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

Xiaoli Wang, Jingjing Wu and Mingzhi Zhang

Department of Oncology, Lymphoma Diagnosis and Treatment Centre of Henan Province, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, People’s Republic of China

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...
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, 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. A LYSA/SFGMTC study 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. 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 LYSAC centers retrospectively evaluated 527 patients with PTCL, but the number of ALK- ALCL patients was not mentioned. Treatments performed were CHOP-like, CHOEAP, 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

**Table 1.** Studies survival outcomes of ALK-ALCL.

| Cases | ALK- ALC | 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  | 49.6% (3-year) | NR | Allo-SCT |
| 22    | 111     | 17  | 3.5 months | 14.5 months | Brentuximab Vedotin |
| 23    | 130     | 21  | 4.0 months | 11.3 months | Brentuximab Vedotin |
| 24    | 129     | 13  | 1.6 months | 7.9 months | Brentuximab Vedotin |
| 25    | 58      | 42  | 13.3 months | Not reached | Brentuximab Vedotin |
| 26    | 38      | 15  | 10.5 months | NR | Brentuximab Vedotin |
| 27    | 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.
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 trans-
plantation 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 trans-
plantation 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 investi-
gated including 618 relapsed and refractory PTCL
patients. The salvage treatments included pralatrexate,
romidepsin, brentuximab vedotin, belinostat, alemtu-
zumab, bendamustine, gemcitabine, lenalidomide,
zanolimumab, 13-cRA + interferon-α, A-DHAP, and ICE.
ORRs treated by salvage therapy in patients with refrac-
tory 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 treat-
ment 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, brentuximab vedotin, belinostat, alemtuzu-
mab, bendamustine, gemcitabine, lenalidomide,
zanolimumab, 13-cRA + interferon-α, A-DHAP, and ICE.

Chimeric antigen receptor T cells treatment is a novel
powerful approach for developing safe and e-
fective cancer therapeutics. The genetic modi-
cation of T-cells allows functionally
distinct T-cell subsets to recognize speci-
cific tumor cells.

Pralatrexate, the first FDA approved drug for recur-
cent 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 romi-
depsin 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 treat-
ment 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 deac-
etylase 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 II
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 cyto-
kines 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, β2 microglobulin level, time of relapse or progression after the first treatment, extranodal 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 ≥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 β2 microglobulin level, short time of relapse or progression after the first treatment, extranodal 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.

Disclosure statement
No potential conflict of interest was reported by the authors.

Funding
The authors have received supports from Natural Science Foundation of Henan Province [grant number 162300410304].

References
[1] Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood. 1985;66(4):848–858.
[2] Morris SW, Kirstein MN, Valetine M, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science. 1994;263(5151):1281–1284. doi:10.1126/science.8122112.
[3] Xing X, Feldman AL. Anaplastic large cell lymphomas: ALK positive, ALK negative, and primary cutaneous. Adv Anat Pathol. 2015;22(1):29–49. doi:10.1097/PAP.0000000000000047.
[4] Steven H, Swerdlow ECSA, Michele Ghielmini GASA. The 2016 revision of the world health organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–2390. doi:10.1182/blood-2016-01-643569.
[5] Swerdlow SHCEHN, Abramson JS. WHO classification of tumours of haematopoietic and lymphoid tissue (M). Lyon: IAAC Press; 2008.
[6] Savage GHAK. The biology and management of systemic anaplastic large cell lymphoma. Blood. 2015;126(1):17–25. doi:10.1182/blood-2014-10-567461.
[7] Ferreri AJM, Govi S, Pileri SA, et al. Anaplastic large cell lymphoma, ALK- negative. Critical Reviews in Oncology/Hematology. 2013;85(2):206–215. doi:10.1016/j.critrevonc.2012.06.004.
[8] Silbon D, Fournier M, Briege J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d’Etude des Lymphomes de l’Adulte trials. J Clin Oncol. 2012;30(32):3939–3946. doi:10.1200/JCO.2012.42.2345.
[9] Querfeld C, Khan I, Mahon B, et al. Primary cutaneous and systemic anaplastic large cell lymphoma: clinicopathologic aspects and therapeutic options. Oncology (Williston Park). 2010;24(7):574–587.
[10] Agnelli L, Merce E, Pellegrino E, et al. Identification of a 3-gene model as a powerful diagnostic tool for the recognition of ALK-negative anaplastic large-cell lymphoma. Blood. 2012;120(6):1274–1281. doi:10.1182/blood-2012-01-405555.
[11] Ong DM, Cummins KD, Pham A, et al. PAX5-expressing ALK-negative anaplastic large cell lymphoma with extensive extranodal and nodal involvement. BMJ Case Rep, 2015. doi:10.1136/bcr-2015-211159.
[12] Abramson JS, Feldman T, Kroll-Desrosiers AR, et al. Peripheral T-cell lymphomas in a large US multicenter cohort: prognostication in the modern era including impact of frontline therapy. Annals of Oncology. 2014;25(11):2211–2217. doi:10.1093/annonc/mdu443.
[13] Broussais-Guillaumot F, Coso D, Belmecheri N, et al. Peripheral T-cell lymphomas: analysis of histology, staging and response to treatment of 208 cases at a single institution. Leuk Lymphoma. 2013;54(11):2392–2398. doi:10.1016/j.leukres.2013.08.011.
[14] Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. Journal of clinical oncology. 2013;31(16):1970–1976. doi:10.1200/JCO.2012.44.7524.
[15] Morel A, Briere J, Lamant L, et al. Long-term outcomes of adults with first-relapsed/refractory systemic anaplastic large-cell lymphoma in the pre-brentuximab vedotin era: a LYSAMFGM-TSC study. Eur J Cancer. 2017;83:146–153. doi:10.1016/j.ejca.2017.06.026.
[16] Han X, Zhang W, Zhou D, et al. Autologous stem cell transplantation as frontline strategy for peripheral T-cell lymphoma: a single-centre experience. Journal of International Medical Research. 2017;45(1):290–302. doi:10.1177/0300060516676725.
[17] Fossard G, Broussais F, Coelho I, et al. Role of up-front autologous stem cell transplantation in peripheral T-cell lymphoma for patients in response after induction: an analysis of patients from LYSAMFGM centers. Ann Oncol. 2017;29(3):715–723. doi:10.1093/annonc/mdx787.
[18] Wei J, Xu J, Cao Y, et al. Allogeneic stem-cell transplantation for peripheral T-cell lymphoma: a systemic review and meta-analysis. Acta Haematol. 2015;133(2):136–144. doi:10.1159/000358579.
[19] Rohlff S, Dietrich S, Wittens-Harig M, et al. The impact of stem cell transplantation on the natural course of peripheral T-cell lymphoma: a real-world experience. Annals of Hematology. 2018;97(7):1241–1250. doi:10.1007/s00277-018-3288-7.
[20] Yang Y, Tai C, Chen C, et al. Highly diverse efficacy of salvage treatment regimens for relapsed or refractory peripheral T-cell lymphoma: a systematic review. Plos one. 2016;11(10):e161811. doi:10.1371/journal.pone.0161811.
[21] Brocacci A, Argnani L, Zinzani PL. Peripheral T-cell lymphomas: focusing on novel agents in relapsed and refractory disease. Cancer Treat Rev. 2017;60:120–129. doi:10.1016/j.ctrv.2017.09.002.
[22] O’Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011;29:1182–1189. doi:10.1200/JCO.2010.29.9024.
[23] Coiffer B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol. 2012;30:631–636. doi:10.1200/JCO.2011.37.4223

[24] O’Connor OA, Horwitz S, Masszi T, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol. 2015;33:2492–2499. doi:10.1200/JCO.2014.59.2782

[25] Shi Y, Dong M, Hong X, et al. Results from a multicenter, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma. Ann Oncol. 2015;26:1766–1771. doi:10.1093/annonc/mdv237.

[26] Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol. 2012;30(18):2190–2196. doi:10.1200/JCO.2011.38.0402

[27] Fanale MA, Horwitz SM, Forero-Torres A, et al. Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. Journal of Clinical Oncology. 2014;32(28):3137–3143. doi:10.1200/JCO.2013.54.2456

[28] Steven M, Horwitz RHAN, Tanya Siddiqi DAKA. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood. 2014;123(20). doi:10.1182/blood-2013-12-542142.

[29] Zinzani PL, Sasse S, Radford J, et al. Experience of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma and relapsed/refractory systemic anaplastic large-cell lymphoma in the Named Patient Program: review of the literature. Critical Reviews in Oncology/Hematology. 2015;95(3):359–369. doi:10.1016/j.critrevonc.2015.03.011

[30] Mathilde Lamargue CBAC. Brentuximab vedotin in refractory or relapsed peripheral T-cell lymphomas: the French named patient program experience in 56 patients. Haematologica. 2016;101(3):e103–e106. doi:10.3324/haematol.2015.135400.

[31] Pro B, Advani R, Brice P, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood. 2017;130(25):2709–2717. doi:10.1182/blood-2017-05-780049.

[32] Chihara D, Fanale MA. Management of anaplastic large cell lymphoma. Hematol Oncol Clin North Am. 2017;31(2):209–222. doi:10.1016/j.hoc.2016.11.001

[33] Arai H, Furuchi S, Nakamura Y, et al. ALK-negative anaplastic large cell lymphoma with loss of CD30 expression during treatment with brentuximab vedotin. Rinsho Ketsueki. 2016;57(5):634–637. doi:10.1140/rinketsu.57.634.

[34] Al-Rohil RN, Torres-Cabala CA, Patel A, et al. Loss of CD30 expression after treatment with brentuximab vedotin in a patient with anaplastic large cell lymphoma: a novel finding. J Cutan Pathol. 2016;43(12):1161–1166. doi:10.1111/cup.12797.

[35] Dai H, Wang Y, Lu X, et al. Chimeric antigen receptors Modified T-cells for cancer therapy. JNCI J Natl Cancer Inst. 2016;108(7):pii:dyv439). doi:10.1093/jnci/dyv439

[36] Ramos CA, Ballard B, Zhang H, et al. Clinical and immunological responses after CD30-specific chimeric antigen receptor-redirected lymphocytes. J Clin Invest. 2017;127(9):3462–3471. doi:10.1172/JCI94306.

[37] Perera LP, Zhang M, Nakagawa M, et al. Chimeric antigen receptor modified T cells that target chemokine receptor CCR4 as a therapeutic modality for T-cell malignancies. Am J Hematol. 2017;92(9):892–901. doi:10.1002/ajh.24794.

[38] Molavi O, Xiong XB, Douglas D, et al. Anti-CD30 antibody conjugated liposomal doxorubicin with significantly improved therapeutic efficacy against anaplastic large cell lymphoma. Biomaterials. 2013;34(34):8718–8725. doi:10.1016/j.biomaterials.2013.07.068.

[39] Kim SJ, Shin DY, Kim JS, et al. A phase II study of everolimus (RAD001), an mTOR inhibitor plus CHOP for newly diagnosed peripheral T-cell lymphomas. Ann Oncol. 2016;27(4):712–718. doi:10.1093/annonc/mdv624.

[40] Vu K, Ai W. Update on the treatment of anaplastic large cell lymphoma. Curr Hematol Malig Rep. 2018;13(2):135–141. doi:10.1007/s11899-018-0436-2

[41] Elisabetta Mereu EPIS. The heterogeneous landscape of ALK negative ALC. Oncotarget. 2017;8(11):18525–18536. doi:10.18632/oncotarget.14503.

[42] Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood. 2014;124(9):1473–1480. doi:10.1182/blood-2014-04-571091.

[43] King RL, Dao LN, McPhail ED, et al. Morphologic features of ALK-negative anaplastic large cell lymphomas with DUSP22 rearrangements. The American Journal of Surgical Pathology. 2016;40(1):36–43. doi:10.1097/PAS.0000000000000500

[44] Gritti G, Boschini C, Rossi A, et al. Primary treatment response rather than front line stem cell transplantation is crucial for long term outcome of peripheral T-cell lymphomas. PLOS ONE. 2015;10(3):e121822). doi:10.1371/journal.pone.0121822

[45] Zhang XM, Li YX, Wang WH, et al. Favorable outcome with doxorubicin-based chemotherapy and radiotherapy for adult patients with early stage primary systemic anaplastic large-cell lymphoma. Eur J Haematol. 2013;90(3):195–201. doi:10.1111/ejh.12060.

[46] Tsuyama N, Sakamoto K, Sakata S, et al. Anaplastic large cell lymphoma: pathology, genetics and clinical aspects. J Clin Exp Hematop. 2017;57(3):120–142. doi:10.3960/j.slt.17023.

[47] Deng XW, Zhang XM, Wang WH, et al. Clinical and prognostic differences between ALK-negative anaplastic large cell lymphoma and peripheral T cell lymphoma, not otherwise specified: a single institution experience. Ann Hematol. 2016;95(8):1271–1280. doi:10.1007/s00277-016-2696-9.

[48] Turner SD, Lamant L, Kenner L, et al. Anaplastic large cell lymphoma in paediatric and young adult patients. British Journal of Haematology. 2016;173(4):560–572. doi:10.1111/bjh.13958