Anaplastic Large-Cell Lymphoma, T-/Null-Cell Type

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Epidemiology and Clinical Presentation

Anaplastic large-cell lymphoma, T-/null-cell type (ALCL), is a rare disease that has only been well characterized for two decades. Despite this, the biology of ALCL is better understood than that of many other more common variants of lymphoma. This review focuses on the pathophysiology, clinical presentation, and therapy of ALCL, including stem cell transplantation. In particular, the text emphasizes how novel prognostic features and the evolving understanding of the biology of this disease will influence treatment selection and drug development.

Epidemiology and Clinical Presentation

Anaplastic large-cell lymphoma, T-/null-cell type (ALCL), is a rare disease, accounting for <5% of all cases of non-Hodgkin’s lymphoma (NHL) [1]. ALCL was first described as a clinical entity in 1985 based upon its unique characteristic of cohesive proliferation of large pleomorphic cells expressing CD 30 (Ki-1) [2]. ALCL has a peak incidence in childhood and accounts for approximately 40% of NHL cases diagnosed in pediatric populations [3]. There appears to be a male predominance, particularly in anaplastic lymphoma kinase (ALK) + cases, in which the male/female ratio is approximately 3:1. In one series, the male predominance of ALK + cases was especially striking in patients under the age of 30, with a male/female ratio of 6.5:1 [4].

There are no clear risk factors for developing ALCL. Some reports have suggested that Epstein-Barr virus (EBV) is important in the pathogenesis of ALCL. However, a recent series of 64 ALCL cases revealed no EBV-encoded RNA (EBER) or immunohistochemistry evidence for EBV-latent membrane protein type 1 [5]. The authors concluded that previous reports of EBV in Western patients with ALCL were probably a result of the inclusion of tumors no longer considered to be ALCL, such as CD30+ anaplastic tumors of B-cell origin. EBV, however, may be important in the pathogenesis of ALCL occurring in Asia and in immune-compromised hosts [6, 7].

ALCL occurs as two distinct clinical entities, a cutaneous and a systemic variant [8]. Cutaneous ALCL falls under...
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the new World Health Organization/European Organization for Research and Treatment of Cancer (WHO-EORTC) category of CD30+ lymphoproliferative disorders of the skin that represents a spectrum of disease ranging from the benign lymphomatoid papulosis (LP) to the malignant primary cutaneous ALCL (PCALCL) [9]. Both PCALCL and LP generally occur in older adults and are rare in children [10]. LP resembles lymphoma and is essentially indistinguishable from PCALCL histologically [11]. Thus the distinction between the two disorders is largely clinical.

Patients with LP tend to have more diffuse lesions, whereas PCALCL is more likely to be solitary [12]. LP lesions are generally <3 cm, whereas PCALCL lesions are often larger. Both distinctions, however, are unreliable. Both processes can also spontaneously remit [13]. If a cutaneous process resembling ALCL progresses consistently over time, it is generally considered PCALCL, whereas if it spontaneously remits or does not progress substantially it is considered LP.

Although a malignant condition, PCALCL is indolent, with disease-specific survival rates at 5 and 10 years of 85% or better [14]. Approximately 10% of patients develop systemic ALCL, usually in lymph nodes draining areas of skin involvement [9]. The prognosis of patients with secondary spread to lymph nodes or with multifocal lesions appears to be no worse than that of patients with solitary lesions [15].

LP also has an excellent prognosis. In a study of 118 LP patients, only five (4%) patients developed a systemic lymphoma, and only two patients died at a median follow-up of 77 months. The overall survival (OS) rate in that study was 92% at 5 and 10 years [14]. Other studies have contradicted this low rate of evolution to lymphoma. One study, for instance, found that 25% of patients with LP developed PCALCL, systemic ALCL, other T-cell lymphomas, or Hodgkin’s disease (HD) [16]. That study was small, however, and selection bias may have accounted for the higher rate of lymphoma in that series.

PCALCL can be confused for systemic ALCL, which often involves the skin. Thus all patients with PCALCL or LP should have complete staging with computed tomography scans, bone marrow biopsy, and a complete blood count to rule out systemic involvement. One useful distinction is the fact that PCALCL rarely, and LP never, has t(2;5) or variant translocations, and therefore generally does not express ALK, whereas systemic ALCL often does [17]. Thus a patient with cutaneous ALCL lesions that are ALK+ should be considered to have systemic disease until proven otherwise. PCALCL often expresses cutaneous lymphocyte antigen (CLA) but does not express epithelial membrane antigen (EMA), whereas the converse is generally true in systemic ALCL [18]. Initial studies suggested that clusterin was differentially expressed in systemic and cutaneous ALCL (positive in the former, negative in the latter), though follow-up studies have suggested that this may not be the case [19, 20].

In contrast to PCALCL, systemic ALCL is generally very aggressive. The majority of patients present with stage III or IV disease and have systemic symptoms [21]. Extramedullary disease occurs in 40%–60% of patients, with skin, bone, soft tissue, and lung being common sites of involvement [4, 22].

Pathology

Morphologically, the systemic and cutaneous variants of ALCL both consist of large blastic cells with round or pleomorphic nuclei (Fig. 1)[23]. The “hallmark” or classic ALCL cell contains an eccentric nucleus that is generally horseshoe shaped or reniform with prominent nucleoli (Fig. 2). The cells have abundant cytoplasm and can resemble histiocytes [24]. A prominent, eosinophilic golgi region is often present [25]. ALCL grows in a cohesive pattern and has a tendency to involve the lymph node sinuses or paracortex [26]. ALCL can contain a large number of Reed-Sternberg-like cells, often admixed with small lymphocytes and eosinophils, creating diagnostic confusion with HD [27].

ALCL has the immunophenotype of mature activated T cells. The cells are generally positive for HLA-DR and CD25. CD30, CD45, and EMA are frequently positive while CD15 is most often negative [28]. Of note, the cutaneous variant of ALCL is typically EMA negative [29]. About 60% of ALCLs express one or more T-cell-associated antigens, such as CD3, CD43, or CD45RO, and cytotoxic granule proteins are often present [30]. A golgi

Figure 1. High- (A) and low- power (B) H and E (hematoxylin and eosin) slides of ALCL showing large blastic cells with eccentric nuclei and abundant cytoplasm.
pattern of reactivity for clusterin is also highly characteristic of ALCL (Fig. 3) [31]. Occasionally, ALCL expresses neither B- nor T-cell antigens and hence the designation ALCL null type [32].

One of the hallmarks of ALCL is a translocation between chromosome 2 and chromosome 5 [t(2;5)(p23;q35)], which occurs in 40%–60% of patients [33]. The translocation generates a fusion gene between nucleophosmin (NPM) and a receptor tyrosine kinase gene, ALK [34]. The NPM-ALK chimeric gene encodes a constitutively activated tyrosine kinase that is oncogenic. NPM-ALK transgenic mice are born with normal lymphoid organs and T cells but very quickly develop malignant lymphoproliferative disorders, including CD30+ T-cell lymphoblastic lymphomas and plasma cell dyscrasias [35]. Interestingly, however, retroviral gene transfer of NPM-ALK in mice generated CD30/Ki-1-negative B-cell lymphoproliferative disorders but not T-cell disorders [36]. The reasons for this remain undefined.

The exact mechanism of NPM-ALK oncogenesis is uncertain but may be partially mediated through the signal transducer and activator of transcription (STAT) pathway. STAT proteins are important in normal cell signaling, and aberrant activation of STAT signaling pathways can inhibit apoptosis [37]. Human ALCLs have tyrosine phosphorylated STAT-3, leading to constitutive activation [38]. Also, forced expression of NPM-ALK in mice results in the constitutive activation of STAT-3 [39]. The pathogenic role of STAT-3 in ALK+ ALCL is supported by a recent observation that STAT-3-negative homozygous immortalized mouse embryonic fibroblasts (MEFs) fail to establish colonies after infection with NPM-ALK retroviruses, whereas STAT-3-positive MEFs do establish rapidly growing colonies [40].

Another important mediator of NPM-ALK oncogenesis may be Janus protein tyrosine kinase 2 (Jak-2), a protein that phosphorylates STATs [41]. Jak-2 was determined to be constitutively tyrosine phosphorylated in ALCL cells and in NPM/ALK-transformed hematopoietic cells, and inhibition of Jak-2 in these cells led to a reduction in NPM/ALK-mediated proliferation and induced apoptosis [42]. Jak-2 inhibitors are currently under development [43].

Variant translocations other than t(2;5) occur in up to 15%–20% of cases [44]. These include t(1;2)(q25;p23), inv(2)(p23;q35), t(2;3), and a CLTCL-ALK fusion transcript typically resulting from a t(2;17) [45–48]. With such translocations, the ALK protein tends to accumulate only in the cytoplasm, though the biologic significance of this phenomenon remains unclear [49]. The prognosis of patients with variant translocations is similar to that of patients with the classic t(2;5) [50]. ALK− ALCL shows recurrent chromosomal gains in 46% of cases, with losses of 6q and 13q both occurring in 23% of cases [51]. The pathogenic and prognostic significance of these chromosomal alterations is unknown.

Figure 2. The “hallmark” cells of ALCL with kidney-shaped nuclei.

Figure 3. Typical immunophenotype of ALCL showing intense expression of CD30 (A), CD43 (B), ALK (C), and clusterin (D) but no expression of the B-cell marker CD20 (E) or T-cell marker CD3 (F).
ALCL can present a diagnostic challenge for the pathologist and clinician. The advances in immunophenotyping and cytogenetic characterization mentioned previously, however, have largely eliminated much of the diagnostic confusion. ALCL can occasionally mimic HD because ALCL often presents in young patients and can have Reed-Sternberg-like cells, prominent sclerosis, and expression of CD30. However, HD is often CD15+ but negative for T-cell markers and ALK, whereas ALCL is generally CD15− and CD30+, and often ALK+ and/or expresses T-cell antigens. Also, t(2;5) and similar translocations do not occur in HD. ALCL can also be confused with diffuse large B-cell lymphoma (DLBCL), particularly mediastinal DLBCL, which has a tendency to present in younger patients and which can be CD30+. However, DLBCL expresses B-cell markers such as CD20 and/or CD79a and does not express T-cell markers and, with very rare exceptions, is not ALK+ and does not have t(2;5) or similar translocations. Cases of DLBCL with a t(2;17) and resulting clathrin-ALK translocation have been reported but are rare. Although these DLBCLs were CD20+ and CD79a+, they tended to have prominent plasmablastic differentiation and were strongly CD138+, making them distinguishable from ALCL [52, 53].

Table 1 outlines the common immunophenotypic features of ALCL and diseases with which ALCL can be confused.

### Risk Stratification

PCALCL has a very good prognosis, as outlined above. Traditionally, the most important prognostic factor in systemic ALCL was the presence or absence of the ALK protein. In a series that included 57 patients with T-cell/null ALCL, the 5-year overall survival (OS) rate was 93% in patients who were ALK+ compared with 37% for those who were ALK− [54]. In that series, a normal lactate dehydrogenase (LDH) and an International Prognostic Index (IPI) score of ≤3 also were independent predictors of better outcome. The importance of the IPI was also demonstrated in an Italian series in which ALK+ patients with a low or low–intermediate IPI score had a 5-year OS rate of 94%, whereas ALK+ patients with a high-intermediate or high IPI score had a 5-year OS rate of only 41% [3]. Univariate analysis from a series of T-cell/null ALCL in Japan also demonstrated better outcome in patients who were ALK+ [55]. However, in multivariate analyses, only high IPI and CD56 positivity were independent predictors of poor outcome. ALK+ patients in that series tended to be younger, with less advanced disease, a normal LDH, and a better performance status, suggesting that ALK status is a useful determinant of outcome but should be interpreted also in the context of the patient’s IPI.

The correlation of CD56 positivity with outcome in the Japanese series is interesting and permitted the investigators to define four risk groups based on IPI and CD56 expression. Patients were stratified into low/low–intermediate IPI and high–intermediate/high IPI with or without CD56 expression. The survival curves are shown in Figure 4.

### Table 1. Immunophenotype of ALCL and diseases with which ALCL can be confused

<table>
<thead>
<tr>
<th>Disease</th>
<th>CD20/CD79a</th>
<th>CD15</th>
<th>CD30</th>
<th>ALK</th>
<th>T-cell markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+/−</td>
<td>−/+</td>
</tr>
<tr>
<td>HD</td>
<td>−</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>DLBCL</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−/−</td>
<td>−</td>
</tr>
</tbody>
</table>

*CD30 can be positive in primary mediastinal DLBCL. Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; DLBCL, diffuse large B-cell lymphoma; HD, classic Hodgkin’s disease.

Figure 4. Overall survival in ALCL stratified by ALK (A) and CD56 (B) expression status. From Suzuki R, Kagami Y, Takeuchi K et al. Prognostic significance of CD56 expression for ALK-positive and ALK-negative anaplastic large-cell lymphoma of T/null cell phenotype. Blood 2000;96:2993-3000. Copyright American Society of Hematology, used with permission.
4. Patients with lower IPIs did better regardless of CD56 expression, but the presence or absence of CD56 did further sub-stratify the IPI groups.

Newer prognostic markers are also becoming apparent. EMA or MUC-1 is frequently expressed in ALCL. MUC-1 is associated with poor outcome in a variety of malignancies. A recent paper found that MUC-1 was also prognostic in ALCL [56]. In ALK+ patients, the 5-year progression free survival (PFS) rate was 52% in those who were MUC-1 positive versus 100% for those who were MUC-1 negative. The OS rate at 5 years was 88.9% versus 100%, respectively, which was not statistically different. In ALK- patients, the 5-year OS rate was 55.6% in those who were MUC-1 positive compared with 93.3% in those who were MUC-1 negative. Both results were highly statistically significant. In multivariate analyses, MUC-1, ALK, age, serum albumin, and B symptoms were all independent prognostic factors.

Survivin is a member of the inhibitor of apoptosis (IAP) family that inhibits cell death via inhibition of apoptotic pathways [57]. Survivin is aberrantly expressed in a variety of cancers, including several types of lymphoma [58]. A recent paper analyzed the prognostic importance of survivin in ALCL [59]. In patients with ALK+ tumors, the 5-year failure free survival (FFS) rate was 34% for patients with survivin-positive tumors versus 100% for patients with survivin-negative tumors. In patients with ALK- tumors, the 5-year FFS rate was 46% for patients with survivin-positive tumors versus 89% for patients with survivin-negative tumors. The 5-year OS rate in ALK+ patients was 56% for survivin-positivetumors versus 100% for survivin-negative tumors. Similarly, in the ALK- group, the 5-year OS rate was 60% for survivin-positive tumors versus 92% for survivin-negative tumors. Survivin expression remained an independent prognostic indicator in multivariate analyses. Table 2 outlines common adverse prognostic features of ALCL.

In most settings, the IPI, ALK status, and CD56 status remain the most readily available and best validated prognostic factors in ALCL. Other factors, such as MUC-1 expression and survivin expression are interesting and potentially useful factors for risk stratification but may not be as readily available in clinical practice. Other potentially adverse features, including Bcl-2 overexpression and elevated serum-soluble interleukin-2 (IL-2) receptor levels, require further validation [60, 61]. At the moment, the impact of all of these factors in selecting the optimal therapy for ALCL remains unknown.

**TREATMENT**

The therapy of ALCL differs depending on whether a patient has the cutaneous or systemic variant. Each is discussed separately below.

**CD30+ Lymphoproliferative Disorder of the Skin**

Given that PCALCL is an indolent disease, treatment should focus on minimally invasive local therapies. Systemic therapies should be reserved for patients with disseminated disease or disease that is refractory to local measures. There are essentially no large series examining the efficacy of local therapy in PCALCL, but anecdotal observations and small case reports suggest that long-term remissions can be achieved with surgical excision and/or localized radiotherapy [62]. Many of the techniques for radiation therapy are extrapolated from treatment series for cutaneous T-cell lymphoma. In general, doses of 30 Gy are adequate, though some series use doses as high as 36 Gy [63]. The response rate to radiation is in excess of 90%. Increasingly, electron beam radiotherapy, which has very minimal tissue penetration, is the treatment of choice to minimize morbidity. Side effects such as localized anhydrosis and erythema are mild. Whether radiation must be used in addition to surgery for completely excised nodules is unknown.

Low-dose, single-agent methotrexate is an effective therapy for PCALCL in patients with widespread cutaneous disease or those in whom radiation and surgery have failed. In a series of 45 patients with PCALCL or severe LP, 87% of patients achieved durable responses with methotrexate doses of 15–20 mg weekly with transition to maintenance therapy at 1- to 4-week intervals [64]. Ten patients remained free of lesions for 24–227 months after stopping methotrexate. The median total duration of methotrexate therapy for all patients exceeded 39 months. Adverse effects were generally mild but early hepatic fibrosis was found in 5 of 10 patients evaluated, all of whom had been treated for >3 years. The optimal duration of therapy remains unknown, but in patients who are responding, indefinite maintenance therapy at 1- to 4-week intervals is not unreasonable in the absence of prohibitive side effects.

One method of methotrexate resistance is impaired facilitated transport. Trimetrexate (TMTX) is a lipophilic antifolate that enters cells by passive diffusion and may

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**Table 2. Adverse prognostic features of ALCL**

<table>
<thead>
<tr>
<th>ALK negative</th>
<th>High–intermediate or high IPI</th>
<th>CD56 positive</th>
<th>MUC-1 positive</th>
<th>Survivin positive</th>
</tr>
</thead>
</table>

**Abbreviations:** ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; IPI, International Prognostic Index; MUC-1, mucin-1.
bypass this mechanism of resistance. TMTX has been studied in three patients with relapsed PCALCL, and one patient responded to therapy [65]. TMTX requires further study before its role in PCALCL is defined. Other agents with reported activity are vinblastine and imiquimod, though neither can be considered established therapies [66, 67]. Patients with advanced disease that is refractory to local therapy and methotrexate can be treated with combination chemotherapy as detailed for systemic disease.

**Systemic ALCL**

*Conventional Chemotherapy*

No standard therapeutic regimen exists for the treatment of ALCL. Most trials of combination chemotherapy have been conducted in children. Some adult trials have been conducted, but most adult treatment series are retrospective, and patients were treated on a variety of protocols. Further complicating matters is the fact that many trials contain patients that now would be categorized as having HD or DLBCL, which have very different natural histories from what we now recognize as ALCL.

The backbone of most treatment protocols consists of alkylating agents, anthracyclines, vinca alkaloids, and corticosteroids (i.e., cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]-like regimens). Pediatric protocols often incorporate high-dose methotrexate and/or cytarabine, though these drugs are less frequently used in adults [68, 69]. An Italian multicentric trial randomized 40 ALCL-Hodgkin-like patients to frontline chemotherapy with MACOP-B (methotrexate with leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin—a third-generation HD-NHL regimen) or ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine—a scheme specific for HD) [70]. Complete response (CR) rates in both arms were in excess of 90%, with an approximately 90% chance of being relapse free at 32 months. Unfortunately, we now know that most cases of ALCL-Hodgkin-like are actually HD, making the results of that trial difficult to interpret.

A French series contained a subset of patients with ALCL treated with three cycles of ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) chemotherapy followed by a consolidation phase with high-dose methotrexate, ifosfamide, etoposide, asparaginase, and cytosine-arabinoside or eight cycles of m-BACOD (methotrexate, bleomycin, cyclophosphamide, vincristine, dexamethasone) [71]. The CR rate was 69% for the T-cell subtype and 64% for the null subtype with an estimated 5-year OS rate of 63.2%. No stratification was performed based upon ALK expression.

In an Italian series that stratified patients by ALK expression, the overall response rate (ORR) for ALK+ patients was 92.3% (77.3% achieved a CR), whereas the ORR in ALK− patients was 84%, with only 56% achieving a CR [3]. Unfortunately, the chemotherapy regimens used were heterogeneous and not reported in the paper. The percentage of patients receiving consolidative radiotherapy also was not reported.

Because of the heterogeneity of reports in the literature and lack of systematic trials, the U.S. standard has generally been to treat ALCL with CHOP chemotherapy. The choice of CHOP is largely an extrapolation from the DLBCL literature. Studies in DLBCL have failed to demonstrate a benefit to so-called third-generation regimens (e.g., m-BACOD, ProMACE-CytaBOM [cyclophosphamide, doxorubicin, etoposide, prednisone, vincristine, bleomycin, cytosine arabinoside, methotrexate, and leucovorin], MACOP-B) over CHOP, and hence, most oncologists are hesitant to use these regimens in related diseases like ALCL [72]. Hopefully, prospective trials will eventually settle the issue of the best initial chemotherapeutic option for this disease.

*Transplantation*

Autologous stem cell transplantation (ASCT) has been studied prospectively and retrospectively in ALCL. In a retrospective series of patients transplanted for relapsed ALCL, the 3-year OS rate was 86%. ALK+ patients had an event-free survival (EFS) rate of 100% at 3 years, compared with 0% in ALK− cases. There was a very small number of patients with cutaneous ALCL, though all relapsed but followed an indolent course after ASCT [73]. A nearly identical result was noted in a Finnish series of 14 patients undergoing ASCT for ALCL after conditioning with BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) or BCNU, cytarabine, etoposide, and melphalan (BEAM). In that report, the 5-year OS rate was 86%, and again the small number of PCALCL patients invariably relapsed [74]. ALK staining was not performed in the Finnish trial, but the poor outcome with ASCT for ALK+ ALCL was confirmed in a separate series of 15 ALK+ patients. In that analysis, 13 patients relapsed after transplant and the median PFS duration was only 12 weeks, with a median OS time of 72 weeks [75].

The European Group for Blood and Marrow Transplantation (EBMT) has reported the largest ASCT series to date [76]. The analysis consisted of 64 patients with T-/null-cell ALCL. The median age was 25. Forty-seven percent of patients were in complete remission, 28% were in partial remission (PR), and 25% had more advanced or chemotherapy-refractory disease at the time of transplant. Eighty-one percent of the patients were conditioned with chemotherapy alone and 75% received marrow stem cells. Of the 15 patients...
transplanted in first complete remission, only one relapsed. In contrast, 6 of 15 patients transplanted in a complete remission subsequent to the first relapsed. Six of 18 patients transplanted in PR and 14 of 16 transplanted in a refractory or relapsed disease state progressed. The actuarial OS rate at 10 years was 70%. Disease status at transplant, younger age, absence of B symptoms, and lack of extranodal disease indicated a better prognosis in multivariate analyses.

Several studies have evaluated the efficacy of upfront ASCT for ALCL. A French series examined 15 patients with ALCL (three with B-cell markers), including seven who were ALK+ treated with chemotherapy consisting of two alternating anthracycline-containing regimens [77]. Patients who responded then underwent BEAM conditioning followed by ASCT. All patients achieved a CR and there were no relapses. The EFS and OS rates at 5 years were both 87%. Based upon the patient’s age-adjusted IPI, the EFS and OS rates would have been expected to be 71% and 69%, respectively. Although these results are excellent, the lack of a prospectively identified control group makes interpretation of the outcome difficult. Other trials of upfront ASCT have shown similarly promising results but are hampered by the same issues of selection bias and lack of a randomized control group [78, 79].

Clearly ASCT has a role in ALCL. The question remains whether to transplant patients upfront or to only transplant patients who have relapsed. Given the favorable prognosis of ALK+ patients, particularly those with low/low-intermediate IPI scores, it is difficult to justify upfront transplantation in that particular subgroup. More refined, molecularly based prognostication systems and homogeneous trials of true ALCL cases will hopefully allow us to better identify those patients who may benefit from upfront ASCT. Limited data would suggest that ASCT is not effective for ALK+ patients with relapsed disease, so these individuals may better be served by participating in clinical trials investigating new therapies. Whether upfront ASCT improves the outcome in ALK+ patients is unclear.

Several reports in the literature have described successful allogeneic stem cell transplantation for ALCL [80, 81]. There is no systematic literature comparing this approach with ASCT. Given the toxicity of allogeneic transplantation and the favorable outcomes obtained with conventional chemotherapy and ASCT, allogeneic transplant can only be recommended for the most refractory patients, preferably in the setting of a clinical trial.

**Emerging Therapies**

CD30 is an attractive target for treating ALCL. Fully humanized anti-CD30 antibodies have been developed and show promising activity in mouse models of ALCL [82]. In vitro evidence suggests that these antibodies may also work synergistically with conventional chemotherapy [83]. The chimeric anti-CD30 monoclonal antibody SGN-30 demonstrated activity against ALCL in phase I protocols and is currently being evaluated in a phase II trial [84]. MDX-60 is a fully human anti-CD30 IgG1k monoclonal antibody also targeting CD30 [85]. In a phase I/II trial, MDX-60 was administered to six heavily pretreated patients with ALCL and induced one partial response and one CR. The CR occurred at a dose of 1 mg/kg given weekly for 4 weeks and the CR lasted for 4 months. The patient achieving CR was retreated at relapse, resulting in a second CR. Of 48 patients treated on this combined ALCL and HD protocol, only two drug-related serious adverse events were reported (grade 3 elevated liver transaminase and grade 3 pneumonia/grade 4 acute respiratory distress syndrome).

Recently, a new radioimmunoconjugate consisting of the murine anti-CD30 monoclonal antibody Ki-4 labeled with iodine-131 was tested in patients with HD [86]. Six of 22 patients responded, including one partial response. Seven patients experienced grade 4 hematologic toxicity. The agent has not been tested yet in ALCL patients.

ALCL is generally CD25 (IL-2 receptor) positive [60]. Denileukin diftitox is a recombinant fusion protein of IL-2 and diphtheria toxin that binds to cells expressing intermediate- and high-affinity IL-2 receptors. The fusion protein is then internalized and cleaved, releasing the diphtheria toxin that subsequently inhibits protein synthesis, causing cell death. Anecdotal reports have described responses to denileukin diftitox in patients with relapsed ALCL [87]. The combination of CHOP and denileukin diftitox is now being studied in the upfront treatment of ALCL as part of an ongoing phase II trial.

Histone deacetylases (HDACs) regulate gene expression in a variety of cells. Deacetylation generally leads to silencing of gene expression. Dysregulated or inappropriate deacetylation of growth-inhibiting genes is thought to be important in the pathogenesis of many cancers, including lymphoma [88]. HDAC inhibitors (HDIs) can induce gene activation, cellular differentiation, cell growth arrest, and apoptosis in cancer cells by restoring the balance between the acetylation and deacetylation of genes important to the cell cycle [89]. Several HDACs are in clinical development, including depsipeptide, SAHA (vorinostat), and PXD101 [90–92]. These agents have shown promising activity in cutaneous and nodal B- and T-cell lymphomas and are currently undergoing phase II testing in a variety of diseases, including ALCL.

Constitutive activity of nuclear factor (NF)-κB p50 homodimer (p50), has been described in ALCL [93]. (p50), interacts with Bcl-3 and may mediate malignant transformation of T cells through an as yet undefined mechanism.
There is evidence that Bcl-3 protects T lymphocytes from apoptotic cell death [94]. Pharmacologic inhibition of the NF-κB pathway with proteasome inhibitors such as bortezomib may therefore be an attractive therapeutic option for ALCL.

The most appealing target for the treatment of ALCL would be ALK itself. In vitro studies of fused pyrrolocarbazole (FP)-derived small molecules with ALK-inhibitory activity inhibited colony formation in agar and cell proliferation and induced apoptosis in MEFs harboring NPM-ALK [95]. The ALK inhibitors had minimal effects on the proliferation and survival of ALK- leukemia cell lines used as controls in the experiment. Specific ALK inhibitors have not yet undergone human testing.

**SUMMARY**

ALCL is a rare but biologically well-characterized disorder. There are two distinct subtypes, ALK+ and ALK-.

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