The biology and management of systemic anaplastic large cell lymphoma

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Abstract

Systemic anaplastic large cell lymphoma (ALCL) is a rare, aggressive CD30-positive non-Hodgkin lymphoma. ALK (anaplastic lymphoma kinase)-positive (ALK+) ALCL is associated with the \textit{NPM-ALK} t(2; 5) translocation, which is highly correlated with the identification of the ALK protein by immunohistochemistry. ALK+ ALCL typically occurs in younger patients and has a more favorable prognosis with 5 year survival rates of 70-90% in comparison to 40-60% for ALK-negative (ALK-) ALCL. Studies support that young age is a strong component of the favorable prognosis of ALK+ ALCL. Until recently, no recurrent translocations were identified in ALK- ALCL. However, emerging data now highlight that ALK- ALCL is genetically and clinically heterogeneous with a subset having either a \textit{DUSP22} translocation and a survival rate similar to ALK+ ALCL or a less common \textit{P63} translocation, the latter associated with an aggressive course. Anthracycline-based regimens such as CHOP remain the standard front-line treatment choice for systemic ALCL but in many patients with ALK- ALCL it is ineffective and thus, it is often followed by consolidative autologous stem cell transplantation (ASCT). However, selection of appropriate patients for intensified therapy remains challenging particularly in light of genetic and clinical heterogeneity in addition to the emergence of new, effective therapies. The antibody drug conjugate brentuximab vedotin is associated with a high response rate (86%) and durable remissions in relapsed/refractory ALCL and is under investigation in the up-front setting. In the future, combining clinical and genetic biomarkers may aid in risk stratification and help to guide initial patient management.
Anaplastic large cell lymphoma: Historical perspective

In 1985, Stein and colleagues \(^1\) identified a subset of non-Hodgkin's lymphomas (NHLs), termed ‘Ki-1 lymphomas’ characterized by large CD30+ (Ki-1) anaplastic cells, which have a tendency to grow cohesively and a predilection to invade lymph node sinuses. Although most cases were T or null-cell lineage, 15% had a B-cell phenotype. In the Revised European American Lymphoma (REAL) classification, the name was updated to anaplastic large cell lymphoma (ALCL) and confined to cases that were T or null-cell type \(^2\). Subsequently, several groups identified the presence of a translocation involving the anaplastic lymphoma kinase (ALK) gene on chromosome 2p23 and the nucleophosmin (NPM) gene on chromosome 5q35 that formed a novel chimeric fusion protein, NPM-ALK \(^3\). Subsequent studies confirmed the favorable prognosis of ALK-positive (ALK+) ALCL (Table 1). In the WHO classification, primary cutaneous ALCL (PCALCL) was separated from systemic ALCL due to its indolent behavior and favorable prognosis \(^4\). Further, the provisional category of ‘Hodgkin-like ALCL’ was removed with emerging molecular genetics and immunophenotyping information to classify borderline cases as either Hodgkin lymphoma (HL) or ALCL. In 2008, systemic ALCL was officially separated into ALK+ ALCL which was recognized as a distinct entity, and ALK-negative (ALK-) ALCL which was still considered a provisional entity due to a lack of defining characteristics \(^5\). However, recent genetic advances have secured ALK- ALCL as a distinct entity in the upcoming revision of the WHO classification (see below) (E. Jaffe, personal communication). Herein, this review will focus on advances in the understanding of the biology and pathogenesis of adult systemic ALCL as well as provide a critical review of studies evaluating prognosis and management.
Epidemiology and clinical features of ALK+ and ALK- ALCL

ALCL comprises approximately 3% of all adult NHLs and 10-20% of childhood lymphomas. The overall frequency of ALK+ ALCL depends on the population studied as it is more commonly seen in children and young adults with a median age of 30 years, whereas ALK- ALCL occurs in older adults (median age of 55 years). For both types, the majority of patients are male and present with advanced stage III-IV disease, often with B symptoms. Extranodal sites frequently occur and include skin, soft tissue, bone, lung, and liver, as well as bone marrow. Central nervous system involvement can occur at diagnosis or at relapse. Of note, systemic ALCL should be distinguished from primary cutaneous ALCL (PCALCL), an indolent entity with disease-specific survival rates of 85-95%. Thus, all patients with PCALCL should have standard staging procedures to rule out systemic involvement.

Pathology

Morphologically, ALCL demonstrates a variable proportion of ‘hallmark’ cells characterized by eccentrically placed horseshoe- or kidney-shaped nuclei with an intermediate nuclear:cytoplasmic ratio and eosinophilic peri-nuclear clearing (Figure 1). In most cases of ALK+ and ALK- ALCL, the nodal or tissue architecture is effaced by solid cohesive sheets of neoplastic cells, although a sinusoidal pattern of infiltration is frequently seen in lymph nodes.

There are five morphological patterns of ALK+ ALCL: common, lymphohistiocytic, small cell, Hodgkin-like and composite. Most cases demonstrate the common type with sheets of large lymphoid cells featuring hallmark cells. The lymphohistiocytic pattern (10%) consists of reactive histiocytes which may mask the anaplastic tumor cells. The small cell pattern (5-10%) consists of small to medium-sized cells which can be misdiagnosed as peripheral T cell lymphoma, not otherwise specified (PTCL-NOS). Both the lymphohistiocytic and small
cell variants are more common in children and can often be misdiagnosed as benign infiltrates. The Hodgkin-like pattern (3%) may resemble nodular-sclerosis classical HL (CHL) with tumor nodules surrounded by fibrous bands. The tumor cells in ALK- ALCL demonstrate similar heterogeneity; however, a small cell pattern is not recognized.

ALCL was originally distinguished by the discovery of CD30 expression in lymphomas with an anaplastic morphology ¹ (Figure 1). This was followed by the discovery of a balanced $t(2;5)(p23;q25)$ chromosomal translocation in a subset of cases involving the ALK gene on chromosome 2p23 and NPM gene on chromosome 5q35 forming the novel chimeric protein NPM-ALK. The $t(2;5)$ occurs in approximately 75%-85% of all ALK+ ALCL and in the remaining cases, a variant rearrangement exists involving 2p23 and a multitude of partner genes¹⁶. These variant translocation partners can be recognized as a result of different ALK protein staining patterns Subsequent studies have shown that the NPM-ALK chimeric protein has constitutive activation of the ALK tyrosine kinase¹⁷.

The detection of ALK protein correlates nearly 100% with the presence of a chromosomal rearrangement involving ALK, thus IHC has largely replaced molecular testing in ALCL. It is recommended that monoclonal antibodies (mouse or rabbit) are used instead of polyclonal antibodies which may lead to false positives ¹⁶. As ALK+ and ALK- ALCL are morphologically indistinguishable, ALK IHC is critical in all cases. ALK expression is absent from all postnatal normal human tissues except for rare cells in the brain¹⁸,¹⁹. ALK staining is cytoplasmic and nuclear in cases of the classic $t(2;5)/NPM-ALK$ translocation but may be membranous or diffuse/granular cytoplasmic in cases with a variant translocation²⁰,²¹. Although, IHC for ALK is highly sensitive it is not specific for ALK+ ALCL. Rare cases of ALK+ lung cancers and other solid tumors have been described ²², in addition to ALK+ diffuse large B-cell lymphoma (DLBCL)²³, the latter characterized in most cases by a $t(2;17)(p23;q23)$, which encodes for a Clathrin-ALK fusion protein ²⁴. These cases are easily
distinguished from ALCL based on morphologic and immunophenotypic criteria. Importantly, ALK+ DLBCL do not express CD30.

The aberrant loss of pan T-cell antigens is characteristic of ALCL and 20% have a “null” immunophenotype but nearly all have a clonal T cell receptor (TCR) gene rearrangement. ALK+ and ALK- ALCL can differ immunophenotypically (Table 2). CD3 is negative in most ALK+ ALCL whereas greater proportion of ALK- ALCL tumors are CD3+ as well as CD2. The majority of ALK+ cases are positive for epithelial membrane antigen (EMA) but it is less common in ALK- ALCL (Table 2, Figure 1). Most cases express cytotoxic markers but are CD8-

**Differential diagnosis of ALK- ALCL**

**ALK- ALCL vs CD30+ PTCL NOS**

The pathological distinction between ALK- ALCL and CD30+ PTCL-NOS can be difficult (Figures 1 and 2). In general, PTCL NOS is more likely to be CD2+ and CD3+ but EMA- and usually lacks cytotoxic proteins (Table 2). The distinction is more challenging in PTCL NOS cases with high expression of CD30. Recently, a three gene model (TNFRSF8, BATF3 and TMOD1) was validated using RT-PCR in formalin-fixed paraffin-embedded tissue that was able distinguish ALK- ALCL from PTCL-NOS, including CD30+ PTCL-NOS, but is not yet routinely applied in clinical practice. Interestingly, one study suggested some biological overlap between CD30+ PTCL-NOS and ALK- ALCL where both entities had low expression TCR signaling and T-cell differentiation proteins.

**ALK- ALCL versus Hodgkin’s lymphoma**

HL tumors rich in HRS cells with lymphocyte depletion and a less prominent mixed inflammatory infiltrate may be misdiagnosed as ALK- ALCL. CD30 and PAX-5 are useful
in this instance as HL is usually weakly positive for PAX-5, whereas ALK- ALCL is negative and CD30 is typically weaker and more heterogeneous in HL.

**Molecular genetics and gene expression profiling in ALK+ and ALK- ALCL**

Comparative genomic hybridization demonstrates that ALK+ and ALK- ALCL harbor different genetic aberrations (Table 3). Overall, secondary genetic imbalances occur in 58% of ALK+ and 65% of ALK- ALCL. Gains of 7, 17p, and 17q and losses of chromosome 4, 11q and 13q have been observed in ALK+ ALCL. Conversely, ALK- ALCL harbors gains of 1q and 6p21.31 (Table 3).

Gene expression profiling studies support a shared origin of ALCL, but distinct signatures can also be seen that have been used to aid molecular classification. One study demonstrated that ALK+ and ALK- ALCLs share a cluster of transcripts, indicating that ALK-independent genes may be part of a common signature that distinguishes them from other PTCLs. Recently, it has also been shown that both subtypes of ALCL are dependent on IRF and MYC signaling. Iqbal and colleagues developed an ALCL molecular signature that included genes previously identified to have high expression in ALCL, including CD30 (TNFTFSF8), BATF3 and TMOD. Further, there was low expression of genes associated with TCR signaling as previously described. A gene signature also distinguished ALK+ from ALK- ALCL and had high concordance with pathological diagnoses. ALK+ ALCL was enriched for HIF1-α target genes as well as IL10 and H-ras/K-ras-induced genes, whereas ALK- ALCL was enriched for PI3K pathway regulated genes and all cases expressed TNFRSF8, GATA3 and TMOD1 in keeping with the described ‘three gene model’. In comparison to PTCL-NOS, ALK- ALCL was enriched for MYC and IRF4 target gene signatures as well proliferation and MTOR gene signatures. A separate genome wide profiling study also found that PRDM1/BLIMP1 is commonly inactivated in ALK- ALCL and may be associated with a more aggressive course.
Next generation sequencing recently identified two recurrent rearrangements in ALK- ALCL\(^{39,40}\) (Table 3). One involves the \(P53\) homolog, \(P63\) on 3q28 and the other involves the \(DUSP22\)-\(IRF4\) locus on 6p25.3 (\(DUSP22\) rearrangement). The presence of a \(DUSP22\) rearrangement was associated with reduced protein expression\(^{39,40}\). An analysis of 73 patients with ALK- ALCL identified \(DUSP22\) and \(P63\) rearrangements in 30% and 8% of ALK- ALCL cases, respectively, but were absent in ALK+ ALCL\(^{41}\). These rearrangements were mutually exclusive and appear to have important prognostic relevance (see below).

Collectively, these key advances defining the unique features of ALK-ALCL, have now secured it as a distinct entity in the upcoming revised WHO classification of lymphomas (E. Jaffe, personal communication).

**Prognostic factors in ALCL**

The International prognostic Index (IPI) is a clinical risk stratification model developed in aggressive lymphomas, primarily DLBCL\(^{42}\). The IPI is also effective in stratifying many of the PTCL subtypes, including ALCL. In the International peripheral T-cell lymphoma project (ITCL) the 5 year OS by low (0,1 risk factors), low-intermediate (2 risk factors), high-intermediate (3 risk factors) and high risk (4,5 risk factors) IPI in ALK+ and ALK- ALCL were, 90% vs 74%, 68% vs 62%, 23% vs 31% and 33% vs 13%, respectively\(^{8}\) (Figure 3). These data highlight that in addition to ALK status, clinical factors are important in estimating prognosis. Numerous other studies have similarly reported the usefulness of the IPI in risk stratifying patients with ALCL\(^{11,27,43-46}\). It is notable that overall, these studies demonstrate that patients with ALK+ ALCL with 3 or more IPI risk factors have a 5 year PFS of 20-30%, similar to other PTCLs. Conversely, patients with low risk ALK- ALCL can have a favorable prognosis. This is underscored in a study by the GELA group, which demonstrated that age is a prominent factor driving the prognostic difference between ALK+ and ALK- ALCL. In a survival comparison limited to patients younger than 40 years, outcomes were similar in ALK+ and ALK- ALCL\(^{11}\), which was also observed in another study\(^{8}\). In addition to age < 40 years, the GELA study also established that a low beta-2-microglobulin (B2M) (< 3mg/dL)
was a favorable prognostic factor (P<0.001) (Figure 4). The model was particularly effective in defining a very favorable low-risk group of patients with ALK- ALCL who had an 8 year OS of 100% (8 year PFS ~ 85%).

As described, two new recurrent chromosomal rearrangements involving DUSP22 and P63 were recently identified in ALK- ALCL, highlighting additional genetic heterogeneity that also appears to be clinically relevant. For the majority of cases of ALK- ALCL that lack either rearrangement (aka ‘triple negative’), the 5 year OS rate was 42%, which is similar to estimates reported in many series lacking the genetic information (Figure 5). However, cases of ALK- ALCL that harbor a DUSP22 rearrangement had a five year OS rate that was indistinguishable from a control group of ALK+ ALCL (5 year OS 90% for DUSP22+ ALK- ALCL vs 85% for ALK+ ALCL), which all lacked DUSP22 translocations. Conversely, TP63-rearranged cases had an extremely poor prognosis with a 5 year OS of only 17%. Adjusting for the IPI in multivariate analysis and using ALK+ as the reference, both TP63 and triple-negative cases had an inferior prognosis, but cases of DUSP22 ALK- ALCL had a similar favorable outcome, including those cases that did not undergo transplant (Figure 5).

The genetic heterogeneity in ALK- ALCL may also explain discordant study results comparing the prognosis of ALK- ALCL and CD30+ PTCL-NOS. Some studies have reported that CD30+ PTCL-NOS is associated with an inferior outcome compared to ALK- ALCL; however, others have demonstrated a non-significant improvement in outcome. The discrepancy may reflect the presence of unadjusted clinical or genetic factors.

Although further validation of the prognostic importance of DUSP22 and TP63 rearrangements is warranted, these data support that important genetic heterogeneity exists.
within ALK- ALCL which impacts prognosis and is relevant in comparing outcomes between studies and evaluating the impact of treatment regimens, including the role of transplant.

Management of Systemic ALCL

Due to disease rarity, there are currently no randomized controlled trials (RCT) to guide treatment decisions in ALCL and as a result, the optimal therapy remains unknown. The majority of evidence describing outcomes of adult patients with systemic ALCL and the impact of various treatment regimens come from retrospective studies or subgroup analyses of completed prospective studies in aggressive lymphomas or PTCLs.

Primary therapy of systemic ALK+ and ALK- ALCL

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the standard chemotherapy for aggressive lymphomas, including ALCL 47. For ALK+ ALCL, outcomes with CHOP or CHOP-like regimens are generally favorable (Table 1), with the exception being those patients with multiple IPI risk factors. Considering patients of all ages, the outcome of ALK- ALCL is consistently worse using CHOP-like regimens than in ALK+ ALCL, but it is also much more variable across studies with 5 year OS rates from 15%-62% which likely reflects disease and clinical heterogeneity (Table 1). The GELA group (Groupe d’Etude des Lymphomes de l’Adulte) reviewed 138 patients with ALCL (64 ALK+, 74 ALK-) prospectively treated across multiple trials from 1997 to 2010, including three unpublished trials11. The most commonly received regimen was ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) followed by sequential consolidation with methotrexate, ifosfamide, etoposide and cytarabine and, in some cases, high dose chemotherapy and stem cell transplant (HDC/ASCT) 11. Overall, the outcome of ALK+ ALCL was superior to ALK- ALCL (Table 1), however, it was similar in patients < 40 years old with an 8 year OS rate of over 80% in both groups. Although this study investigated a regimen that is more intensive than CHOP, it supports that young low risk ALK- ALCL patients have outcomes similar to ALK+ ALCL.
Several studies have evaluated the impact of more dose-intensive or alternate chemotherapy strategies in PTCLs but due to disease rarity, they have largely combined all subtypes in outcome analyses. A US multicentre retrospective analysis evaluated the outcome of PTCLs, including 88 cases of ALCL (ALK+ n=23; ALK- n=43; ALK status unknown n=22) and did not demonstrate improved survival with the dose intensive hyperCVAD regimen but the impact in ALCL was not analyzed 48. Similarly, the MD Anderson Cancer Centre retrospectively evaluated the survival of 135 PTCL patients by type of treatment regimen received, including 40 cases of ALCL (ALK+ n=12; ALK- n=19; unknown n=9) and found no improvement in outcome using dose-intensive chemotherapy but again, all subtypes were combined 49. CHOP was compared to the dose intensive VIP regimen (etoposide, ifosphamide, cisplatin)-ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) in a phase 3 RCT which included 32 patients with ALCL (22 ALK+ and 10 ALK) and showed similar outcomes between the treatment arms50.

It has been suggested that the addition of etoposide may improve outcome in PTCLs, including ALCL. This is largely based on the German Non-Hodgkin Lymphoma Group (DSHNHL) retrospective analysis of 289 cases of PTCL subtype enrolled on completed prospective aggressive lymphoma studies, which included 78 ALK+ and 113 ALK- ALCL patients. For select young good risk patients (< 60 years of age, normal LDH), the addition of etoposide improved the 3 year EFS (70.5% vs 51%, P=0.003). The impact was most evident in ALK+ ALCL (3 year EFS 91% vs 57%) and a similar trend was observed for other nodal PTCLs which included ALK- ALCL, 60.7% vs 48.3% (P=0.057) 43. However, for all comparisons, the OS was not statistically different and the analyses were not adjusted for the IPI. Excluding ALK+ ALCL patients, a Swedish registry study showed use of CHOEP was associated with an improvement in PFS (P=0.008) in multivariate analysis with a trend towards an improved OS (P=0.052) in PTCL patients < 60 years 44. However, there was no improvement of PFS or OS if an upper age limit of 70 was used and efficacy in ALCL was
not reported. The US retrospective study did not find a benefit of etoposide (P=0.80) but patient numbers were small. Further studies are needed evaluating the added benefit of etoposide in the up-front therapy of PTCLs, including ALCL. Of note, a number of studies have also evaluated the addition of another agent to CHOP, including targeted therapies and monoclonal antibodies such as alemtuzumab in an effort to improve outcome in PTCLs. However, a detailed review is outside the scope of this paper.

Following induction chemotherapy with CHOP, patients with ALK-ALCL often receive a consolidative transplant in first remission; however, it remains challenging to know which patients to select for this intensified approach. The Nordic group completed the largest prospective phase 2 trial (NLG-T-01) in 160 patients with PTCL which included 31 cases of ALK-ALCL. The planned treatment schedule was CHOEP (or CHOP14 for patients > 60 years) for 6 cycles followed by BEAM/ASCT in responding patients. The transplant rate was 70% and with a median follow-up of almost 4 years, the 5 year PFS was 44% and 5 year OS was 51% for all patients but was superior in ALK-ALCL compared to non-anaplastic subtypes with a 5 year PFS and OS of 61% (P=0.04) and 70% (P=0.03), respectively. ALK-ALCL remained a favorable prognostic factor in multivariate analysis. It would be of interest to determine the frequency of DUSP22 rearrangements in this subgroup. In contrast to these results, the DSHNHL retrospectively evaluated the outcome of 33 patients with T-cell NHL, primarily PTCLs (n=32/33) including 39% with ALK-ALCL, who were treated with intensified MegaCHOEP and SCT on phase 2 or 3 trials and reported a disappointing 3 year EFS of only 26%. Further, in the U.S. retrospective study, a multivariate analysis was performed controlling for CR to initial therapy failed to demonstrate a benefit of consolidative ASCT; however, ALCL patients were not evaluated separately (Abramson, 2014 #7086.

There may still be a role for consolidative ASCT in the primary treatment of ALK-ALCL, but more information is needed to select high risk patients who may benefit, ideally incorporating clinical and genetic factors, particularly in the landscape of new highly effective therapies
(see below). Conversely, ALK+ ALCL patients with a high IPI score have poor outcomes and alternate strategies should be considered.

**Limited stage ALCL**

The majority of patients with ALCL present with advanced stage disease; however, a subset present with limited stage. The largest study evaluated the outcome of 46 patients with early stage systemic ALCL (stage 1 n=20, stage 2 n=26) and demonstrated favorable outcomes with primarily short course CHOP-based chemotherapy with planned radiotherapy (RT). In 39 patients with ALK-status information available, 54% were ALK- and 46% were ALK+. Overall, the 5 year PFS and OS were 64% and 86%, respectively (Zhang, 2013 #7958). There was a trend towards improved outcomes in patients with stage 1 compared to stage 2 disease (5 year PFS 78% vs 54%, P=0.078; 5 year OS 95% vs 79.5%, P=0.075). In contrast, a more recent study evaluated the outcome of 75 patients with PTCL, including 35 patients with ALCL (40% ALK+, 40% ALK-, 6% unknown) and failed to show an improved outcome with radiotherapy in an analysis restricted to those with responding disease. However, the patient numbers are small and information specifically for ALCL patients is not provided. None of these studies establish the optimal number of cycles of chemotherapy, however, following a similar approach for limited stage DLBCL is appropriate.

**Breast implant-associated ALCL**

Breast implant-associated ALCL (BIA ALCL) was first described in 1997 and after multiple cases were reported, the FDA issued a statement noting the increased risk of ALCL in women who have had breast implants. A long-term follow-up of 60 published cases of BIA ALK- ALCL was recently reported. The tumor was confined to the capsule in 42 patients, while in 18 patients there was a tumor mass. Capsulectomy and implant removal were
performed in 93% of cases. Therapeutic data were available in 55 patients and 39 (71%) received chemotherapy (primarily CHOP (like) +/- RT), four had RT alone and 12 (22%) were observed. With a median follow-up of 2 years (range 0.1 to 14 years), the 5 year OS in patients with a breast mass was inferior to those without a mass (100% vs 75%, P=0.0308).

Most patients with BIA ALCL present with an isolated effusion and removal of the implant and capsule results in excellent outcomes. Conversely, patients presenting with a breast mass may have a more aggressive course that would justify chemotherapy in addition to implant removal; however, the precise role for chemotherapy is uncertain.

**Relapsed or refractory ALCL**

**Role of transplant**

HDC and ASCT represents the standard of care for relapsed ALCL, if chemosensitivity is demonstrated. The phase 3 PARMA RCT established the superiority of HDC/ASCT over salvage therapy alone and subsequent analyses of prognostic factors showed no difference in OS by T vs B-cell phenotype; however, only 35 had T-NHL and ALCL was not yet recognized. Although retrospective in nature, there have been numerous other studies evaluating the efficacy of ASCT in relapsed PTCLs reporting 3 and 5 year EFS rates ranging from 25-75% with some studies demonstrating salvage rates comparable to those seen in DLBCL, especially for ALCL.

The good salvage rates of relapsed/refractory ALCL who receive HDC/ASCT were also observed in a CIBMTR (Centre for International Blood and Bone Marrow Transplant Research) study which evaluated 241 patients with PTCL (ALCL n=112, ALK + n=14, ALK- n=8, ALK status unknown n=90) who had undergone either an ASCT or allogeneic transplant (alloSCT). In total, 61 patients with ALCL were included that received an HDC/ASCT, 39 of which were beyond CR1. For the latter group, the 3 year PFS and OS were 50% and 65%, respectively. In stark contrast to these studies, one report evaluating
the impact of ASCT in 16 cases relapsed/refractory ALK- ALCL demonstrated dismal outcomes with a median PFS of only 12 weeks\textsuperscript{64}. The discrepancy is unclear but the latter study could have included cases of CD30+ PTCL-NOS or were enriched for early relapses.

There is more limited information on the role of alloSCT in relapsed/refractory ALCL and many studies pool all PTCL subtypes. Taken together, myeloablative alloSCT in this setting results in approximately 30% remaining alive and disease-free at 3 to 5 years with a full myeloablative transplant, however, treatment related mortality (TRM) rates are also ~ 30% and very few studies have reported results for ALCL.\textsuperscript{58,63,65,66} The CIBMTR study demonstrated that ASCT was associated with a better PFS (55% vs 35%, P=0.0319) and OS (68% vs 41%, P=0.0034) compared to alloSCT if all ALCL patients were considered\textsuperscript{63}. Restricting the analysis to patients beyond CR1 showed a superior 3 year OS for ASCT (62% vs 33%, P=0.0088) but no difference in PFS. A separate retrospective analysis of 77 patients with PTCL who received an alloSCT demonstrated a 5 year EFS and OS of 48\% and 55\%, respectively, for patients with ALCL (n=27) but this study included patients who had received only one line of chemotherapy prior to alloSCT\textsuperscript{65}. A subset PTCL patients with either stable or progressive disease (PD) at the time of transplant benefited from alloSCT with a 5 year OS of 29\% suggesting there may be a role in refractory ALCL\textsuperscript{65}. With the high TRM of myeloablative alloSCT, several studies have explored reduced intensity conditioning (RIC) in relapsed/refractory PTCL. A phase II trial evaluating RIC and allogeneic SCT in 17 relapsed/refractory PTCL patients (ALK-ALCL n=4), demonstrated a 3-year PFS of 64\% with a TRM of 6\% suggesting it may have a role in select circumstances\textsuperscript{67}.

In relapsed/refractory ALCL patients ineligible for transplant or who fail second-line salvage therapy, the outcome has historically been poor. The BCCA evaluated the survival of PTCL patients following first relapse or progression who had received chemotherapy and the median OS and PFS were only 3.0 months and 1.8 months, respectively for patients with ALCL, supporting a role for novel therapies and clinical trials for this poor risk group.
**Novel therapies in Systemic ALCL**

There have been an unprecedented number of trials evaluating novel therapies in relapsed/refractory PTCLs. Most have included all PTCL subtypes but there have been a minority specifically in systemic ALCL. The antibody drug conjugate (ADC) brentuximab vedotin (SGN-35) is the most widely studied agent in ALCL. It is composed of an anti-CD30 antibody conjugated by a protease-cleavable dipeptide linker to the anti-microtubule agent monomethyl auristatin E (MMAE). Following binding of the ADC to CD30, the complex is internalized and MMAE is released by proteolytic cleavage to exert its cytotoxic effect. A phase 2 study in relapsed/refractory ALCL (42 ALK-, 16 ALK+)\(^{68}\) demonstrated an ORR of 86% and CR of 57%. The estimated median PFS was 13.3 months and for those who achieved a CR it was 14.6 months. The most notable side effect was peripheral sensory neuropathy, occurring in 41% with 12% considered grade 3. Based on these data, brentuximab vedotin was FDA approved in 2012 for relapsed/refractory ALCL following one line of therapy. A subsequent analysis of patients followed for almost 3 years demonstrated a median duration of response for CR patients of 26.3 months and 16/34 (47%) remained in remission\(^{69}\). Further, the median PFS had not yet been reached for those who received a SCT (8 ASCT, 9 alloSCT) and was 18.4 months for those who did not. Interestingly, the efficacy of brentuximab vedotin is much less striking in CD30+ PTCL-NOS with an ORR of 33% (CR 17%) and a median duration of response of 7.6 months but the overall median PFS was only 1.6 months highlighting that these are different diseases\(^{70}\).

Brentuximab vedotin was recently evaluated in the front-line setting in CD30+ PTCLs, including ALCL either as a sequential treatment for 2 cycles followed by CHOP or in combination with CHP (with vincristine removed due to overlapping neurotoxicity)\(^{71}\). Responders could receive 8-10 additional cycles. The majority of patients had ALCL (n=32, ALK+ n=6, ALK- n=26). Considering all CD30+ PTCL patients (n=39), the ORR was 85% (CR 62%) for the sequential therapy and 100% (CR 88%) for the combination treatment and no patients received a consolidative ASCT. With a median follow-up of 21 months, 9/19
patients with ALCL had PD or death. The median PFS and OS have not been reached. These data form the basis of the ongoing ECHELON-2 phase 3 RCT comparing standard CHOP to CHP and brentuximab vedotin in newly diagnosed CD30+ PTCLs (NCT01777152).

Crizotinib is an oral ALK inhibitor that has been explored in ALK+ ALCL. A phase I pediatric dose-escalation study included nine patients with relapsed/refractory ALK+ ALCL, seven of whom responded. Although data is more limited in adult patients, a recent case series described 9 cases of adults (19-55 years) with relapsed/refractory ALCL, all of which had complete remissions following treatment with crizotinib, some of which are quite durable at over 40 months.

There have been a number of additional studies evaluating novel treatments more broadly in all PTCLs. The first FDA approved drug in relapsed/refractory PTCLs was the anti-folate pralatrexate based on a phase 2 study in relapsed/refractory PTCL which included 17 patients with ALCL (ALK- n=11; ALK+ n=4; unknown n=2). The ORR was 29% (CR 10%) with a median PFS of 3.5 months and efficacy was similar in ALCL patients (ORR 35%) for ALCL patients. Romidepsin was evaluated in a phase 2 study of 130 patients with relapsed/refractory PTCLs and demonstrated an ORR of 25% for all PTCLs with a median PFS of 4 months, leading to FDA approval in this setting. The efficacy was comparable in ALK- ALCL (n=21, ORR 24%). Similarly, a phase 2 study has been completed evaluating the efficacy of belinostat in 129 patients with relapsed/refractory PTCL, including 15 patients with ALCL. The ORR was 26% with a median PFS of 1.6 months but the results by PTCL subtype have not yet been reported.

Preliminary studies have explored the efficacy of other agents in relapsed/refractory PTCL including the aurora A kinase inhibitor alisertib (ORR 24%) and the PI3K inhibitor Duvelisib.
The PD1 inhibitor Nivolumab is under evaluation in NHLs, including PTCLs\textsuperscript{79}. A number of the above therapies are also being explored in combination due to complementary anti-tumor effects.

**Future directions**

Recent insights into the genetic heterogeneity of ALK- ALCL will aid risk stratification and will provide critical prognostic information when comparing treatment strategies. The success of brentuximab vedotin in relapsed/refractory ALCL compares favorably to historically poor outcomes in this setting and results from the up-front phase 3 study are eagerly awaited. Future research exploring genetic factors driving disease pathogenesis and biomarkers of treatment response will be key in the development of a more personalized approach to treatment of patients with systemic ALCL.

**Author contribution**

GH and KJS wrote and approved the manuscript.

**Conflict of Interest**

GH has no disclosures. KJS has received honoraria from Seattle Genetics, Celgene and Bristol Meyers Squibb.

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Table 1. Studies comparing survival outcomes between ALK+ and ALK- systemic anaplastic large cell lymphoma.

* Ages are mean

** median follow-up for the entire cohort in this study (n=320)

‡ Estimated from Kaplan-Meier curves

<table>
<thead>
<tr>
<th>Author</th>
<th>Median follow-up (yrs)</th>
<th>Median age (yrs)</th>
<th>Progression free survival (P value)</th>
<th>Overall survival (P value)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gascoyne</td>
<td>4.2</td>
<td>30</td>
<td>61</td>
<td>5yr 82%</td>
<td>5yr 79% 5yr 46%</td>
</tr>
<tr>
<td>Falini</td>
<td>2.1</td>
<td>22*</td>
<td>43*</td>
<td>10yr 82%</td>
<td>10yr 28%</td>
</tr>
<tr>
<td>Suzuki</td>
<td>NR</td>
<td>21</td>
<td>57</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ten Berge</td>
<td>2.1</td>
<td>23</td>
<td>54</td>
<td>5yr 85%‡</td>
<td>5yr 90% 5yr 40%</td>
</tr>
<tr>
<td>Savage</td>
<td>3.5</td>
<td>34</td>
<td>58</td>
<td>5yr 60%</td>
<td>5yr 36%</td>
</tr>
<tr>
<td>Schmitz</td>
<td>3.7**</td>
<td>37</td>
<td>50</td>
<td>3yr 75%</td>
<td>3yr 45%</td>
</tr>
<tr>
<td>Sibon</td>
<td>8.0</td>
<td>31</td>
<td>56</td>
<td>5yr 76% 8yr 72%</td>
<td>5yr 48% 8yr 39%</td>
</tr>
<tr>
<td>Parilla Castellar</td>
<td>6.5</td>
<td>27</td>
<td>58</td>
<td>NR</td>
<td>NR</td>
</tr>
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</table>

* = n=ALK + n=ALK -

** = median follow-up for the entire cohort in this study (n=320)

‡ = Estimated from Kaplan-Meier curves
NR – not reported

<table>
<thead>
<tr>
<th>Immunophenotype</th>
<th>Cut-off (%)</th>
<th>ALK + ALCL (%)</th>
<th>ALK – ALCL (%)</th>
<th>PTCL NOS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>&gt;20</td>
<td>100</td>
<td>100</td>
<td>23</td>
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<tr>
<td>ALK</td>
<td>Any</td>
<td>100</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CD3</td>
<td>&gt;20</td>
<td>11.5</td>
<td>45</td>
<td>95</td>
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<tr>
<td>CD4</td>
<td>&gt;20</td>
<td>46</td>
<td>68</td>
<td>57</td>
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<tr>
<td>CD8</td>
<td>&gt;20</td>
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<td>16</td>
<td>19</td>
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<tr>
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<td>&gt;20</td>
<td>22</td>
<td>58</td>
<td>92</td>
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<tr>
<td>CD5</td>
<td>&gt;20</td>
<td>36</td>
<td>19</td>
<td>67</td>
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<tr>
<td>TIA1</td>
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<td>CD45</td>
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<td>48</td>
<td>59</td>
<td>79</td>
</tr>
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</table>

Table 2. Immunophenotypic features of ALK+ ALCL, ALK- ALCL and PTCL-NOS. Reproduced with permission from Hsi et al. AJSP 2014; 38(6): 768-775

<table>
<thead>
<tr>
<th>Cytogenetic abnormalities</th>
<th>ALK+ ALCL</th>
<th>ALK- ALCL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent translocations involving ALK t(2;5)(p23;25) ALK:NPM1 85%</td>
<td>Recurrent translocations involving DUSP22:IRF4 (6p25.3) 30%</td>
</tr>
<tr>
<td></td>
<td>t(2;v) 15%*</td>
<td>Recurrent translocations involving TP63 (3q28) 8%</td>
</tr>
<tr>
<td></td>
<td>Gains: 7, 17p, 17q</td>
<td>Gains: 1q, 6p, 8q, 12q</td>
</tr>
<tr>
<td></td>
<td>Deletions: 4, 11q, 13q</td>
<td>Deletions: 6q, 4q, 13q</td>
</tr>
</tbody>
</table>

Table 3 Cytogenetic and molecular features of ALK+ ALCL versus ALK- ALCL v=variant partner

[^31]:[^39]:[^41]
References


55. Administration: UFaD. FDA medical device communication: Reports of anaplastic large cell lymphoma (ALCL) in women with breast implants. 2013.


Figure 1. ALK-positive (ALK+ panel A) versus ALK-negative (ALK- panel B) ALCL. Hematoxylin and eosin (H&E) staining demonstrating hallmark cells in both cases. Tumor cells demonstrate positive ALK, CD30 and EMA staining in ALK+ ALCL. Tumor cells demonstrate positive CD30 but negative ALK and EMA staining in ALK- ALCL.
Figure 2. CD30+ PTCL NOS. Hematoxylin and eosin (H&E) staining demonstrating predominantly small to medium sized lymphocytes with pleomorphism and the absence of hallmark cells. Only scattered tumor cells demonstrate CD30 positivity compared to ALCL.
Figure 3. Overall survival of ALK+ (A) and (B) ALK- ALCL by the International Prognostic Index (IPI). Reprinted with permission. © (2008). American Society of Hematology All rights reserved. Savage, KJ et al. Blood 2008;124:1473-1480.
Figure 4. Overall survival in ALCL patients according to age (<40 or ≥40) and B2-microglobulin (normal or abnormal). Adapted and reprinted with permission. © (2012) American Society of Clinical Oncology. All rights reserved. Sibon, D. et al. J Clin Oncol Vol. 30(32), 2012: 3939-3946.
Figure 5. Overall survival stratified by ALK, DUSP22, TP63 translocations and triple negative status in patients with ALCL who did not undergo transplant. Adapted and reprinted with permission. © (2014). American Society of Hematology. All rights reserved. P. Castellar et al. Blood 2014 Vol 111:5496-5504.
The biology and management of systemic anaplastic large cell lymphoma

Greg Hapgood and Kerry J. Savage

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