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Advances in the treatment and prognosis of anaplastic lymphoma kinase negative anaplastic large cell lymphoma

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ABSTRACT

Anaplastic lymphoma kinase negative anaplastic large cell lymphoma (ALK- ALCL) is a definite entity in the WHO 2016 Classification that represents 2–3% of non-Hodgkin lymphoma (NHL) and 12% of T-cell NHL cases. ALK- ALCL lacks ALK protein expression, but expresses CD30 and has morphologic features similar to ALK positive anaplastic large cell lymphoma (ALK+ ALCL). Some studies indicate that ALK- ALCL and ALK+ ALCL possess different molecular and genetic characteristics. Besides, ALK- ALCL is worse than ALK+ ALCL in terms of treatment outcome, prognosis, and long-term survival. This review is aimed at summarizing information about ALK- ALCL, especially with respect to the treatment and prognosis.

KEYWORDS

Anaplastic large cell lymphoma; anaplastic lymphoma kinase; treatment; prognosis

Background

Anaplastic large cell lymphoma (ALCL) is a rare and heterogeneous malignant tumor, with high expression of CD30 (Ki-1) and large cell proliferation. It was named ALCL after Stein et al. [1]. Morris et al. [2] found 2;5 chromosomal translocation in ALCL, this rearrangement can fuse the amino terminus of nucleophosmin (NPM) nucleolar phosphoprotein gene on chromosome 5q35 to a protein tyrosine kinase gene ALK on chromosome 2p23. According to the expression state of ALK protein, ALCL is classified into ALK+ ALCL and ALK- ALCL. The WHO 2008 classification recognized 3 ALCL entities: ALK+ ALCL, ALK- ALCL (a provisional entity), and primary cutaneous ALCL (pcALCL) [3]. Recently, ALK- ALCL was recognized as a definite entity in the WHO 2016 Classification; additionally, the breast implant-associated ALCL (BIA ALCL) was newly proposed [4].

The etiology and pathogenesis of ALK- ALCL is uncertain. ALK+ ALCL has 5 morphologic forms: common, lymphohistiocytic, small cell, Hodgkin-like, and composite [5]. The first form has 70% occurrence with characteristic embryoid, rosette-like and R-S-like giant cells commonly observed. The second form has 10% occurrence and is made up of reactive histiocytes. The third form has about 5% to 10% occurrence and is made up of small-to-medium sized cells. This pattern can be misdiagnosed as peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). The fourth form has 3% occurrence, consists of tumor nodules surrounded by fibrous bands and this form can be misdiagnosed as Hodgkin Lymphoma (HL), nodular-sclerosis. The morphology of ALK- ALCL is similar to ALK+ ALCL with the absence of small cell pattern is absent. In ALK- ALCL, CD30 is expressed strongly in all tumor cells, usually in the cell membrane and the Golgi region. A majority of ALK- ALCL tumor cells are positive for CD3 and CD2 [6]. A substantial minority of cases are positive for EMA (epithelial membrane antigen) and granzyme B. ALK-ALCL is negative for CD15 and PAX5 [7].

ALK- ALCL can occur in all age groups, with peak onset age at 40 to 65 years old and no significant difference between males and females with a male to female ratio of 0.9:1 [5]. During diagnosis, ALK- ALCL patients were older than ALK+ ALCL patients, with median ages of 56 and 31.5 years, respectively [8]. Various clinical manifestations can be observed in ALK- ALCLs, the typical symptom being peripheral and/or abdominal lymphadenopathy. Patients often reveal advanced disease, with B symptoms, high International Prognostic Index (IPI) score, elevated lactate dehydrogenase (LDH) serum levels, and an aggressive clinical course [7]. ALK- ALCL presenting with extranodal disease (20% of cases) is less common than that in ALK+ ALCL. The most frequent extranodal sites include the skin, liver and lung, while bone and soft tissue are commonly involved in ALK+ ALCL [9]. ALK- ALCL can be diagnosed according to morphology and immunohistochemistry. It might easily be misdiagnosed as PTCL-NOS and HL, nodular-sclerosis. The 3-gene model (TNFRSF8, BATF3 and TMOD1) distinguishes between ALK- ALCL and PTCL-NOS with an accuracy rate 97% [10]. ALK- ALCL is always negative for PAX5 while HL, nodular-sclerosis is weakly positive [11]. Furthermore, HL, nodular -sclerosis

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Table 1. Studies survival outcomes of ALK-ALCL.

	Cases	ALK- ALCL	PFS	OS	Treatment regimen
12	341	43	32% (3-year)	52% (3-year)	CHOP-like/HyperCVAD/MA/Other
13	208	10%	18.4% (5-year)	28.5% (5-year)	CHOP/SCT
14	153	27	16% (3-year)	7% (3-year)	Chemotherapy/Pralatrexate/Romidepsin/Brentuximab Vedotin
15	138	74	5.3 months (mPFS)	8.1 months (mOS)	ACVBP-like/CHOP-like/SCT
16	46	8	61.9% (5-year)	77.1% (5-year)	ASCT
18	299	NR	NR	49.6% (3-year)	Allo-SCT
22	111	17	3.5 months	14.5 months	Pralatrexate
23	130	21	4.0 months	11.3 months	Romidepsin
24	129	13	1.6 months	7.9 months	Belinostat
26	58	42	13.3 months	Not reached	Brentuximab Vedotin
30	38	15	10.5 months	NR	Brentuximab Vedotin
31	58	42	39% (5-year)	60% (5-year)	Brentuximab Vedotin

Notes: CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; HyperCVAD/MA: Hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone/methotrexate, cytarabine; SCT: Stem cell transplant; ACVBP: Doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; ASCT: Autologous hematopoietic stem cell transplantation; Allo-SCT: Allogeneic stem cell transplantation; mPFS: Median progression-free survival; mOS: Median overall survival; NR: Not reported.

tumor cells express both CD30 and CD15, and are negative for granulocyte B and EMA.

Treatment

There is no standard treatment for ALK- ALCL yet. Treatment by hematopoietic stem cell transplantation (HSCT) after first-line remission remains controversial. Targeted therapy by CD30 monoclonal antibody remains a topic of interest for many. The relevant efficacy results of some studies are shown in Table 1.

Traditional treatment

At present, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOP-like (cyclophosphamide, doxorubicin, vincristine and prednisone plus etoposide or ifosfamide) regimen is widely used in clinical practice as the initial treatment regimen for ALK- ALCL. A retrospective analysis of PTCL in US, patients treated with CHOP-like, hyperCVAD/MA, or other regimens, showed the overall response rate to be 73%. The 3-year progression-free survival (PFS) and overall survival (OS) were 32% and 52%, respectively. Regarding OS, PTCL-NOS was found to be inferior to ALK+ ALCL, ALK- ALCL, and angioimmunoblastic T cell lymphoma (AITL) [12]. Since this is a clinical analysis of various PTCL subtypes, understanding the therapeutic effect in ALK- ALCL is impossible. It can only be understood that the prognosis of ALK- ALCL may be better than that of PTCL-NOS. Reportedly [6], the 5-year PFS and OS of ALK- ALCL and ALK+ ALCL are 28–48% and 15–62%, and 60–85% and 70–90%, respectively. In an analysis of 208 PTCL cases [13], 10% were ALK- ALCL. The total 5-year OS and PFS were 28.5% and 18.4%, respectively. It was found that conventional chemotherapy combined with intensive therapy could not improve the effective rates.

There has been lot of research for relapsed refractory cases. Vivien Mak et al. analyzed the survival of 153 PTCL patients (including 27 ALK- ALCL patients) and found that the median OS and PFS after the first relapse or progression were just 5.5 and 3.1 months, respectively. They also found that someone who had good performance status with better outcomes after first-line therapy [14]. A LYSA/SFGMTC study [15] summarized the survival of 64 ALK+ ALCL and 74 ALK- ALCL adult patients with first-relapsed/refractory disease. The median PFS and OS were 3.8 and 13.6 months; 5.3 and 8.1 months, respectively. These two study results were different, possibly because the former study was done on PTCL patients and the latter was done on adults with ALK+ and ALK-ALCL subtypes. However, the results showed that the prognosis of patients with refractory recurrence was poor. Since this disease relapses easily, improving the curative effect on relapsed and refractory patients is necessary. With respect to relapsed refractory patients, transplant or salvage treatment is usually carried out according to the patient's condition. The survival of 46 PTCL patients (including 8 ALCL) after autologous hematopoietic stem cells treatment was studied [16]. The 5-year OS and PFS were 77.1% and 61.9%, respectively. However, only patients who reached CR or PR after transplantation were studied, and so the survival may be better than that of all transplant patients. The LYSA centers retrospectively evaluated 527 patients with PTCL, but the number of ALK- ALCL patients was not mentioned. Treatments performed were CHOP-like, CHOEP, ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) or COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin and methotrexate). A total of 269 patients with achieved complete (81%) or partial response (19%); half of these patients were treated with autologous stem-cell transplantation (ASCT) using intention-to-treat (ITT), and with a median follow-up of 4.8 years, the 5-year PFS was 45% and the 5-year OS was 60.4%. However, these data cannot support that patients with PTCL-NOS, AITL or ALK-ALCL with CR or PR after induction do not show an improved outcome. The current data does not support the use of ASCT for up-front consolidation in all PTCL-NOS, AITL or ALK-ALCL patients with partial or complete

response after induction [17]. A meta-analysis of PTCL Allogeneic Transplantation suggested that the 3-year OS of PTCL patients with allogeneic transplantation was 49.6%. There was no significant difference between allogeneic and autologous transplantation [18]. However, the study of the effect of stem cell transplantation on the natural course of PTCL had a different perception [19]. In recurrent cases, sustained remission could only be achieved by allogeneic transplantation, with a 5-year overall survival rate of 52%, while salvage therapy and autologous transplantation can only achieve a very short median OS. It was suggested that early autologous transplantation can be used for recurrent/refractory PTCLs (especially given that PTCL patients cannot receive further treatment). More samples and more prospective studies are needed to analyze the role of autologous and allogeneic transplantation in ALK- ALCL patients.

Few patients are physically intolerant of transplants, especially with salvage treatment. Ya-Ting Yang et al. retrospectively analyzed the results of various salvage treatments in patients with relapsed and refractory PTCL [20]. Twelve different rescue schemes were investigated including 618 relapsed and refractory PTCL patients. The salvage treatments included pralatrexate, romidespsin, brentuximab vedotin, belinostat, alemtuzumab, bendamustine, gemcitabine, lenalidomide, zanolimumab, 13-cRA + interferon-α, A-DHAP, and ICE. ORRs treated by salvage therapy in patients with refractory recurrence of ALCL was from 22% for lenalidomide to 86% for brentuximab vedotin. It is necessary to carry out a comparative study to obtain more salvage treatment effects for PTCL patients with recurrent or severe pretreatment.

New strategies

Due to the poor prognosis and easy recurrence of ALK- ALCL with conventional chemotherapy, the role of transplantation is not accurate. In recent years, more and more new treatment methods have been explored. The four most representative and US FDA approved novel single-agents for treatment are pralatrexate, romidepsin, belinostat and brentuximab vedotin [21]. Chimeric antigen receptor T cells treatment is a novel treatment strategy.

Pralatrexate, the first FDA approved drug for recurrent and refractory PTCL, is a new folic acid antagonist. In a prospective study conducted in patients with relapsed or refractory PTCL [22], the ORR of 17 ALCL patients was 35%.

Histone deacetylase inhibitors, represented by romidepsin and belinostat, have shown good effects in the treatment of recurrent and refractory PTCL. Romidepsin was approved by the FDA in June 2011 for the treatment of patients with relapsed PTCL based on the results of the pivotal multicenter phase II study that evaluated romidepsin in 130 patients with relapsed/refractory PTCL (ALK- ALCL, $n = 21$ [16%]). The ORR was 24% for patients with ALK- ALCL [23]. The BELIEF trial evaluated belinostat in 129 patients with relapsed or refractory PTCL (ALK- ALCL, $n = 13$ [10%]). The ORR was 15.3% for patients with ALK- ALCL [24]. A phase II multi-center clinical trial of Chidamide, a histone deacetylase inhibitor, for the treatment of recurrent and refractory PTCL was conducted in China, which included 17 ALCL patients, with an ORR of 41.2% and 23.5% patients achieved CR [25].

Brentuximab Vedotin is an immuno-crosslinked compound that anti CD30 mono-clonal antibody chemically linked antitubulin monomethyl auristatin. It can target kill CD30+ cells by mitotic mechanism. In a phase II multicenter study of 58 patients with ALCL, 53% of the patients received CR, 29% received PR and the median PFS is 13.3 months [26]. In a phase I study of 13 ALCL patients received brentuximab vedotin followed by standard-dose CHOP, 26 PTCL patients received brentuximab vedotin combined with CHP [27]. CR rate and estimated 1-year PFS rate were 62% and 77% for the former and 88% and 71% for the latter. This study suggested that CD30+ PTCL patients treated with bentuximab vedotin followed by CHOP or combined with CHP had good safety and anti-tumor activity. There were also many researches about relapsed and refractory T cell lymphoma [28–31]. The objective response rate (ORR) ranged from 41% to 86%, and the median PFS from 2.6 to 20.0 months. For CD30+ relapsed and refractory ALCL patients, bentuximab vedotin is a wise choice. While bentuximab vedotin also had side effects, the biggest adverse reaction is peripheral neuropathy. Although the curative effect of bentuximab vedotin is definite, the prognosis is especially poor after recurrence with a median OS of less than two months [32]. It has become particularly important to identify the cause of recurrence. Some studies found that patients after bentuximab vedotin treatment have CD30 deficiency, which may be related to the poor outcomes in some patients, and the related mechanism requires further study [33,34].

Recent successes suggest that the modification of T-cells with chimeric antigen receptors (CARs) could be a powerful approach for developing safe and effective cancer therapeutics. The genetic modification and characterization of T-cells with CARs allow functionally distinct T-cell subsets to recognize specific tumor cells. The incorporation of costimulatory molecules or cytokines can enable engineered T-cells to eliminate tumor cells [35]. Ramos et al. [36] conducted a phase I dose escalation study in which 9 patients with relapsed/refractory HL or ALCL were treated with CD30-specific CAR. Of the 2 patients with ALCL, 1 had a CR that persisted 9 months after the fourth infusion of CD30. CAR-Ts. No serious adverse reactions were

observed. Perera et al. [37] through *in vitro* and *in vivo* experiments suggested that CCR4 CAR may be a new method for the treatment of T-cell tumors. At present, a number of clinical trials of CART therapy for CD30+ lymphoma (HL and ALCL) are under way locally and abroad, and it is believed that the maturity and optimization of CART technology will bring more treatment options and survival benefits for recurrent and refractory ALCL.

There are also studies that focus on combined treatment with ALCL to improve the effectiveness of the treatment. An *in vitro* animal experiment was conducted to compare the therapeutic effects of liposomal doxorubicin with liposomal doxorubicin in combination with anti-CD30 antibody [38]. The results showed that the inhibition of tumor growth in the combined group was significantly greater than that in the single drug group. Since this is only an animal experiment, more data are required to be appropriate for clinical use. In another phase II study which evaluated the curative effect of PTCL with mTOR inhibitor plus CHOP [39], the objective response rate was 90% of all, while the CR rate was 29% of ALK- ALCL. It is also assumed that the different therapeutic effects of PTCL subtypes may be related to PTEN loss. This conjecture needs further verification. There are still some studies in the exploratory stage using therapeutic agents such as JAK inhibitors, ERBB4/BET inhibitors, nivolumab, and ipilimumab [40,41].

Prognosis

It is well known that the prognosis of ALK- ALCL is very poor, and there are numerous studies on the prognostic factors related to ALK- ALCL. The relationship between gene rearrangement and prognosis of ALK- ALCL was the research hotspot in recent years. Edgardo R. Parrilla Castellar, et al. evaluated the relationship between gene and prognosis by immunohistochemistry and FISH detection in 72 ALK- ALCL patients and 32 ALK+ ALCL patients [42]. The five-year OS rate of ALK+ ALCLs, DUSP22-rearranged ALCLs, TP63-rearranged ALCLs and lacking ALK, DUSP22- rearranged, TP63-rearranged ALCLs were 85%, 90%, 17%, and 42%, respectively. It is speculated think that DUSP22 and TP63 rearrangement can be used as a prognostic indicator in ALCLs patients. Rebecca L. King et al. agree with this hypothesis [43]. Giuseppe Gritti et al. [44] retrospectively evaluated the results of first-line SCT consolidation in 209 patients with PTCL and found that the response to primary treatment is the key determinant of the efficacy of PTCL and not the post-remission planning. There have been similar findings. Xiao Han et al. analyzed 46 PTCL patients and found that CR and disease status before transplantation and gender were significant in univariate analysis, while CR before transplantation was the only significant prognostic factor in multivariate analysis [16]. However, Zhang et al. [45] found that the 5-year OS and PFS rates for Ann Arbor stage I disease and Ann Arbor stage II disease were 95.0% and 77.4%,75.1% and 51.7% respectively for 46 ALCLs. Early stage ALCL may indicate a better prognosis. In addition, prognostic factors include age, serum LDH level, β_2 microglobulin level, time of relapse or progression after the first treatment, extranodular involvement, histological type, etc. Naoko Tsuyama et al. [46] concluded previous study stating that the prognosis of ALK- ALCL and ALK+ ALCL before age 40 is not significantly different. After 40 years of age, the prognosis of ALK- ALCL is worse than that of ALK + ALCL. In Xiu-Wen Deng et al.'s study [47], which analyzed 48 ALK- ALCLs and 119 PTCL-NOS patients, the 5-year OS rates was 57.9% and 23.9% ($P = 0.002$), respectively. Elevated LDH, extranodal sites $\geq$2, and advanced-stage disease were associated with unfavorable OS and PFS for ALK-ALCLs. Suzanne D. Turner et al. summarized extranodal involvement, high risk histological subtype such as lymphohistiocytic or small cell component, a short time to relapse may be related to poor prognosis [48].

Conclusion

ALCL is a rare and heterogeneous malignant tumor, with high expression of CD30 and includes ALK+ ALCL, ALK- ALCL, pcALCL, and BIA ALCL subtypes. In this review, the molecular biology, clinical manifestation, treatment and prognosis of ALK- ALCL are summarized, which is a definite entity in the WHO 2016 Classification. The etiology and pathogenesis of ALK- ALCL is uncertain. Morphologic patterns include common, lymphohistiocytic, small cell, Hodgkin-like, and composite. The first is the most common. ALK- ALCL tumor cells are positive for CD3 and CD2, and negative for CD15 and PAX5. Some patients exist with DUSP22 rearrangement and TP63 rearrangement. Peak onset age is 40 to 65 years. The ratio of male to female is 0.9:1. Patients often reveal advanced disease, with B symptoms, high IPI score, elevated LDH, extranodal involved and an aggressive clinical course. ALK- ALCL is easily misdiagnosed as PTCL-NOS and HL, nodular-sclerosis. There is no standard treatment yet for ALK- ALCL. Currently, CHOP or CHOP-like regimens are first-line treatment regimens. HSCT is a controversial treatment after first-line remission. Targeted therapy is a hot topic, as represented by CD30 monoclonal antibody. Small molecule inhibitors can benefit patients. Substantial clinical studies are still needed for CART treatment. The prognosis of DUSP22-rearranged ALCLs is similar to that of ALK+ ALCL. The prognosis of TP63-rearranged ALCLs is worse than that of ALK- ALCL patients lacking

DUSP22 and TP63 rearrangement. Besides, CR before transplantation is related to better outcomes. Early stage ALCL may indicate a better prognosis. Older age, elevated LDH, elevated β_2 microglobulin level, short time of relapse or progression after the first treatment, extranodular involvement, and histological type of lymphohistiocytic or small cell component are associated with poor prognosis. More research is needed to explore more effective treatments to improve patient survival.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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