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Diagnostic and therapeutic challenges of ALK-positive anaplastic large cell lymphoma: case report and literature review

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Abstract

ALK-positive anaplastic large cell lymphoma (ALK+ ALCL) is an extremely rare and aggressive T-cell lymphoma exhibiting chromosomal translocation involving the *ALK* gene. It accounts for 0.5% of adult lymphomas. We present below the case of a 36-year-old female patient admitted to hospital in poor overall condition with hyperleukocytosis, lymphadenopathy, organomegaly, tachycardia, dyspnea, and overall weakness, who was diagnosed with ALK-positive ALCL. In the first line of treatment, a standard CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) chemotherapy was given. In second-line therapy, a combination of brentuximab vedotin (BV) and conventional chemotherapy resulted in the achievement of complete remission (CR).

This paper aims to highlight the challenges involved in making a definitive diagnosis of ALCL, emphasizing the importance of cytogenetic techniques, and discussing current treatment options based on a literature review.

Keywords: anaplastic large cell lymphoma, ALK gene, cytogenetic, brentuximab vedotin

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Introduction

Anaplastic large cell lymphoma (ALCL) is a rare and aggressive type of peripheral T cell lymphoma (PTCL), which is a heterogeneous group of lymphomas accounting for 1–2% of adult non-Hodgkin lymphomas (NHLs) and c.15% of T cell lymphomas [1]. Diagnosis of ALCL depends mainly on biopsy of the tumor tissue. ALCL is usually associated with B symptoms (fever, night sweats, and weight loss of >10% of total body mass in the past six months), which can help determine the prognosis [2]. The 2023 revised World Health Organization (WHO) lymphoma classification includes three distinct entities under ALCL: ALK-positive ALCL (ALK+ ALCL), ALK-negative ALCL (ALK–ALCL), and a provisional entity known as breast implant-associated ALCL (BI-ALCL) [3].

ALK+ ALCL, also termed 'CD30 positive anaplastic large cell lymphoma' because of being strongly positive for CD30 staining, has been associated with the (2;5)(p23;q35) translocation and expression NPM-ALK fusion protein, and has been distinguished from ALK- ALCL based on its distinct pathogenesis. ALK+ ALCL is encompassed among a group of CD30-positive lymphoproliferative disorders and can affect lymph nodes and various organs such as the subcutaneous tissue, lungs, spleen, liver, bones, and bone marrow [3]. Prospective clinical studies have indicated the usefulness of the International Prognostic Index (IPI) for T-cell lymphoma [2, 4]. Overall, ALK+ ALCL shows

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a better prognosis than ALK- ALCL, with 5-year overall survival (OS) of 80% compared to 48% [3, 5, 6]. The BV-CHP regimen (brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone) is the preferred first-line treatment for patients with ALCL [7]. At the time of treating the patient in question, BV-CHP was not available in Poland due to no refund. Therapeutic decisions must depend on the prognostic index, the subtype of lymphoma, the stage, and comorbidities [8]. For example, high-risk patients with a primary advanced stage of systemic ALCL should go through high-dose consolidation chemotherapy and hematopoietic cell transplantation (HCT) if they are not responsive to the chemotherapy regime. Refractory ALK+ ALCL patients may benefit from ALK inhibitors or CD30 antibody-drug conjugates when not treated in the first line [1, 9].

Case report

In August 2019, a 36-year-old woman was admitted to the Department of Hematooncology and Bone Marrow Transplantation in the Medical University of Lublin, Poland due to hyperleukocytosis, generalized lymphadenopathy, overall weakness, dyspnea and tachycardia. On admission, the patient was in poor general condition, with shortness of breath at rest, mostly confined to bed, and an ECOG performance status of 3, international prognostic index (IPI) of high-risk group, and advanced stage IV ALCL. Weakness, night sweats, bone pain, and abdominal pain had started about two weeks before admission. In physical examination, she presented: vesicular murmur decreased below the right angle of the scapula, crepitus; abdomen hard and tense; and right supraclavicular lymph node 2 × 3 cm, axillary diameter of c.2 cm. Complete blood counts (CBC) were: WBC (white blood count) 233 G/L, LYMPH (lymphocytes) 173.56 G/L, NEU (neutrophils) 33.51 G/L, MONO (monocytes) 21.89 G/L, EOS (eosinophils) 1.39 G/L, BASO (basophils) 0.15 G/L, HGB (hemoglobin) 11.7 g/dL, and PLT (platelets) 230 G/L. The biochemical parameters were presenting elevated liver parameters (total serum bilirubin level of 2.46 (normal 0.1–1.2) mg/dL, alanine aminotransferase (ALT) of 128.9 (normal 5–34) U/L, extremely high lactate dehydrogenase activity (LDH) of 1,699 (normal 10–480) IU/L, and higher concentrations of C-reactive protein (CRP) = 125.8 (normal <5) mg/L and β_2-microglobulin = 3.79 (normal 0.7–2.4) mg/L.

Chest X-ray showed widening and thickening of the right lung's hilum and parenchymal densification and fluid in the pleural cavities. CT scan confirmed fluid in the pleural cavities, in the pericardial sac, hepatomegaly (21 × 13 cm), splenomegaly (15 × 5.5 cm), and generalized lymphadenopathy with the most prominent mediastinal lymph nodes (23 × 14 mm) (Fig. 1A and 1B). Bone marrow smear showed an increase of 47% in atypical lymphocytes. Flow cytometry revealed a dominant (c.85%) population of CD30+, CD5+, CD3+, CD2+, CD8-, CD7+, CD16–, CD56–, and CD34– T lymphocytes.

As life-saving treatment, CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) was administered, resulting in an improvement and stabilization of the clinical condition.

In bone marrow biopsy, abundant interstitial infiltrates from small and medium-sized lymphoid cells (CD45+, CD3+, CD5+ weakly, CD4+, CD8–, TdT+ weakly in some cells, CD20) were described, constituting c.50–60% of all cells. Histopathological examination pointed to a diagnosis of T-cell lymphoma.

Karyotype analysis from bone marrow and right supraclavicular node (presented below) was performed using the classical cytogenetics technique (GTG staining and RHG bands). An abnormal complex female karyotype was observed in 20 metaphases. A normal female karyotype was found in 10 metaphases. Abnormal karyotype: 46,X,der(X)t(X;11)(q13;q12)ins(X;5)(q13;q13q23),der(5)t(5;X)(q12;q22),der(11)t(11;5)(q12;q23)[10]/46,idem,t(2;5)(p23;q35)[8]/47,idem,t(2;5)(p23;q35),+7[2]/46,XX[10] (see Fig. 2). The presence of t(2;5)(p23;q35) rearrangement involving the *ALK* and *NPM1* genes in the karyotype indicated a diagnosis of ALCL. Additional tests were performed using the fluorescence in situ hybridization (FISH) technique. *ALK* gene rearrangement confirmed: nuc ish(ALKx2)(3'ALK sep 5'ALKx1)[84/210]-bone marrow (40% hybridization pattern — 1F101G), nuc ish(ALKx2)(3'ALK sep 5'ALKx1) [76/100]-lymph node (76% hybridization pattern — 1F101G). In other words, using the Break Apart reporter molecule during the FISH procedure, we received 40% of bone marrow cells with ALK mutation and 70% of lymph node cells with ALK mutation.

As treatment, the CHOEP scheme was continued. Nevertheless, after the second cycle of chemotherapy, signs of disease progression (i.e. general symptoms, increasing lymphocytosis) were observed, which indicated primary resistance to chemotherapy. Second-line therapy with brentuximab vedotin (BV), a conjugate of anti-CD30 antibody and auristatin E was initiated and given alongside CHOEP. After the 4th cycle, a decision to enhance the treatment was made due to progression in immunophenotype examination. Bone marrow aspirate flow cytometry revealed 65% of cells positive for CD5, CD2, CD7, CD3, CD30, and CD4. ESHAP chemotherapy (etoposide, cisplatin, cytosine arabinoside, methylprednisolone) was started, which resulted in regression of lymphocytosis with leukocytosis and skin changes. At the same time, a procedure of preparation for bone marrow allotransplantation (allo-SCT) was started. Total body irradiation (TBI 12G y) with fludarabine was used for conditioning. In February 2020, the allo-SCT procedure was performed using the patient's brother (an HLA 10/10 match).

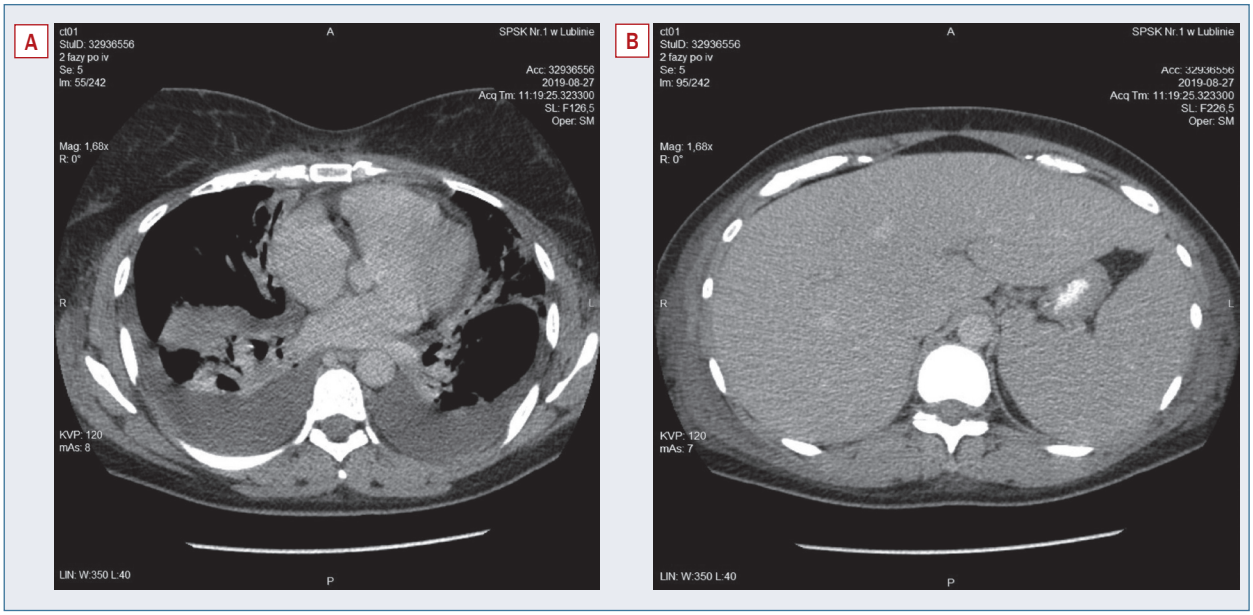

Figure 1A. CT after admission, **B.** CT scan after admission

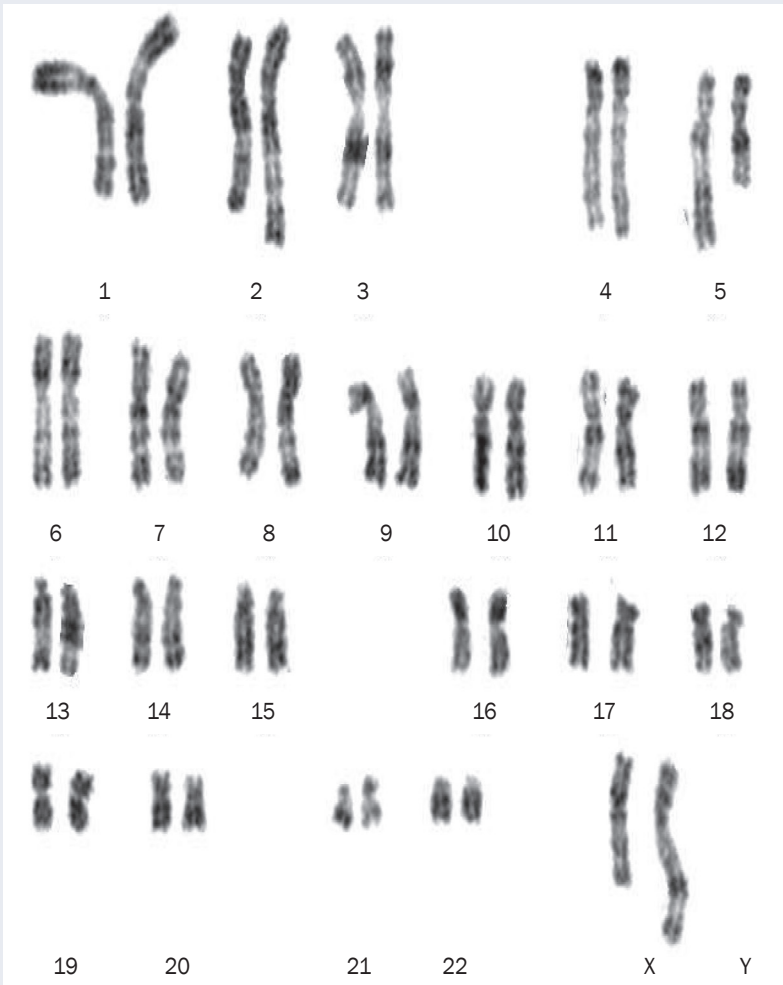

Figure 2. Cytogenetics analysis

34 days after transplantation, the patient was confirmed to have an EBV infection. Treatment included two infusions of rituximab; BV was temporarily suspended (19 weeks) until hematopoiesis regenerated after allo-SCT and virus eradication was confirmed. The patient did not develop post-transplant lymphoproliferative disease (PTLD). BV therapy was continued for a total of 16 cycles. Control CT scan after the 8th cycle of treatment showed CR.

The patient was confirmed to have a severe form of cGvHD with skin grade 3, liver grade 2, lungs grade 1, and musculoskeletal system grade 2, according to the organ scoring of the cGvHD scale. Treatment included steroid therapy, ruxolitinib, and extracorporeal photoapheresis (ECP). Additionally, there were endocrine complications such as hyperprolactinemia, diabetes, and arrhythmias. In March 2021, fatal pneumonia developed with severe, rapidly progressive, respiratory failure. No SARS-CoV-2 infection was confirmed, and no growth of pathogenic bacteria was confirmed in sputum or blood cultures. No autopsy was performed.

Discussion

Our case describes a 36-year-old woman suffering from a fast-growing, aggressive ALK+ ALCL lymphoma primarily refractory to the standard anthracycline-based chemotherapy regimen of CHOEP. American NCCN guidelines from 2023 indicate that multi-drug regimens are preferred in the first-line treatment of ALK+ ALCL. The suggested first-choice therapy is BV, along with CHP (cyclophosphamide, doxorubicin, and prednisone). In addition to that, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP, and dose-adjusted EPOCH (etoposide, prednisone, vincristine cyclophosphamide, and doxorubicin) are recommended. Based on a prospective study in which patients with PTCL had OS and progression-free survival (PFS) of respectively 70% and 61% after a 5-year observation, the ESMO recommendations from 2015 state that CHOEP 14 (i.e. given every 14 days) with peripheral stem cell transplantation (PBSCT) is an efficient way to treat patients with ALK– ALCL. Moreover, this program was suggested for patients with ALK+ ALCL with IPI >2. In the guidelines of the Polish Society of Clinical Oncology from 2020, CHOEP is suggested in the treatment of sALCL, and factors such as ALK– sALCL, young age, high IPI, advanced disease, autoPBSCT and multi-drug treatment should be taken into consideration [10–14].

As mentioned in the introduction, the therapeutic decision must depend on the prognostic index, the subtype of lymphoma, the stage, and comorbidities. Considering the patient's overall well-being, our patient received BV and CHOEP therapy. Antibody-drug conjugates BV allowed our patient to be in CR for one year after allo-SCT. However, due to a strong cGVHD response, our patient died two years after the first (described in this paper) hospital visit and one year after allo-HSCT. The prognosis for refractory/relapsed ALCL (R/R ALCL) is poor, and there is still not enough data evaluating the outcomes of allo-HCT. A 9-year study evaluating 182 adults suffering from R/R ALCL who underwent allo-HCT showed that survivors' median follow-up was 62 months, along with 1-year non-relapse mortality of 18%. The 5-year PFS and OS were 41% and 56%, respectively [15]. Our patient received treatment with BV after allo-HSCT. The rationale behind that decision was data suggesting efficacy in patients with risk factors or relapse/progression. Autologous cell transplantation was considered; however, the transplantation crew did not qualify the patient for this procedure at that time. In a study examining 16 patients with advanced Hodgkin's lymphoma (HL) who received BV with (10 patients) or without (six patients) DLI after allo-HSCT, 13 patients relapsed, and the OR rate after BV was 69%. The rest of the patients (n = 3), who did not show disease progression after allo-HSCT, achieved CR after BV. After 13 months of follow-up, the survival rate was 81%, and the median PFS was six months [16]. BV, a CD30 antibody conjugated to the anti-microtubule agent monomethyl auristatin E (MMAE), is a promising immunotherapeutic tool to fight ALCL, and is characterized by rich expression of CD30. When BV binds to pathogenic cells, it shows its cytotoxic effect by releasing MMAE by proteolytic cleavage [17]. However, data indicates that BV can have cytotoxic effects in CD30-negative cells. In a study conducted on cell lines, CD30- cells treated solely with BV showed no signs of vulnerability to the drug; however, when put in a co-culture with CD30+ cells, they showed an increased proliferation and death rate in response to BV [18].

Scientists came to similar conclusions by studying the toxicity of BV in DLBCL (diffuse large B cell lymphoma) [19]. In 2012, this drug was approved by the US Food and Drug Administration (FDA) for R/R ALCL based on results from previous studies which showed promising effects. In the initial phase of those studies, the overall response rate (ORR) reached 38% with a CR rate of 11%, followed by an ORR of 86% with a 57% CR subsequently in the second phase in R/R ALCL. The median PFS was 13.3 months [17]. Moreover, in a later study of a 5-year follow-up which examined 58 patients who had 79% OS and 57% PFS, the most significant side effect was neuropathy, but the majority experienced improvement at the time of their last assessment [20].

For R/R patients, other novel therapeutic agents are also being investigated. Alectinib is a second-generation tyrosine kinase inhibitor for ALK+ ALCL, inhibiting intracellular pathways responsible for tumor proliferation and survival. It was first approved as a first-line treatment of non-small cell lung cancer (NSCLC) in Japan in 2014 with a dose of 300 mg, and then in the European Union and United States in 2017 with a dose of 600 mg [21]. Alectinib has been shown to have favorable clinical outcomes with

Table I. Ongoing clinical trials during 1 phase

	NCT number	Phase	Number of participants	Status	Location	Drug
1.	NCT04925609	1/2	65	Recruiting	Paris, France	Brigatinib
2.	NCT01606878	1	46	Completed with results	22 locations in USA and Canada	Crizotinib and combination chemotherapy
3.	NCT06176690	1	90	Active, not yet recruiting	Houston, Texas, USA	Biological: C7R.CD30.CAR-EBVST cells
4.	NCT00585195	1	596	Completed with results	28 locations in USA and South Korea	PF-02341066 (c-Met/Hepatocyte growth factor receptor tyrosine kinase inhibitors), rifampicin, itraconazole
5.	NCT04058470	1/2	140	Recruiting	Guangzhou, Guangdong, China	Toripalimab, rituximab, R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
6.	NCT02561273	1/2	54	Completed with results	8 locations in USA	Autologous hematopoietic stem cell transplantation, cyclophosphamide, doxorubicin hydrochloride, etoposide, laboratory biomarker analysis, lenalidomide, peripheral blood stem cell transplantation, prednisone, vincristine sulfate

minimum toxicity and, based on a study from 2020, has been approved in Japan for treating recurrent or relapsed ALK+ ALCL [22]. As a drug that penetrates the brain-blood barrier, it is a promising tool in fighting brain metastases compared to the other second-generation inhibitor, crizotinib, as data from a retrospective observational study conducted on 120 patients from 2022 indicates, as well as a review paper from 2019 describing preclinical and clinical experiments [23, 24]. However, sustained and solid results have also been noted in pediatric patients with refractory tumors treated with a combination of cytotoxic chemotherapy and crizotinib [25]. A multicentered, Chinese, retrospective study from 2022 pointed to long-term benefits from treatment with sequential therapy with first-line crizotinib followed by alectinib [26].

Crizotinib is an ATP inhibitor of receptor kinase. Besides inhibition of ALK, it also inhibits c-met, ROS-1, and possibly other targets. Therefore, it is used in the treatment of different types of malignancies such as colon cancer, gastric carcinoma, glioma, and especially NSCLC [27]. In a study conducted in 2017 on 26 patients with relapsed/refractory ALCL, the overall response rates treated at doses of 165 and 280 mg/m^2 were 83% and 90%, respectively. Five of six patients treated with 165 mg/m^2 showed signs of an initial response four weeks after initiating treatment with two CRs. Moreover, an NPM:ALK level decrease in most patients in the same study was noted [28]. It has also been proven to have similar pharmacokinetics in children as in adults if given orally, which makes it a more widely used therapeutic drug [29]. The efficacy of adding crizotinib to the standard chemotherapy in the first line is worth mentioning. This combination has developed from a 2023 study, wherein 66 children were given crizotinib twice daily during six 21-day cycles. The study was temporarily discontinued to evaluate toxicity. Results indicated that adding crizotinib prevented relapses during therapy for children with ALCL and MDD (minimal disseminated disease), predicted EFS (event-free survival rate), and resulted in unexpected thromboembolic events. The 2-year EFS was 78.6%, and the overall survival rate was 95.2%. Fifteen patients relapsed, and one died. The 66 patients completed 384 cycles of chemotherapy [30].

A search of ClinicalTrials.gov (accessed on 24 July 2024) for 'ALCL', 'ALK+', and 'phase 1' revealed 12 registered clinical trials with different statuses. Six of them were withdrawn, and one is listed as 'terminated with results'. The rest of the trials are set out in Table I.

In summary, there is still a need to investigate and widen perspectives in the treatment of rare diseases such as ALCL so as to optimize the best strategy for patients with that tumor. In the presented case, cytogenetics were crucial in the process of planning the treatment for our patient, who was able to receive a precise diagnosis and, as a result, personalized therapy. With the help of modern diagnostic techniques and the latest discoveries in immunology and genetics, it is possible to achieve promising results.

Article information and declarations

Authors' contributions

AS-S, DM-K, DK, AF, MH, TG, SC — collected data; AB, AS-S, DM-K, DK, AF, MH, TG, SC — analyzed data and wrote paper; AB, AS-S, DM-K, DK, AF, MH, TG, SC — critically revised manuscript. All authors approved the submitted version.

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Conflicts of interest
The authors declare no conflict of interest.

Supplementary material
None.

References

1. Kaseb H, Mukkamalla S, Rajasurya v. Anaplastic Large Cell Lymphoma. StatPearls. Treasure Island (FL): StatPearls. 2023; [Internet], indexed in Pubmed: 30725835.
2. Gromowsky MJ, D'Angelo CR, Lunning MA, et al. ALK-positive anaplastic large cell lymphoma in adults. Fac Rev. 2023; 12: 21, doi: 10.12703/r/12-21, indexed in Pubmed: 37655119.
3. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022; 36(7): 1720–1748, doi: 10.1038/s41375-022-01620-2, indexed in Pubmed: 35732829.
4. Chiattone C, Civallero M, Fischer T, et al. Characteristics and clinical outcomes of patients with ALK-positive anaplastic large cell lymphoma: Report from the prospective international T-cell lymphoma project. Hematol Oncol. 2022; 40(5): 953–961, doi: 10.1002/hon.3074, indexed in Pubmed: 36083035.
5. Irshaid L, Xu ML. ALCL by any other name: the many facets of anaplastic large cell lymphoma. Pathology. 2020; 52(1): 100–110, doi: 10.1016/j.pathol.2019.09.007, indexed in Pubmed: 31706671.
6. Falini B, Lazzi S, Pileri S. A comparison of the International Consensus and 5th WHO classifications of T-cell lymphomas and histiocytic/dendritic cell tumours. Br J Haematol. 2023; 203(3): 369–383, doi: 10.1111/bjh.18940, indexed in Pubmed: 37387351.
7. Martinez-Calle N, Kirkwood AA, Lamb M, et al. Systemic ALCL Treated in Routine Clinical Practice: Outcomes Following First-Line Chemotherapy from a Multicentre Cohort. Adv Ther. 2021; 38(7): 3789–3802, doi: 10.1007/s12325-021-01764-0, indexed in Pubmed: 34037958.
8. Chmielowska E. Rzadkie postacie chłoniaków T-komórkowych – aktualne postępowanie. Acta Haematologica Polonica. 2019; 50(3): 103–108, doi: 10.2478/ahp-2019-0017.
9. 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, indexed in Pubmed: 23301725.
10. Swerdlow W, Campo E, Harris N. classification of tumours of hematopoeietic and lymhoid tissues. Revised 4th edition. IARS, Lyon 2017: 413–418.
11. Sibon D, Nguyen DP, Schmitz N, et al. ALK-positive anaplastic large-cell lymphoma in adults: an individual patient data pooled analysis of 263 patients. Haematologica. 2019; 104(12): e562–e565, doi: 10.3324/haematol.2018.213512, indexed in Pubmed: 31004022.
12. Guru Murthy GS, Hamadani M, Bhatt VR, et al. Systemic Anaplastic Lymphoma Kinase-positive Anaplastic Large Cell Lymphoma: A Population-based Analysis of Incidence and Survival. Clin Lymphoma Myeloma Leuk. 2017; 17(4): 201–206, doi: 10.1016/j.clml.2017.02.003, indexed in Pubmed: 28395812.
13. NCCN Guidelines® Updates: T-Cell Lymphomas. Journal of the National Comprehensive Cancer Network. 2022; 20(3), doi: 10.6004/jnccn.2022.203glup.
14. d'Amore F, Gaulard P, Trümper L, et al. ESMO Guidelines Committee. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015; 26 Suppl 5: v108–v115, doi: 10.1093/annonc/mdv201, indexed in Pubmed: 26314772.
15. Furqan F, Ahn KW, Chen Y, et al. Allogeneic haematopoietic cell transplant in patients with relapsed/refractory anaplastic large cell lymphoma. Br J Haematol. 2023; 200(1): 54–63, doi: 10.1111/bjh.18467, indexed in Pubmed: 36120837.
16. Ishizawa K, Yanai T. Hematopoietic Stem Cell Transplantation and Brentuximab Vedotin for Patients with Relapsed or Refractory Hodgkin Lymphoma and Systemic Anaplastic Large-Cell Lymphoma. Adv Ther. 2019; 36(10): 2679–2696, doi: 10.1007/s12325-019-01046-w, indexed in Pubmed: 31392578.
17. 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-z, indexed in Pubmed: 29516333.
18. Schönberger S, van Beekum C, Götz B, et al. Brentuximab vedotin exerts profound antiproliferative and pro-apoptotic efficacy in CD30-positive as well as cocultured CD30-negative germ cell tumour cell lines. J Cell Mol Med. 2018; 22(1): 568–575, doi: 10.1111/jcmm.13344, indexed in Pubmed: 28941150.
19. Lobastova L, Lettau M, Babatz F, et al. CD30-Positive Extracellular Vesicles Enable the Targeting of CD30-Negative DLBCL Cells by the CD30 Antibody-Drug Conjugate Brentuximab Vedotin. Front Cell Dev Biol. 2021; 9: 698503, doi: 10.3389/fcell.2021.698503, indexed in Pubmed: 34395429.
20. 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, indexed in Pubmed: 28974506.
21. Hsu JC, Jaminion F, Guerini E, et al. Pharmacometric analyses of alectinib to facilitate approval of the optimal dose for the first-line treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer. CPT Pharmacometrics Syst Pharmacol. 2021; 10(11): 1357–1370, doi: 10.1002/psp4.12702, indexed in Pubmed: 34547184.
22. Fukano R, Mori T, Sekimizu M, et al. Alectinib for relapsed or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: An open-label phase II trial. Cancer Sci. 2020; 111(12): 4540–4547, doi: 10.1111/cas.14671, indexed in Pubmed: 33010107.
23. Tomasini P, Egea J, Souquet-Bressand M, et al. Alectinib in the treatment of ALK-positive metastatic non-small cell lung cancer: clinical trial evidence and experience with a focus on brain metastases. Ther Adv Respir Dis. 2019; 13: 1753466619831906, doi: 10.1177/1753466619831906, indexed in Pubmed: 30786826.
24. Bernabé-Caro R, Garrido P, García-Campelo R, et al. Alectinib after failure to crizotinib in patients with ALK-positive non-small cell lung cancer: results from the Spanish early access program. Oncotarget. 2022; 13: 812–827, doi: 10.18632/oncotarget.28244, indexed in Pubmed: 35720977.

25. Greengard E, Mosse YP, Liu X, et al. Safety, tolerability and pharmacokinetics of crizotinib in combination with cytotoxic chemotherapy for pediatric patients with refractory solid tumors or anaplastic large cell lymphoma (ALCL): a Children's Oncology Group phase 1 consortium study (ADVL1212). Cancer Chemother Pharmacol. 2020; 86(6): 829–840, doi: 10.1007/s00280-020-04171-4, indexed in Pubmed: 33095287.
26. Zou Z, Hao X, Zhang C, et al. Clinical outcome, long-term survival and tolerability of sequential therapy of first-line crizotinib followed by alectinib in advanced ALK+NSCLC: A multicenter retrospective analysis in China. Thorac Cancer. 2022; 13(1): 107–116, doi: 10.1111/1759-7714.14232, indexed in Pubmed: 34851035.
27. Heigener DF, Reck M. Crizotinib. Recent Results Cancer Res. 2018; 211: 57–65, doi: 10.1007/978-3-319-91442-8_4, indexed in Pubmed: 30069759.
28. Mossé YP, Voss SD, Lim MS, et al. Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. J Clin Oncol. 2017; 35(28): 3215–3221, doi: 10.1200/JCO.2017.73.4830, indexed in Pubmed: 28787259.
29. Balis FM, Thompson PA, Mosse YP, et al. First-dose and steady-state pharmacokinetics of orally administered crizotinib in children with solid tumors: a report on ADVL0912 from the Children's Oncology Group Phase 1/Pilot Consortium. Cancer Chemother Pharmacol. 2017; 79(1): 181–187, doi: 10.1007/s00280-016-3220-6, indexed in Pubmed: 28032129.
30. Lowe EJ, Reilly AF, Lim MS, et al. Crizotinib in Combination With Chemotherapy for Pediatric Patients With ALK+ Anaplastic Large-Cell Lymphoma: The Results of Children's Oncology Group Trial ANHL12P1. J Clin Oncol. 2023; 41(11): 2043–2053, doi: 10.1200/JCO.22.00272, indexed in Pubmed: 36534942.