ultrasonography and MRI are useful for investigating the involvement of breast, soft tissue, salivary glands or orbits. Surgical procedures such as laparotomy or laparoscopy with multiple liver biopsies and splenectomy play a major role in histopathological diagnosis but are not included as part of the routine staging procedures.

4.2. Staging system

The standard staging system used for ALCL is the same as that proposed for Hodgkin’s disease at the Ann Arbor Conference in 1971 [28]. This system is currently used for all non-Hodgkin’s lymphomas, even if other staging systems are used in some extranodal lymphomas with particular biological behaviours. The Ann Arbor staging system reflects both the number of sites of involvement and the presence of disease above or below the diaphragm (Table 2). Patients are divided into two subsets according to the presence (A) or absence (B) of systemic symptoms. Fever of no evident cause, night sweats and weight loss of more than 10% of body weight are considered systemic symptoms. The presence of bulky mass, such as a lesion of 10 cm or more in the longest diameter is signalled as “X”, while the extranodal involvement should be identified by a symbol (O: bone, L: lung, D: skin, etc.).

5. Prognosis

5.1. Natural history

Adult patients with ALCL-ALK– generally receive CHOP-like or MACOP-B regimens, while paediatric patients are usually treated following lymphoblastic leukaemia protocols [20]. ALCL-ALK– is generally responsive to doxorubicin-containing chemotherapy, but relapses are frequent. In the published series, the prognosis of patients with ALCL-ALK– is poor, with a 5-year overall survival (OS) of 30–49%, versus 70–86% in ALK+ ALCL [2,3,20,29]. Patients with systemic ALCL exhibit a significantly better survival compared with patients with PTCL-NOS [30], with a 5-year progression free survival (PFS) and OS of 39% versus 20% ($p=0.01$) and 51% versus 32% ($p=0.02$), respectively [2], but not all analyses support this observation [31].

Table 3
Prognosis in ALK+ and ALK– ALCL according to reported series after upfront CHOP-like chemotherapy.

	ALK-positive	ALK-negative
Gascoyne (1999)	5-y OS 93%	5-y OS 37%
	5-y PFS 88%	5-y PFS 37%
Savage (2008)	5-y OS 70%	5-y OS 49%
	5-y FFS 60%	5-y FFS 36%
Falini (1999)	ORR 92%	ORR 84%
	10-y DFS 82%	10-y DFS 28%
Schmitz (2010)	3-y OS 89%	3-y OS 62%
	3-y EFS 76%	3-y EFS 46%

5.2. Prognostic factors

The impact of NPM-ALK expression on patient outcome was first observed in a series of 105 cases of adult ALCL, including T-cell and null-cell phenotypes [32]. In another series, stratification of ALCL according to ALK expression demonstrated a significantly favourable prognosis for patients with ALK-positive ALCL, with a 5-year OS of 93% vs. 37% ($p < 0.00001$) and 5-year PFS of 88% vs. 37% ($p < 0.0001$) [32] (Table 3). From these and other reported series, a range of prognoses has been observed with more favourable outcomes reported in recent large, comprehensive analyses (Table 3). Differences may reflect varying stringency in pathologic review as well as the proportion of patients with high-risk disease by the IPI, which also impacts survival in both ALK+ and ALK– ALCL [2,18,31]. However, overall, the observed 5 year failure-free survival is approximately 35–45% and OS ranges from 30 to 49%. The latter variability may also be due to variable duration of follow-up as well differences in the salvage rate if younger patients are able to receive high dose chemotherapy and stem cell transplant at relapse. It is matter of debate whether it is solely the presence of ALK fusion protein that explains the difference in prognosis between ALK– and ALK+ patients. If the comparison of ALK– and ALK+ patients is confined to a specific age group (e.g., <40 y), there is no difference in outcome – suggesting that age is a critical determinant of prognosis [2,3]. In addition to the IPI, the prognosis in T-cell lymphoma (PIT) scoring system, which was originally developed for PTCL-NOS patients and incorporates age, performance status, LDH, and bone marrow involvement [33] has also been shown to be predictive of PFS and OS in ALCL [2]. A study from the GELTAMO (Spanish Cooperative Group for Bone Marrow Transplants in Lymphomas) in 123 patients with relapsed/refractory T-cell NHL (31 were ALCL, 25%) showed that at least two among adjusted IPI factors, >1 extranodal site of disease, and elevated β 2-microglobulin at time of transplant were associated with inferior survival [34].

In the GELA trials, in addition to age <40 y, β -2 microglobulin was prognostic for OS in multivariate analysis both in ALCL-ALK+ and ALCL-ALK–; liver involvement,

albumin level and IPI were prognostic factors in ALCL-ALK– [35].

The expression of proteins involved in the regulation of apoptosis, such as activated caspase 3, Bcl-2 and PI9, is related to clinical outcome [31]. The expression of CD56, a neural cell adhesion molecule, predicted a poor prognosis in a series of 143 patients with ALK± ALCL, with a 5-year OS of 28% vs. 65% ($p = 0.002$), respectively for CD56-positive and CD56-negative ALCL [31]. Bone marrow infiltration seems to be associated with worse prognosis, regardless of the ALK-expression [37].

6. Treatment

6.1. Treatment of primary ALCL-ALK–

The optimal therapy for ALCL-ALK– is controversial due to: the rarity of this disease, the heterogeneity of clinical presentation, and the lack of randomized trials focused on this lymphoma. ALCL-ALK– is usually analysed together with other T-cell lymphomas and patients are enrolled in prospective trials designed to include most peripheral T-cell lymphoma categories. Series focused exclusively on adult patients with ALCL are small and retrospective.

Chemotherapy for peripheral T-cell lymphomas has been derived from experiences in aggressive B-cell lymphoma. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the most commonly used regimen to treat systemic ALCL. In a retrospective series, ALCL-ALK– patients treated with second- and third-generation chemotherapy regimens showed an ORR and complete remission rates (CRR) of 84% and 56%, respectively, with a 10-year disease-free survival (DFS) of 28% suggesting that more dose intensive regimens did not impact outcome [38]. Encouraging results have been reported with ACVBP chemotherapy (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) followed by a consolidation therapy with high-dose methotrexate, ifosfamide, etoposide, asparaginase, and cytosine-arabioside or m-BACOD (methotrexate, bleomycin, Adriamycin, cyclophosphamide, vincristine, dexamethasone), VIMMM (VM26, ifosfamide, mitoxantrone, methyl-gag, methotrexate)/ACVBP, and CHOP [36]. Patients with T-cell ALCL had a CR rate of 69% and a 5-year OS of 63%, however, patients were not stratified by ALK expression; 75% were <60 years of age and 40% had stage I or II disease. The NHL-B1 trial added etoposide to CHOP and reduced the treatment interval from 21 to 14 days in young patients with aggressive NHL and good prognostic markers. In this trial, 710 patients were enrolled; 14% of patients had peripheral T-cell lymphoma; 9.4% ($n = 67$) had systemic ALCL, but ALK status was not defined in the original publication [36]. The addition of etoposide improved CR from 79% to 88% and 5-year EFS by 12%; CHOEP-14 resulted in an increased OS;

Table 4

Therapeutic results of published studies containing patients with ALCL-ALK⁻.

Paper (year of publication)	No.	FFS/EFS/PFS	OS	Comment
Shiota (1995)	75	Not reported	5 y: 33%	Retrospective study
Gascoyne (1999)	26	5 y: 37%	5 y: 37%	Retrospective study
ten Berge (2003)	44	~5 y: 40% ^a	5 y: 40%	Retrospective study
Savage (2008)	72	5 y: 36%	5 y: 49%	International PTCL project retrospective study
Schmitz (2010)	113	3 y: 46%	3 y: 62%	Retrospective study of PTCL patients enrolled in German high grade studies
Sibon (2010 abstract)	74	8 y: 39%	8 y: 49%	Retrospective study of 3 GELA studies

No.: Number of pts with ALCL-ALK⁻.^a Estimate from PFS curve.

however, the subgroup of ALCL was too small to draw reliable conclusions. In the NHL-B2 study, among 689 patients, 6% had T-cell histology including 23 cases of ALCL (3.5%). In a multivariate analysis, CHOP-14 was associated with improved EFS and OS compared to CHOP-21 in aggressive lymphomas, but there were limited number of patients with T-cell lymphoma [37]. More recently the German high grade aggressive NHL study compiled a retrospective series of 320 patients with peripheral T-cell lymphoma from 7 phase II and III trials, including NHL-B1 and NHL-B2 [39]. In total, there were 191 patients with ALCL including 113 cases of ALCL-ALK⁻ treated with CHOP (CHOP-14, CHOP-21), CHOEP (CHOP-14/21 plus etoposide) or intensified CHOEP (High-CHOEP14/21 or Mega-CHOEP). The 3-year EFS and OS were 46% and 62%, respectively, in patients with ALCL-ALK⁻ (Table 4). In younger patients with a normal LDH an improved EFS, but not OS, was observed. However, there was only a trend to improved EFS ($p=0.057$) when patients with ALK⁺ ALCL were excluded. The analysis was not exclusively confined to patients with ALK-ALCL.

An Italian trial has analysed the role 4–8 cycles of an alemtuzumab-CHOP regimen (combination of the anti-CD52 monoclonal antibody alemtuzumab and CHOP chemotherapy) in 24 patients with PTCL, including three with ALCL-ALK⁻. Alemtuzumab has been administered on day 1 of each cycle at dose of 30 mg subcutaneously and patients were treated on a Q28 day schedule. All patients with ALCL-ALK⁻ achieved a CR and were still alive at time of analysis. Median duration of response was 11 months. Major observed toxicities were infections (aspergillosis, staphylococcus sepsis, bacterial pneumonia and Jacob-Creutzfeldt viral encephalitis) [40].

The role of high-dose chemotherapy supported by autologous stem cell transplant (ASCT) has not been investigated in a trial of exclusively ALCL patients. Patients with ALCL-ALK⁻ are usually treated in the same way as and analysed together with all other aggressive T-cell lymphomas, whereas patients with ALCL-ALK⁺ are usually excluded. An exception was a retrospective series of 62 PTCL patients with stage II–IV disease, among which there were 19 ALK⁺ ALCLs and four ALCL-ALK⁻, who were treated

with debulking chemotherapy, followed by intensified treatment and ASCT. The associated 12-year OS, DFS and EFS were 34%, 55% and 30%, respectively [41].

One hundred and thirty-eight patients with ALCL (64 ALK⁺ and 74 ALK⁻) were retrospectively reviewed from the LNH87–LNH93–LNH98 GELA prospective trials and were analysed to address the role of high-dose chemotherapy supported by ASCT in aggressive lymphomas. All but one patient received an anthracycline-based regimen; 22 ALCL patients (16 ALK⁺ and 6 ALK⁻) underwent upfront HDT-ASCT. The ORR was 76% in ALCL-ALK⁻ subgroup, with an OS of 49% at a median follow-up of 8 years [35]. In this study, patients who were transplanted had an improved 8 year OS, however only 6 patients with ALCL-ALK⁻ were included. Bone marrow involvement, more than one extranodal site, liver involvement, albumin level, and IPI all were adverse prognostic factors [35,42].

The role of ASCT in patients with ALCL in first remission has been investigated in some small studies ($n=16–40$), with 5-year OS rates of up to 80%, however, in many of these studies, ALK expression was not assessed, and lymphomas with B, T and null Immunophenotype were included [43,44]. Treatment with four to six courses of dose-escalated CHOP plus etoposide followed by ASCT has been associated with a disappointing 3-year EFS and OS of 26% and 45%, respectively, for the whole group of patients with T-cell lymphoma [45]. The Nordic group has completed the largest prospective phase II trial of upfront transplant in 160 patients with PTCL, excluding ALCL-ALK⁺. The subgroup of patients with ALCL-ALK⁻ was analysed separately ($n=31$) and had an encouraging 5 year PFS (64%) which was superior to either PTCL-NOS or AILT. Unfortunately, there are no prospective phase III trials assessing the question of whether to transplant patients upfront, at first remission, or to keep transplant for relapsed disease, conducted in series exclusively comprised of patients with ALCL. Prospective randomized studies comparing conventional chemotherapy with HDC/ASCT are needed before ASCT may be considered standard therapy. Examination of high-risk patients by IPI and/or molecularly based prognoses may help to identify patient groups that will benefit from consolidative ASCT.

6.2. Treatment of relapsed or refractory disease

The standard therapeutic option for patients with relapsed or refractory disease has not been established. Treatment with gemcitabine, cisplatin and methylprednisolone has been undertaken in 16 patients with relapsed PTCL, two of whom had ALCL-ALK⁻; both patients achieved a partial response, which lasted 3 and 14 months, respectively [46]. Several retrospective studies support the finding that high-dose chemotherapy with ASCT (HDC/ASCT) can salvage patients with relapsed ALCL [35,47–50]; however, these were retrospective studies focused on patients with different relapsed/refractory T-cell lymphomas, including a variable proportion of patients with ALCL, where often ALK status was not specified. Some studies showed an association between ALCL category and better outcome [49,50], while others did not show this difference [35]; this discrepancy could be explained by an unbalanced distribution of ALCL-ALK⁺ cases among studies.

The role of allogeneic transplantation in patients with relapsed/refractory ALCL remains to be defined but there are data to support the contention that a graft-versus-lymphoma effect does exist. An older study on patients with relapsed/refractory aggressive NHL treated with myeloablative conditioning showed comparable outcomes among B-cell and T-cell lymphoma, with 5-year PFS and OS of 40% and 41% for the whole series [51]. In a recent retrospective analysis of 77 T-cell lymphomas treated with myeloablative conditioning and allo-SCT after at least one previous treatment line (ALCL = 35%) [52], the 5-year EFS and OS for ALCL patients were 48% and 55%, respectively. This was similar to that observed in the other T-cell lymphomas where a 5-year treatment-related mortality of 33% was reported. ALK status did not impact survival. Patients with chemorefractory lymphoma have benefited from allo-SCT, with 5-year OS of 29%. A study of chemotherapy followed by allo-SCT with reduced-intensity conditioning and planned donor lymphocyte infusions was conducted in 17 patients with relapsed T-cell NHL (ALCL = 4) [53]. All four ALCL patients were event-free at a median follow-up of 17 months. AlloSCT can be an option for relapsed/refractory ALCL in younger patients, preferably in the setting of a clinical trial.

6.3. New drugs or experimental approaches

Pralatrexate, a novel antifolate methotrexate analogue, has shown higher affinity for the reduced folate carrier type 1 (RFC-1) and increased intracellular uptake than methotrexate. The maximum tolerated dose is 30 mg/m² weekly for 6 weeks every 7 weeks [54]. Among 57 patients with B- and T-cell lymphomas, ORR was 60%. Two patients with ALCL (one ALK⁻) achieved CR; response was longer in the ALCL-ALK⁺ patient (48 months vs. 8 months).

CD30 is a promising therapeutic target. After an initial phase where several anti-CD30 antibodies showed considerable *in vitro* activity (i.e., the human IgG1k antibody MDX-060, the human antibody 5F11, the humanized antibody XmAb 2513, the chimeric antibody SGN-30, the immunotoxin ki-4dgA), but modest clinical activity in patients with CD30-positive lymphomas (i.e., Hodgkin lymphoma and ALCL) [55–57], recently reported studies showed relevant clinical activity with some interesting molecules. Noteworthy, an anti-CD30 antibody–drug conjugate was developed: brentuximab vedotin (SGN-35). This promising agent is a conjugate constituted by the antitubulin agent monomethyl auristatin E and a CD30-specific monoclonal antibody that has shown excellent activity both in Hodgkin lymphoma and ALCL. In preclinical mouse xenograft models it induced durable responses, showing significant clinical activity in relapsed systemic ALCL [58]. Recently, a phase II multicentre study evaluated activity and safety in 58 patients with relapsed or refractory ALCL (72% of cases were ALK-negative); the ORR was 86%, with a CRR of 53% [59]. The response rate was comparable in ALK⁺ and ALK⁻ patients and the median duration of response had not yet been reached at the time of the analysis. Observed toxicities were peripheral sensory neuropathy, nausea, fatigue and diarrhoea. A study combining CHOP and brentuximab in the primary therapy of systemic ALCL is underway.

Radioimmunoconjugates have potential therapeutic value in T-cell NHL. A radioimmunoconjugate in preclinical development is ¹³¹I-anti-CD45 radioantibody [60]. Other radioimmunoconjugates that could be useful are iodine-anti-CD25, yttrium-anti-CD25 and yttrium anti-CD5 [61].

Histone deacetylase inhibitors induce chromatin relaxation, gene expression of tumour suppressors and cell growth arrest. Related trials have demonstrated safety and activity in pre-treated cutaneous T-cell lymphomas, but no data specifically in systemic ALCL are available [62].

Because constitutive activation of the nuclear factor (NF)-kappaB has been described in ALCL, single agent bortezomib has been tested in these malignancies [63]. Combinations of bortezomib with gemcitabine or vorinostat are being addressed in relapsed/refractory T-cell NHL (including ALCL) in ongoing trials. Synergistic effects between proteasome inhibitors and histone deacetylase inhibitors have been shown in preclinical studies [64].

In preliminary analyses, single-agent lenalidomide also displayed activity in relapsed/refractory T-cell NHL, including ALCL (ORR 30%) [65]. Continued research is warranted to predict the potential responses of tumours to novel chemotherapy and/or targeted agents.

Conflict of interest statement

The authors have no conflict of interest to be disclosed.

Reviewer

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<p>TYPE of OPTION</p> <p><i>START provides the following diagnostic and treatment options. The "standard" and the "individualised" options are coupled with ranked types of basis,</i></p>	<p>● STANDARD ("standard", "recommended" [or "not recommended"]) This can be considered a conventional choice for the average patient.</p> <p>● INDIVIDUALIZED ("suitable for individual clinical use") This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient.</p> <p>● INVESTIGATIONAL ONLY ("investigational") This is something which, in principle, can be offered to the patient only within a clinical study.</p>
<p>TYPE of BASIS for available options</p> <p><i>START provides an appropriate basis for each clinical option. Types of basis are ranked in five levels.</i></p>	<p>● There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed</p> <p>● "TYPE 1 evidence" (Randomised trial(s) available, strong evidence) Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary.</p> <p>● "TYPE 2 evidence" (Randomised trial(s) available, weak evidence) One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable.</p> <p>● "TYPE 3 evidence" (External controlled comparisons available) Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable.</p> <p>● "TYPE R basis" (Rational inference) Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).</p>

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