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Diagnosis and management of ALK-positive anaplastic large cell lymphoma in children and adolescents

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ABSTRACT

Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) is a CD30-positive T cell lymphoma characterized by signalling from constitutively activated ALK fusion proteins. Most children and adolescents present in advanced stages, often with extranodal disease and B symptoms. The current front-line therapy standard of six cycles polychemotherapy reaches an event-free survival of 70%. The strongest independent prognostic factors are minimal disseminated disease and early minimal residual disease. At relapse, ALK-inhibitors, Brentuximab Vedotin, Vinblastine, or second line chemotherapy are effective re-inductions. Survival at relapse exceeds 60–70% with consolidation according to the time of relapse (Vinblastine monotherapy or allogeneic hematopoietic stem cell transplantation) so that the overall survival reaches 95%. It needs to be shown whether check-point inhibitors or long-term ALK-inhibition may substitute for transplantation. The future necessitates international cooperative trials testing whether a shift of paradigm to a chemotherapy-free regimen can cure ALK-positive ALCL.

1. Introduction

1.1. Case vignette

A 9-year-old boy presented with fever, lymphadenopathy, lung nodules and skin lesions. ALK-positive anaplastic large cell lymphoma (ALCL) was diagnosed from a skin biopsy. He showed minimal disease dissemination in his peripheral blood which persisted after the first course chemotherapy. Two months after treatment with 6 courses of polychemotherapy according to ALCL99 he suffers a relapse. A second remission was obtained by an ALK inhibitor. Currently, allogeneic hematopoietic stem cell transplantation (SCT) for consolidation is discussed by the treating physicians and the family.

This review focusses on the diagnosis and treatment of ALK-positive anaplastic large cell lymphoma in children and adolescents.

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1.2. History and classification

ALCL was first described in 1985 as a CD30-positive mature T cell lymphoma [1]. ALCL is a rare disease with about 10–15% of all childhood and adolescent NHL cases and an incidence of about 1.2/10^6/year [2,3]. In children and adolescents, about 95% of cases are ALK-positive ALCL [4].

The molecular basis and clinical characteristics of ALK-positive ALCL were described in the early 1990s. During the following years the molecular pathogenesis was unravelled [5–7], the ALK1-antibody detected which facilitated diagnostics, and the clinical characteristics described in national cohort studies [8–10]. In the 2000s the role of immunology in tumour biology and control was described [11], targeted therapeutics developed [12,13] and multinational clinical trials were performed [4,12–15]. All this not only led to the implementation of ALK-positive as a separate entity in the WHO classification [16], but also to an array of successful early clinical trials [17–21] testing targeted drugs during the last 10 years. These rapid developments form the basis for a future outlook on chemotherapy-free therapeutic strategies.

2. Pathogenesis, pathology, clinical presentation, diagnosis and staging

2.1. Molecular pathogenesis and biology

The *nucleophosmin-1 (NPM1):: anaplastic lymphoma kinase (ALK)* fusion from the t(2; 5) translocation was identified as the driver for tumorigenesis in ALCL by Morris and colleagues in 1994 [5]. The constitutively activated ALK initiates multiple signalling pathways leading to proliferation, inhibition of apoptosis and immune escape [22]. Oncogenic signalling pathways activated by ALK include JAK/STAT [23,24], RAS/MAPK, PI3K/AKT [25] and PLC-ɣ.

Variant ALK-partner genes are detected in about 10% of cases and include TPM3, ATIC, CTLC, MYH9 among others [26,27]. NPM1-ALK, but not the variant fusion proteins are expressed in the nucleus and not only in the cytoplasm [27].

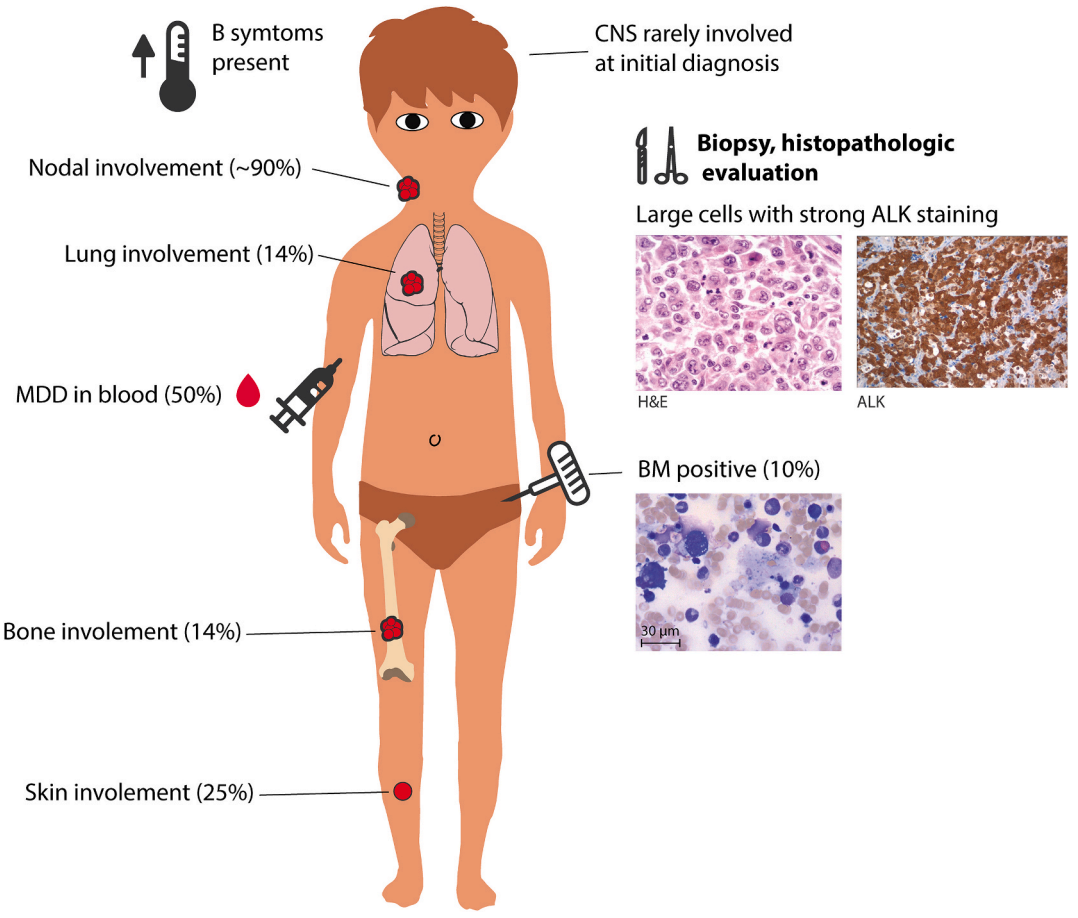

Fig. 1. Clinical presentation and pathology of ALK-positive ALCL in children and adolescents.

2.2. Pathology

ALCL are characterized by infiltration of variable amounts of so-called CD30-positive "hallmark" cells which typically show abnormal horseshoe-shaped nuclei [28]. The WHO classification defines five distinct patterns: the common pattern (65% of cases) characterized by large anaplastic cells, a small cell pattern (6% of cases), a lymphohistiocytic pattern with small lymphoma cells and histiocytic infiltration (9%), a rare Hodgkin-like pattern, and the composite pattern with characteristics of two or more of the above-mentioned patterns (24%) [29].

Besides CD30 and ALK, the tumour cells are usually positive for CD2, CD4, CD25, cytotoxic markers like perforin and granzyme B, and often for CD8, while CD3 is absent in more than 75% of cases [30].

2.3. Clinical presentation

Patients usually present with an advanced lymphoma (stage III/IV in 71%), often with involvement of the peripheral lymph nodes (90%), mediastinum (45%), skin (26%), bone (14%), soft tissue (10%), and the lung (14%) (see Fig. 1) [8–10,31–36]. Initial CNS involvement is uncommon. A leukemic presentation is rare [37]. The presence of B symptoms, observed in 55% of patients along with extranodal presentations in 60% extends the list of differential diagnoses, which includes soft-tissue sarcoma and inflammatory diseases. Occasionally, patients present with secondary haemophagocytic lymphohistiocytosis.

2.4. Diagnosis and staging

The diagnostic workup in patients with suspected ALCL includes a biopsy of sufficient size, minimal disseminated disease (MDD) evaluation in blood, bone marrow aspirates, and lumbar puncture. Initial imaging includes at minimum chest x-rays and abdominal and cervical ultrasound. Imaging of involved regions, thoracic and cervical lymph node areas, and abdomen with magnetic resonance imaging (MRI) or computed tomography (CT) supplemented or not with FDG-PET is a useful staging-procedure. Cranial or spinal MRI are indicated in cases of neurological symptoms. The presence of unequivocal blasts in the bone marrow or craniospinal fluid should be considered as involvement of the respective organ, which occurs in about 10–15% and less than 5% of patients, respectively [4].

The current staging system, the Revised International Pediatric Non-Hodgkin-Lymphoma Staging system [38] was introduced as an

Table 1
Clinical trials for ALCL in children and adolescents and outcome.

Protocol	**Study group (period of the study)**	Treatment strategy	**Treatment duration**	Nb of pts	**2–5 y EFS (95% CI)**	**2–5 y OS (95%CI)**	
Front-line treatment							
HM86-89	SCFE	B-cell regimen + short maintenance	8 m	82	66%	83%	[10]
NHL-BFM 90	BFM (1990–1995)	B-cell regimen (BFM)	4.5 m	89	76%	n.a.	[31]
NHL 9000 & 9602	UKCCSG (1990–98)	B-cell regimen (LMB)	4 .5 m	72	59%	65%	[32]
LNH92	AIEOP (1993–97)	T-cell regimen	24 m	34	65%	85%	[34]
POG9315	POG (1994–2000)	APO + randomization of HDMTX & HDAra-C	12 m	86	72%	88%	[51]
CCSG5941	CCSG (1996–2001)	Compressed T-cell regimen	11 m	86	68%	80%	[35]
ALCL99	EICNHL (1999–2006)	B-cell regimen (BFM-B) + randomization of vinblastine	4–12 m	352	73%	92%	[73]
ANHL0131	COG (2004–08)	APO* + randomization of vinblastine	12 m	125	VCR: 74% (95%CI, 61–84%) VBL: 79% (95% CI, 65–87%)	84% (69–92%) 86% (73–93%)	[94]
ANHL 12P1	COG (2013–2019)	Randomization ALCL99+BV vs. ALCL99+Crizotinib	4–5 m	BV: 68 Crizo: 66	79.1% (95%CI: 67–87) 76.8% (95% CI: 68–88)	97.0% (95% CI: 88–99) 95.2% (95% CI: 85–98)	[58, 59]
Second-line treatment							
ALCL-Relapse	EICNHL (2014–2014)	Stratification by time of relapse + CD3-expression	4–24 m	105	53 ± 5% Very early (allo SCT): 41% CD3 pos (allo SCT): 62% CD3 neg (auto SCT): 44% Late CD3 neg (VBL): 81%	78 ± 4% 59% 73% 78% 90%	[15]

extension of the St. Jude's [39].

2.5. Minimal disseminated disease (MDD) and minimal residual disease (MRD)

MDD defined as detection of ALK fusion RNA in peripheral blood and/or bone marrow cells, is found in 47–63% of ALCL patients [40–43]. MDD in blood and bone marrow correlate, with a higher sensitivity in blood [44]. MDD as well as early minimal residual disease (MRD) in paediatric ALCL are validated prognostic factors (see below and Table 2). With established quality-controlled investigation and further improvement of the techniques (e.g., by digital PCR [44]), MDD and MRD will likely inform future prospective trials.

2.6. Immunology

Antibodies against ALK [45] and T-cell responses [46,47] to ALK have been detected in patients with ALK-positive ALCL, both at diagnosis and during remission with a significant inverse correlation between ALK-antibody titres and the incidence of relapses [42].

Pediatric ALCL patients are characterized by marked cytokine elevations in their peripheral blood [48,49]. ALK-positive ALCL cells

Table 2
Prognostic factors in children and adolescents with ALK-positive anaplastic large cell lymphoma (ALCL).

Marker	Definition of risk patients	Percentage of patients with risk factor	EFS/PFS of high-risk patients	Advantages	Disadvantages	Validated in new cohort	RF in multivariate analysis?	References
clinical risk factors	mediastinum, lung, liver, spleen, skin	60–65%	~60%	simple, readily available	no VHR, no LR	No	No	[68]
histological subtype	SC/LH components ("not common")	35%	~50%	paraffin, available from all patients	no VHR, no LR, interobserver variability	Yes	Yes	[29,36]
qualitative MDD (RT-PCR for NPM-ALK in PB/BM)	positive versus negative	50–60%	~50%	simple, easy QC, standardized	no VHR, no LR	Yes	Yes	[36,40–42,44,70,95]
MRD before course 2 (RT-PCR)	positive versus negative	20–25%	20%	simple, easy QC, standardized	dependent on ALCL99-therapy	Yes	n.a.	[43,70,95]
quantitative MDD (RQ-PCR for NPM-ALK, control ABL)	>10 copies NPM-ALK/10^4 copies ABL	25–35%	30–40%	VHR at diagnosis	Not standardized, difficult to transfer, QC, expensive, no LR	Yes	n.a.	[44,58,69,70]
quantitative MDD (dPCR for NPM-ALK, control ABL)	>30–50 copies NPM-ALK/10^4 copies ABL	25%	35–40%	HR or VHR at diagnosis depended on cut-off, QC possible, transfer possible	QC to be implemented, expensive	Yes	Yes	[44,95,96]
ALK antibody titre	≤1/750	30%	40%		no LR, no VHR, labour-intensive, subjective, assay not standardized	Yes	yes	[42,71,72]
Combination of risk factors								
qualitative MDD + histological subtype		no RF 30% 1 RF 50% 2 RF 20%	86% 75% 40%	LR + VHR	interobserver variability	No	Yes	[36]
qualitative MDD + ALK antibody titre		no RF 30% 1 RF 50% 2 RF 20%	>90% 70% 30%	LR + VHR, measurable from 1 EDTA blood sample	Antibody assay not standardized	no	Yes	[42]
qualitative MDD + MRD		No RF 45% 1 RF 30% 2 RF 25%	82% 70% <20%	One method, standardized, easy QC available		yes	yes	[43,70,95]

MDD: minimal disseminated disease, MRD: minimal residual disease, EFS: event-free survival, PB: peripheral blood, BM: bone marrow, RF: risk factor, HR: high relapse risk, VHR: very high relapse risk, LR: low relapse risk, QC: quality control.

strongly express the immunosuppressive PD-L1 induced by NPM1-ALK -signaling [22]. Moreover, vaccination using ALK cDNA has been reported to induce potent and long-lasting protection from local and systemic lymphoma growth in a murine model [50].

3. Current front-line therapy, prognostic factors and outcome

Given the rarity of ALCL in children as well as in adults, very few comparative randomized trials are available. In the late 1990s, several national groups reported results obtained in small series of patients treated with diverse first-line chemotherapy regimens in term of number of drugs, cumulative doses, and duration of treatment. Even though therapeutic approaches were quite different, event-free survival (EFS) rates were very similar in all these reports ranging 65–75% (Table 1) [10,31,32,34,35,51].

The European Intergroup for childhood non-Hodgkin Lymphoma (EICNHL) established guidelines for the treatment of ALCL in children and adolescents and evaluated their efficacy in the ALCL99 trial run in Europe and Japan between 1999 and 2006. Except for few patients belonging to specific risk groups such as isolated skin lesion, stage 1 completely resected and patients with initial CNS involvement, all patients received a chemotherapy regimen combining a pre-phase with dexamethasone, low dose cyclophosphamide and a triple intrathecal injection followed by 6 alternating courses A (dexamethasone, high-dose methotrexate, ifosfamide, cytarabine, etoposide) and B (dexamethasone, high-dose methotrexate, cyclophosphamide, doxorubicin) over a period of 4–5 months.

With this regimen, most patients achieve complete remission, but 5% of the patients suffered from an early progression during chemotherapy and 25% experience a relapse mostly in the first months following the end of treatment. Despite high-dose methotrexate, a few patients experience relapses with CNS involvement. The 5-year cumulative risk of CNS relapses has been estimated to be around 5% [52].

The 2-year EFS and overall survival (OS) rates were 74% and 92.5%, respectively, in the large series of more than 350 patients included in the ALCL99 trial [4]. These results stayed stable over time with a 10-year EFS and OS of 70% and 90%, respectively [36].

Acute toxicity is quite significant with 1% of treatment related deaths, grade 4 neutropenia reported in 60% of the courses, grade 3–4 mucositis in 15% and significant weight gain in 20% of patients [53]. Long-term toxicity is expected to be limited given the low cumulative doses of agents associated with long-term side effects such as anthracyclines and alkylating agents.

The ALCL99 trial also defined the therapeutic strategy for rare subgroups. The six patients with an isolated skin lesion of an ALK-positive ALCL included in the trial were cured, five of them with surgery and/or local radiotherapy [54]. The outcome of patients with completely resected stage 1 also was excellent, with no event among six patients treated with only three courses of chemotherapy [55]. ALCL99 guidelines for patients with CNS involvement recommended a chemotherapy including high-dose methotrexate and high-dose cytarabine derived from protocols designed for mature B-cell lymphoma with CNS involvement and a cranial radiotherapy. The 5-year EFS of patients included in the ALCL99 trial was only 50% underlining the need for new strategies [56]. The availability of ALK-inhibitors with good CNS penetration now offers new therapeutic perspectives for these patients [57].

Given the high efficacy of vinblastine for relapses, one of the aims of ALCL99 was to evaluate the impact of adding vinblastine during induction and as a maintenance a total duration of 12 months for clinically defined high-risk patients. In this trial including 217 patients, we could show that the addition of vinblastine significantly delayed the occurrence of relapses after the end of treatment but did not reduce the overall risk of failure. The Children's Oncology Group (COG) also examined whether a maintenance substituting 3-weekly vincristine by weekly vinblastine in the standard APO (doxorubicin, prednisone, vincristine, methotrexate, 6-mercaptopurine) regimen would result in superior EFS in the trial ANHL0131 including 125 patients. No difference in failure rate was observed between patients treated with vincristine and those with vinblastine (EFS 74% vs 79%).

The most recent trial ANHL12P1 of the COG (NCT01979536) aimed at assessing tolerance and efficacy adding brentuximab vedotin (BV) or crizotinib to ALCL99 chemotherapy in newly diagnosed children and adolescents with ALK-positive ALCL. Patients were randomized at diagnosis to receive either crizotinib or BV. Sixty-eight patients were enrolled in the BV arm. The addition of BV to standard chemotherapy was not associated with any significant increase in toxicity and the 2-year-EFS (79.1%, 95%CI: 67.2–87.1) and OS (97.0%, 95% CI: 88.1–99.2) compare favourably with results obtained with conventional chemotherapy alone [58]. Of note only one patient (1.5%) experienced a relapse during treatment. While 2-year EFS (76.8%, 95% CI: 68.5–88.1) and OS (95.2%, 95% CI: 85.7–98.4) of the 66 patients enrolled in the crizotinib-arm were comparable to the one of the BV-arm, the addition of crizotinib to ALCL99 chemotherapy was associated with an unexpected increased risk for thromboembolic events leading to two periods of temporary closure of the trial [59].

A current EICNHL single-arm trial tests the efficacy of 2-year weekly vinblastine monotherapy for children with stage I-III MDD-negative ALCL (EudraCT: 2017-002935-40).

Adults are generally treated according to protocols designed for diffuse large-cell lymphoma mostly with anthracycline-containing regimens [60–65]. Results are very similar to those obtained in children with a 5-year EFS and OS of around 65–80% and 70–90%, respectively, in ALK-positive ALCL. Although there have been no randomized studies, recent studies suggest that the addition of etoposide to CHOP reduces the risk of failure in ALK-positive ALCL [66].

The role of the addition of BV to standard chemotherapy was studied in the ECHELON-2 trial (No. NCT01777152), a randomized trial comparing CHOP to BV-CHP in which vincristine is replaced by BV in patients with previously untreated CD30-positive peripheral T cell lymphoma. Treatment with BV-CHP led to a 29% reduction in the risk of a PFS event and a 34% lower risk of death. The group of patients with ALK-positive ALCL (98 patients randomized) was the group who had the highest benefit [67].

3.1. *Prognostic factors*

Several factors have been shown to be associated with a higher risk of treatment failure in children (Table 2), i.e. clinical factors

such as presence of mediastinal disease, visceral (defined as lung, liver, or spleen), or cutaneous involvement [68], high-risk histologic subtype defined by the presence of a lympho-histiocytic or small cell component [29], positive MDD in blood or bone marrow [40,41,43,58,69] studied either by qualitative PCR, quantitative PCR or digital PCR with different cut-offs, and detection of MRD in the blood after the first course of chemotherapy [43,70], low anti-ALK antibody titres at diagnosis [42,71,72].

Due to the need for improved reproducibility of the assessment only MDD and MRD using qualitative PCR are currently used for risk stratification of treatment in ALK-positive ALCL patients defining 3 risk groups: a standard risk group with negative MDD, a high-risk group with positive MDD but negative MRD after the first course A1 and the very high-risk group with positive MRD after course A1. Work in progress should allow very soon to have reproducible results for quantitative MDD/MRD as well as antibody levels.

4. Therapy, prognostic factors, and outcome at relapse

Almost one third of children and adolescents with ALK-positive ALCL relapse after current standard polychemotherapy. A second remission can be obtained in more than 80% of patients by re-inductions as different as polychemotherapy, vinblastine monotherapy, BV or ALK-inhibitors [15,18–21,73,74]. Retrospective analyses from the 1990s already showed a survival of more than 50% for children with relapsed ALCL and that these children even have a chance to survive after several relapses [74–76]. However, consolidations as different as vinblastine monotherapy, autologous or allogeneic SCT were effective [74–77]. The time of relapse turned out as major independent risk factor for further relapse and survival besides bone marrow and CNS-involvement [74,75]. Children with progression during initial therapy had a particularly poor prognosis and survivors were observed only after allogeneic SCT [74]. Children with a late relapse (>1 year from initial diagnosis) fared well with almost any consolidation [73–76]. In the NHL-BFM-group analysis, patients with CD3-positive ALCL had a high risk of failure after autologous SCT [74]. Based on these observations, the EICNHL performed a prospective stratified clinical trial for children with a first relapse of an ALCL between 2004 and 2014. Children with progression during front-line therapy and those with relapse of a CD3-positive ALCL were scheduled for intensive re-induction-chemotherapy followed by consolidation with an allogeneic SCT after total body irradiation (TBI)-based conditioning. Those patients reached a 5-year EFS and survival of 59% and 73%, respectively, which met the pre-specified superiority to historical data obtained with mainly autologous SCT [15]. An important observation was the high rate of further progression during re-induction before SCT of 50% among very high-risk patients, suggesting that new targeted therapies might be more appropriate for re-induction. Patients with an early relapse of a CD3-negative ALCL were scheduled to receive consolidation by autologous SCT after high-dose BEAM. Unexpectedly, those patients also had a relatively high risk of further progression before SCT (25%) and EFS after autologous SCT was only 30%. Most all of these children could be rescued, so that the survival reached 78%. Almost one third of patients with an early relapse did not receive the intended autologous, but an allogeneic SCT with equal high efficacy (EFS 78%) as compared to children with a CD3-positive relapse after therapy (EFS 65%). The treatment arm with autologous SCT had been closed early, and five further children with an early relapse received consolidation by 24-months vinblastine. Although none progressed during therapy, all five patients relapsed again early after the end of therapy. Taken together, these observations suggest that neither high-dose therapy nor long-term vinblastine are effective consolidation for early relapsed ALCL, and that these patients might also benefit from non-chemotherapy re-induction. Therefore, current consolidation for early relapsed ALCL outside of clinical trials should be an allogeneic SCT. Children with a late relapse (>1 year from diagnosis) of a CD3-negative ALCL had a 5-year EFS of more than 80% with 24-months weekly vinblastine therapy. So far, there is no explanation for the extraordinary efficacy of vinblastine for the treatment of late but not for early ALCL relapses.

Despite not being a randomized trial and several patients consolidated differently from the protocol-recommendations, the results allowed several important conclusions regarding re-induction and consolidation for relapsed ALCL. In addition, the time of relapse was confirmed as major risk factor while CD3-expression likely does not distinguish further. However, the re-induction chemotherapy as performed in the ALCL-Relapse study for all, but late relapses can no longer be regarded as state of the art.

Due to the described high risk of further progression during re-induction therapy and the toxicity of the intensive chemotherapy, new options for remission induction are needed. The single agent response rate for BV exceeds 50% at relapse and the ALK-inhibitors crizotinib, ceritinib and alectinib reach remissions in 60–90% of relapsed ALK-positive ALCL in early clinical trials [18–21]. In order to reach a stable remission with limited toxicity before a planned allogeneic SCT in progressive or early relapsed ALCL, re-induction by an ALK-inhibitor or BV can be recommended. Given the risk of CNS-progression especially in high-risk relapse patients, a CNS-penetrable ALK-inhibitor should be selected, while Crizotinib and BV need to be combined with CNS-prophylaxes [78]. Combination therapy of crizotinib with vinblastine for re-induction of very high-risk relapse patients was effective, however, associated with severe unexpected toxicity so that this combination can no longer be recommended [79].

Conditioning by TBI is associated with a high risk of secondary tumours and late, especially endocrine effects. Although there are several preclinical hints for an existing graft-versus-ALCL effect and some clinical experiences with reduced-intensity or TBI-free conditioning regimen [11,80,81], more data are needed to allow for a general recommendation to substitute TBI.

Less than 5% of ALCL-patients experience a CNS-relapse. Their outcome with intensive CNS-directed chemotherapy and SCT historically has been poor with survival rates between 10% and more recently 50% [52,74]. Due to poor CNS-penetration, neither BV nor crizotinib or vinblastine are effective. A recent report shows a very high and persisting complete response rate in 9 of 10 children with CNS-relapse by second or third generation ALK-inhibitors [57].

In summary, weekly vinblastine monotherapy for two years can currently be regarded as standard therapy for children with a late relapse (>7 months after end of front-line therapy) of an ALK-positive ALCL. Re-induction by CNS-penetrable ALK-inhibitors is currently under investigation (*NCT04925609*). Outside of a clinical trial, crizotinib or BV augmented by CNS-prophylaxes seem reasonable choices. Whether cure can be reached without an allogeneic SCT for consolidation by e.g. long-term ALK-inhibitor-therapy

or PD1-inhibitors is currently studied in early phase clinical trials (*NCT03703050,* NCT04925609).

5. Targeted therapeutic options and future developments

Based on the detection and understanding of the molecular basis of ALK-positive ALCL, multiple targeted therapeutic options have been developed and already tested in early clinical trials.

5.1. Brentuximab vedotin (BV)

BV is an anti-CD30 antibody conjugated to the anti-microtubule agent monomethyl auristatine E. It was tested early on not only in patients with relapsed Hodgkin lymphoma but also in adult ALCL-patients. Overall response and CR rates in ALK-positive ALCL were 81% and 69%, respectively. These results led to the approval of BV by the FDA and EMA for the treatment of relapsed ALCL in adults [82]. Mainly due to its peripheral neurologic toxicity in adult patients, long-term treatment may be difficult [83], so that this drug mostly is employed as a bridge to transplant. This safety issue was less prominent in the paediatric population in a single agent phase 2 study [19]. As described above, the combination of BV with standard chemotherapy has already been studied in adults and in children with very promising results [58,67]. For adults, BV-CHP could be established as one new standard. The combination of BV with ALCL99-type chemotherapy will be considered as the new standard of care for front-line treatment in children with ALCL treated in COG centres.

5.2. ALK inhibitors

ALK-positive ALCL is the key-disease dependent on activated ALK-signalling. A phase 1–2 trial of crizotinib performed by the COG included children with refractory or relapsed ALK-positive ALCL. Single agent therapy achieved a remission in almost 90% of patients in this trial as well as in adult series [12,17,18]. Only few progressions during crizotinib therapy have been described so far, almost all occurring within 2–5 months of treatment initiation.

Next generation ALK-inhibitors are more potent and with sufficient CNS-penetration in contrast to crizotinib [57,78] have been developed and investigated in children with relapsed ALK-positive ALCL. Fischer and colleagues conducted a phase 1–2 trial testing ceritinib in patients with ALK-rearranged paediatric malignancies (12 patients with ALK-positive ALCL). An overall response rate of 75% was reported for ALCL-patients [21]. A Japanese phase 1 trial of alectinib in patients with ALK-positive ALCL included four children. Ten patients received alectinib, six of them achieved CR and two a PR, resulting in an overall response rate of 80% [20]. A phase 1–2 trial evaluating the safety and efficacy of the second generation ALK-inhibitor brigatinib as monotherapy is currently recruiting patients with refractory and relapsed ALK-positive ALCL (NCT04925609). The activity of the 3rd generation ALK-inhibitor lorlatinib has not been explored yet in children with ALK-positive ALCL, but a trial including adult patients is open for accrual in Italy (NCT03505554).

Whether treatment with next generation ALK-inhibitors can be curative in relapsed ALCL is currently explored in the BrigaPED trial. Abrupt relapses following discontinuation of crizotinib have been described [84]. In light of sometimes long duration of therapy, long-term safety of this class of drugs has to be studied further. Especially in children concerns regarding e.g. neuropsychological complications, weight gain, growth and fertility observed in adults treated with alectinib and lorlatinib and also in children with neuroblastoma ask for caution [85–87].

Furthermore, studies testing combinations of second generation ALK-inhibitors with chemotherapy are needed.

5.3. Checkpoint blockade

Based on the universal PD-L1 expression and the role of the immune system in the control of ALK-positive ALCL, anti-PD1-therapy could be effective. Case-reports demonstrated prolonged responses of refractory ALK-positive ALCL to PD1-inhibitors [88–90]. Based on these observations and the good safety profile of PD1 inhibitors the NIVOALCL trial (NCT03703050) tests nivolumab monotherapy either in case of progression after targeted therapies or as consolidative immunotherapy in children and adults with refractory or relapsed ALCL.

5.4. CAR-T cells

Lastly, with the development of chimeric antigen receptor (CAR) T-cells against CD30, the potential therapeutic arsenal available for the management of ALCL has been further expanded. Initially developed for the treatment of patients with relapsed/refractory Hodgkin lymphoma two patients with relapsed ALCL were enrolled in a phase 1 study with CD30 CAR-T cells one of whom reached a prolonged CR [91–93]. Several trials testing these CD30 CAR T-cells in CD30-positive lymphoma including ALCL are currently recruiting (NCT03049449, NCT03383965, NCT04008394, NCT05208853, NCT02274584, NCT03602157, NCT04526834).

In summary, targeted agents, mainly developed for other ALK-positive or CD30-positive malignancies and checkpoint inhibitors have opened new treatment options for patients with ALK-positive ALCL. Given the efficacy and limited toxicity compared to poly-chemotherapy, these treatments are ready to be tested front-line to increase cure rates with decreased treatment burden. Furthermore, even chemotherapy-free regimens can be envisioned and should be clinically tested. However, despite the remarkable activity of these agents in monotherapy and the promise of future combinations, long-term tolerance of such molecules and combinations need to be

assessed in the paediatric population.

6. Summary

ALK-positive ALCL often present with B-symptoms and extranodal disease. Confirmation of diagnosis and staging includes CD30- and ALK-staining, appropriate imaging and MDD evaluation.

The current front-line therapy standard for children with ALK-positive ALCL consists of six courses of ALCL99-type chemotherapy, possibly augmented by BV. Therapy is stratified according to MDD and MRD in current clinical trials. Responses to ALK-inhibitors, BV and check-point-inhibitors are excellent. However, their role in front-line therapy has not been established. The main future front-line questions are whether a "chemotherapy-free" regimen can cure children with ALK-positive ALCL. The development of studies testing this shift of paradigm are under way.

The current approaches for relapsed ALCL are stratified according to the time of relapse, CNS-and bone-marrow involvement. Children with a late relapse (>7 months after initial therapy) can be treated with two-year weekly vinblastine monotherapy while those with an early relapse within in few months after the end of front-line therapy should receive re-induction by ALK-inhibitors or BV with CNS-prophylaxis followed by a consolidation with an allogeneic SCT. Whether long-term ALK-inhibitor-therapy or check-point-inhibitors can substitute for an allogeneic SCT is under investigation.

Given the role of the immune-response to ALK in the final control of ALCL, further immunotherapies like vaccination against ALK might be developed and tested in future.

7. Practice points

- Front-line therapy of children with ALK-positive anaplastic large cell lymphoma consists of six courses of ALCL99-type chemotherapy, possibly augmented by brentuximab vedotin.
- High- and very high-risk patients can be detected by measurement of minimal disseminated and early minimal residual disease in blood. These standard of care parameters are used for patient stratification in clinical trials.
- Weekly vinblastine monotherapy for two years can currently be regarded as standard therapy for children with a late relapse (>7 months after end of front-line therapy) of an ALK-positive ALCL.
- Re-induction by ALK-inhibitors or brentuximab vedotin augmented by CNS-prophylaxes in case of crizotinib and brentuximab vedotin followed by consolidation with an allogeneic SCT or inclusion in a trial of long-term therapy is indicated for children with progressive disease or early relapse.

8. Research agenda

- As 2-year weekly vinblastine reaches a 5-year EFS of 80% in late ALCL-relapses, this approach is currently tested front-line for standard-risk patients (MDD negative).
- Based on the efficacy of ALK-inhibitors and brentuximab vedotin for remission induction in relapsed ALK-positive ALCL, a combination of these drugs is planned to be tested front-line in order to investigate whether a chemotherapy-free regimen can cure children with ALK-positive ALCL.
- Checkpoint-inhibitors are already being tested in clinical studies for relapsed ALK-positive ALCL. They should be evaluated in combination with other agents effective in ALCL.
- Further development of immunotherapies and tools to measure the immune-response against ALK in clinical practice are needed.
- Understanding the mechanisms of treatment failure in ALK-positive ALCL forms an important research goal to enable development of individualized therapies in the future.

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, 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;66:848–58.
[2] Alessandri AJ, Pritchard SL, Schultz KR, Massing BG. A population-based study of pediatric anaplastic large cell lymphoma. Cancer 2002;94:1830–5.
[3] Erdmann FKP, Grabow D, Mainz Spix C. German childhood cancer registry - annual report 2019 (1980-2018), vol. 2020. Mainz, Germany: Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University; 2020.
[4] Brugieres L, Le Deley MC, Rosolen A, Williams D, Horibe K, Wrobel G, et al. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL Group. J Clin Oncol 2009;27:897–903.
[5] Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 1994;263:1281–4.
[6] Pulford K, Lamant L, Morris SW, Butler LH, Wood KM, Stroud D, et al. Detection of anaplastic lymphoma kinase (ALK) and nucleolar protein nucleophosmin (NPM)-ALK proteins in normal and neoplastic cells with the monoclonal antibody ALK1. Blood 1997;89:1394–404.
[7] Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. Nat Rev Cancer 2008;8:11–23.
[8] Reiter A, Schrappe M, Tiemann M, Parwaresch R, Zimmermann M, Yakisan E, et al. Successful treatment strategy for Ki-1 anaplastic large-cell lymphoma of childhood: a prospective analysis of 62 patients enrolled in three consecutive Berlin-Frankfurt-Munster group studies. J Clin Oncol 1994;12:899–908.

[9] Sandlund JT, Pui CH, Santana VM, Mahmoud H, Roberts WM, Morris S, et al. Clinical features and treatment outcome for children with CD30+ large-cell non-Hodgkin's lymphoma. J Clin Oncol 1994;12:895–8.
[10] Brugieres L, Deley MC, Pacquement H, Meguerian-Bedoyan Z, Terrier-Lacombe MJ, Robert A, et al. CD30(+) anaplastic large-cell lymphoma in children: analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology. Blood 1998;92:3591–8.
[11] Stadler S, Singh VK, Knorr F, Damm-Welk C, Woessmann W. Immune response against ALK in children with ALK-positive anaplastic large cell lymphoma. Cancers 2018;10.
[12] Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. N Engl J Med 2011;364:775–6.
[13] Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, 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;30:2190–6.
[14] Le Deley MC, Rosolen A, Williams DM, Horibe K, Wrobel G, Attarbaschi A, et al. Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. J Clin Oncol 2010;28:3987–93.
[15] Knorr F, Brugieres L, Pillon M, Zimmermann M, Ruf S, Attarbaschi A, et al. Stem cell transplantation and vinblastine monotherapy for relapsed pediatric anaplastic large cell lymphoma: results of the international, prospective ALCL-relapse trial. J Clin Oncol 2020;38:3999–4009.
[16] WcoTE Board. In: Cancer IAfRo, editor. WHO classification of tumours of haematopoietic and lymphoid tissues. 4h ed. Lyon (France): IARC; 2016.
[17] Mosse YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncol 2013;14:472–80.
[18] Mosse YP, Voss SD, Lim MS, Rolland D, Minard CG, Fox E, 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;35:3215–21.
[19] Locatelli F, Mauz-Koerholz C, Neville K, Llort A, Beishuizen A, Daw S, et al. Brentuximab vedotin for paediatric relapsed or refractory Hodgkin's lymphoma and anaplastic large-cell lymphoma: a multicentre, open-label, phase 1/2 study. Lancet Haematol 2018;5:e450–61.
[20] Fukano R, Mori T, Sekimizu M, Choi I, Kada A, Saito AM, et al. Alectinib for relapsed or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: an open-label phase II trial. Cancer Sci 2020;111:4540–7.
[21] Fischer M, Moreno L, Ziegler DS, Marshall LV, Zwaan CM, Irwin MS, et al. Ceritinib in paediatric patients with anaplastic lymphoma kinase-positive malignancies: an open-label, multicentre, phase 1, dose-escalation and dose-expansion study. Lancet Oncol 2021;22:1764–76.
[22] Marzec M, Zhang Q, Goradia A, Raghunath PN, Liu X, Paessler M, et al. Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1). Proc Natl Acad Sci U S A 2008;105:20852–7.
[23] Zhang Q, Raghunath PN, Xue L, Majewski M, Carpentieri DF, Odum N, et al. Multilevel dysregulation of STAT3 activation in anaplastic lymphoma kinase-positive T/null-cell lymphoma. J Immunol 2002;168:466–74.
[24] Zamo A, Chiarle R, Piva R, Howes J, Fan Y, Chilosi M, et al. Anaplastic lymphoma kinase (ALK) activates Stat3 and protects hematopoietic cells from cell death. Oncogene 2002;21:1038–47.
[25] Slupianek A, Nieborowska-Skorska M, Hoser G, Morrione A, Majewski M, Xue L, et al. Role of phosphatidylinositol 3-kinase-Akt pathway in nucleophosmin/anaplastic lymphoma kinase-mediated lymphomagenesis. Cancer Res 2001;61:2194–9.
[26] Perkins SL, Pickering D, Lowe EJ, Zwick D, Abromowitch M, Davenport G, et al. Childhood anaplastic large cell lymphoma has a high incidence of ALK gene rearrangement as determined by immunohistochemical staining and fluorescent in situ hybridisation: a genetic and pathological correlation. Br J Haematol 2005;131:624–7.
[27] Damm-Welk C, Klapper W, Oschlies I, Gesk S, Rottgers S, Bradtke J, et al. Distribution of NPM1-ALK and X-ALK fusion transcripts in paediatric anaplastic large cell lymphoma: a molecular-histological correlation. Br J Haematol 2009;146:306–9.
[28] Elenitoba-Johnson K, Ott G, Takeuchi K, Klapper W, Lamant L, d'Amore E, et al. Haematolymphoid tumours [Internet; beta version ahead of print] : [cited YYYY Mmm D]. In: WCoTE Board, editor. ALK-positive anaplastic large cell lymphoma. fifth ed., vol. 11. Lyon (France): International Agency for Research on Cancer; 2022. fifth ed., Available from: https://tumourclassificationiarcwhoint/chapters/63.
[29] Lamant L, McCarthy K, d'Amore E, Klapper W, Nakagawa A, Fraga M, et al. Prognostic impact of morphologic and phenotypic features of childhood ALK-positive anaplastic large-cell lymphoma: results of the ALCL99 study. J Clin Oncol 2011;29:4669–76.
[30] WcoTE Board. In: Cancer IAfRo, editor. Haematolymphoid tumours, beta version ahead of print. fifth ed. Lyon (France): IARC; 2022.
[31] Seidemann K, Tiemann M, Schrappe M, Yakisan E, Simonitsch I, Janka-Schaub G, et al. Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: a report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 2001;97:3699–706.
[32] Williams DM, Hobson R, Imeson J, Gerrard M, McCarthy K, Pinkerton CR. Anaplastic large cell lymphoma in childhood: analysis of 72 patients treated on the United Kingdom Children's Cancer Study Group chemotherapy regimens. Br J Haematol 2002;117:812–20.
[33] Mori T, Kiyokawa N, Shimada H, Miyauchi J, Fujimoto J. Anaplastic large cell lymphoma in Japanese children: retrospective analysis of 34 patients diagnosed at the National Research Institute for Child Health and Development. Br J Haematol 2003;121:94–6.
[34] Rosolen A, Pillon M, Garaventa A, Burnelli R, d'Amore ES, Giuliano M, et al. Anaplastic large cell lymphoma treated with a leukemia-like therapy: report of the Italian Association of Pediatric Hematology and Oncology (AIEOP) LNH-92 protocol. Cancer 2005;104:2133–40.
[35] Lowe EJ, Sposto R, Perkins SL, Gross TG, Finlay J, Zwick D, et al. Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents: final results of Children's Cancer Group Study 5941. Pediatr Blood Cancer 2009;52:335–9.
[36] Mussolin L, Le Deley M-C, Carraro E, Damm-Welk C, Attarbaschi A, Williams D, et al. Prognostic factors in childhood anaplastic large cell lymphoma: long term results of the international alcl99 trial. Cancers 2020;12:2747.
[37] Spiegel A, Paillard C, Ducassou S, Perel Y, Plantaz D, Strullu M, et al. Paediatric anaplastic large cell lymphoma with leukaemic presentation in children: a report of nine French cases. Br J Haematol 2014;165:545–51.
[38] Rosolen A, Perkins SL, Pinkerton CR, Guillerman RP, Sandlund JT, Patte C, et al. Revised international pediatric non-hodgkin lymphoma staging system. J Clin Oncol 2015;33:2112–8.
[39] Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol 1980;7:332–9.
[40] Mussolin L, Pillon M, d'Amore ES, Santoro N, Lombardi A, Fagioli F, et al. Prevalence and clinical implications of bone marrow involvement in pediatric anaplastic large cell lymphoma. Leukemia 2005;19:1643–7.
[41] Damm-Welk C, Busch K, Burkhardt B, Schieferstein J, Viehmann S, Oschlies I, et al. Prognostic significance of circulating tumor cells in bone marrow or peripheral blood as detected by qualitative and quantitative PCR in pediatric NPM-ALK-positive anaplastic large-cell lymphoma. Blood 2007;110:670–7.
[42] Mussolin L, Damm-Welk C, Pillon M, Zimmermann M, Franceschetto G, Pulford K, et al. Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis. Leukemia 2013;27:416–22.
[43] Rigaud C, Abbas R, Grand D, Minard-Colin V, Aladjidi N, Buchbinder N, et al. Should treatment of ALK-positive anaplastic large cell lymphoma be stratified according to minimal residual disease? Pediatr Blood Cancer 2021;68:e28982.
[44] Damm-Welk C, Kutscher N, Zimmermann M, Attarbaschi A, Schieferstein J, Knorr F, et al. Quantification of minimal disseminated disease by quantitative polymerase chain reaction and digital polymerase chain reaction for NPM-ALK as a prognostic factor in children with anaplastic large cell lymphoma. Haematologica 2020;105:2141–9.
[45] Pulford K, Falini B, Banham AH, Codrington D, Roberton H, Hatton C, et al. Immune response to the ALK oncogenic tyrosine kinase in patients with anaplastic large-cell lymphoma. Blood 2000;96:1605–7.
[46] Passoni L, Scardino A, Bertazzoli C, Gallo B, Coluccia AM, Lemonnier FA, et al. ALK as a novel lymphoma-associated tumor antigen: identification of 2 HLA-A2.1-restricted CD8+ T-cell epitopes. Blood 2002;99:2100–6.
[47] Singh VK, Werner S, Hackstein H, Lennerz V, Reiter A, Wolfel T, et al. Analysis of nucleophosmin-anaplastic lymphoma kinase (NPM-ALK)-reactive CD8(+) T cell responses in children with NPM-ALK(+) anaplastic large cell lymphoma. Clin Exp Immunol 2016;186:96–105.

[48] Mellgren K, Hedegaard CJ, Schmiegelow K, Muller K. Plasma cytokine profiles at diagnosis in pediatric patients with non-hodgkin lymphoma. J Pediatr Hematol Oncol 2012;34:271–5.
[49] Knörr F, Damm-Welk C, Ruf S, Singh VK, Zimmermann M, Reiter A, et al. Blood cytokine concentrations of pediatric anaplastic lymphoma kinase-positive anaplastic large cell lymphoma patients. Haematologica 2018;103:477–85.
[50] Chiarle R, Martinengo C, Mastini C, Ambrogio C, D'Escamard V, Forni G, et al. The anaplastic lymphoma kinase is an effective oncoantigen for lymphoma vaccination. Nat Med 2008;14:676–80.
[51] Laver JH, Kraveka JM, Hutchison RE, Chang M, Kepner J, Schwenn M, et al. Advanced-stage large-cell lymphoma in children and adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial. J Clin Oncol 2005;23:541–7.
[52] Del Baldo G, Abbas R, Woessmann W, Horibe K, Pillon M, Burke A, et al. Neuro-meningeal relapse in anaplastic large-cell lymphoma: incidence, risk factors and prognosis - a report from the European intergroup for childhood non-Hodgkin lymphoma. Br J Haematol 2021;192:1039–48.
[53] Wrobel G, Mauguen A, Rosolen A, Reiter A, Williams D, Horibe K, et al. Safety assessment of intensive induction therapy in childhood anaplastic large cell lymphoma: report of the ALCL99 randomised trial. Pediatr Blood Cancer 2011;56:1071–7.
[54] Oschlies I, Lisfeld J, Lamant L, Nakazawa A, d'Amore ES, Hansson U, et al. ALK-positive anaplastic large cell lymphoma limited to the skin: clinical, histopathological and molecular analysis of 6 pediatric cases. A report from the ALCL99 study. Haematologica 2013;98:50–6.
[55] Attarbaschi A, Mann G, Rosolen A, Williams D, Uyttebroeck A, Marky I, et al. Limited stage I disease is not necessarily indicative of an excellent prognosis in childhood anaplastic large cell lymphoma. Blood 2011;117:5616–9.
[56] Williams D, Mori T, Reiter A, Woessman W, Rosolen A, Wrobel G, et al. Central nervous system involvement in anaplastic large cell lymphoma in childhood: results from a multicentre European and Japanese study. Pediatr Blood Cancer 2013;60:E118–21.
[57] Rigaud C, Abbou S, Ducassou S, Simonin M, Le Mouel L, Pereira V, et al. Profound and sustained response with next-generation ALK inhibitors in patients with relapsed or progressive ALK-positive anaplastic large cell lymphoma with central nervous system involvement. Haematologica 2022;107:2255–60.
[58] Lowe EJ, Reilly AF, Lim MS, Gross TG, Saguilig L, Barkauskas DA, et al. Brentuximab vedotin in combination with chemotherapy for pediatric patients with ALK + ALCL: results of COG trial ANHL12P1. Blood 2021;137:3595–603.
[59] Lowe EJ, Reilly AF, Lim MS, Gross TG, Saguilig L, Barkauskas DA, 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 2022:JCO2200272. 0.
[60] Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peeters C, et al. ALK+ lymphoma: clinico-pathological findings and outcome. Blood 1999;93:2697–706.
[61] Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913–21.
[62] Suzuki R, Kagami Y, Takeuchi K, Kami M, Okamoto M, Ichinohasama R, 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.
[63] Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496–504.
[64] Schmitz N, Trumper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116:3418–25.
[65] Sibon D, Fournier M, Briere J, Lamant L, Haioun C, Coiffier B, 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;30:3939–46.
[66] Sibon D, Nguyen DP, Schmitz N, Suzuki R, Feldman AL, Gressin R, et al. ALK-positive anaplastic large-cell lymphoma in adults: an individual patient data pooled analysis of 263 patients. Haematologica 2019;104:e562–565.
[67] Horwitz S, O'Connor OA, Pro B, Trümper L, Iyer S, Advani R, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol 2022;33:288–98.
[68] Le Deley MC, Reiter A, Williams D, Delsol G, Oschlies I, McCarthy K, et al. Prognostic factors in childhood anaplastic large cell lymphoma: results of a large European intergroup study. Blood 2008;111:1560–6.
[69] Iijima-Yamashita Y, Mori T, Nakazawa A, Fukano R, Takimoto T, Tsurusawa M, et al. Prognostic impact of minimal disseminated disease and immune response to NPM-ALK in Japanese children with ALK-positive anaplastic large cell lymphoma. Int J Hematol 2018;107:244–50.
[70] Damm-Welk C, Mussolin L, Zimmermann M, Pillon M, Klapper W, Oschlies I, et al. Early assessment of minimal residual disease identifies patients at very high relapse risk in NPM-ALK-positive anaplastic large-cell lymphoma. Blood 2014;123:334–7.
[71] Ait-Tahar K, Damm-Welk C, Burkhardt B, Zimmermann M, Klapper W, Reiter A, et al. Correlation of the autoantibody response to the ALK oncoantigen in pediatric anaplastic lymphoma kinase-positive anaplastic large cell lymphoma with tumor dissemination and relapse risk. Blood 2010;115:3314–9.
[72] Mussolin L, Pillon M, Zimmermann M, Carraro E, Basso G, Knoerr F, et al. Course of anti-ALK antibody titres during chemotherapy in children with anaplastic large cell lymphoma. Br J Haematol 2018;182:733–5.
[73] Brugieres L, Pacquement H, Le Deley MC, Leverger G, Lutz P, Paillard C, et al. Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: a report from the French Society of Pediatric Oncology. J Clin Oncol 2009;27:5056–61.
[74] Woessmann W, Zimmermann M, Lenhard M, Burkhardt B, Rossig C, Kremens B, et al. Relapsed or refractory anaplastic large-cell lymphoma in children and adolescents after Berlin-Frankfurt-Muenster (BFM)-type first-line therapy: a BFM-group study. J Clin Oncol 2011;29:3065–71.
[75] Brugieres L, Quartier P, Le Deley MC, Pacquement H, Perel Y, Bergeron C, et al. Relapses of childhood anaplastic large-cell lymphoma: treatment results in a series of 41 children–a report from the French Society of Pediatric Oncology. Ann Oncol 2000;11:53–8.
[76] Mori T, Takimoto T, Katano N, Kikuchi A, Tabuchi K, Kobayashi R, et al. Recurrent childhood anaplastic large cell lymphoma: a retrospective analysis of registered cases in Japan. Br J Haematol 2006;132:594–7.
[77] Gross TG, Hale GA, He W, Camitta BM, Sanders JE, Cairo MS, et al. Hematopoietic stem cell transplantation for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. Biol Blood Marrow Transplant 2010;16:223–30.
[78] Ruf S, Hebart H, Hjalgrim LL, Kabickova E, Lang P, Steinbach D, et al. CNS progression during vinblastine or targeted therapies for high-risk relapsed ALK-positive anaplastic large cell lymphoma: a case series. Pediatr Blood Cancer 2018;65:e27003.
[79] Knörr F, Schellekens KPJ, Schoot RA, Landman-Parker J, Teltschik H-M, Förster J, et al. Combination therapy with crizotinib and vinblastine for relapsed or refractory pediatric ALK-positive anaplastic large cell lymphoma. Haematologica 2022. https://doi.org/10.3324/haematol.2022.281896. online ahead of print.
[80] Fukano R, Mori T, Fujita N, Kobayashi R, Mitsui T, Kato K, et al. Successful outcome with reduced-intensity condition regimen followed by allogeneic hematopoietic stem cell transplantation for relapsed or refractory anaplastic large-cell lymphoma. Int J Hematol 2019;110:723–8.
[81] Woessmann W, Peters C, Lenhard M, Burkhardt B, Sykora KW, Dilloo D, et al. Allogeneic haematopoietic stem cell transplantation in relapsed or refractory anaplastic large cell lymphoma of children and adolescents–a Berlin-Frankfurt-Munster group report. Br J Haematol 2006;133:176–82.
[82] Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood 2017;130:2709–17.
[83] Moskowitz AJ. Optimizing the role of brentuximab vedotin in classical Hodgkin lymphoma therapy. Hematology Am Soc Hematol Educ Program 2018;2018:207–12.
[84] Gambacorti-Passerini C, Mussolin L, Brugieres L. Abrupt relapse of ALK-positive lymphoma after discontinuation of crizotinib. N Engl J Med 2016;374:95–6.
[85] Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018;19:1654–67.
[86] Goldsmith KC, Kayser K, Groshen SG, Chioda M, Thurm HC, Chen J, et al. Phase I trial of lorlatinib in patients with ALK-driven refractory or relapsed neuroblastoma: a New Approaches to Neuroblastoma Consortium study. J Clin Oncol 2020;38:10504.

[87] Ou SI, Gadgeel SM, Barlesi F, Yang JC, De Petris L, Kim DW, et al. Pooled overall survival and safety data from the pivotal phase II studies (NP28673 and NP28761) of alectinib in ALK-positive non-small-cell lung cancer. Lung Cancer 2020;139:22–7.
[88] Chan TSY, Khong P-L, Kwong Y-L. Pembrolizumab for relapsed anaplastic large cell lymphoma after allogeneic haematopoietic stem cell transplantation: efficacy and safety. Ann Hematol 2016;95:1913–5.
[89] Hebart H, Lang P, Woessmann W. Nivolumab for refractory anaplastic large cell lymphoma: a case report. Ann Intern Med 2016;165:607–8.
[90] Rigaud C, Abbou S, Minard-Colin V, Geoerger B, Scoazec JY, Vassal G, et al. Efficacy of nivolumab in a patient with systemic refractory ALK+ anaplastic large cell lymphoma. Pediatr Blood Cancer 2018;65.
[91] Ramos CA, Ballard B, Zhang H, Dakhova O, Gee AP, Mei Z, et al. Clinical and immunological responses after CD30-specific chimeric antigen receptor-redirected lymphocytes. J Clin Invest 2017;127:3462–71.
[92] Ramos CA, Grover NS, Beaven AW, Lulla PD, Wu MF, Ivanova A, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory hodgkin lymphoma. J Clin Oncol 2020;38:3794–804.
[93] Sang W, Wang X, Geng H, Li T, Li D, Zhang B, et al. Anti-PD-1 therapy enhances the efficacy of CD30-directed chimeric antigen receptor T cell therapy in patients with relapsed/refractory CD30+ lymphoma. Front Immunol 2022;13:858021.
[94] Alexander S, Kraveka JM, Weitzman S, Lowe E, Smith L, Lynch JC, et al. Advanced stage anaplastic large cell lymphoma in children and adolescents: results of ANHL0131, a randomized phase III trial of APO versus a modified regimen with vinblastine: a report from the children's oncology group. Pediatr Blood Cancer 2014;61:2236–42.
[95] Damm-Welk C, Lovisa F, Contarini G, Lüdersen J, Carraro E, Knörr F, et al. Quantification of minimal disease by digital PCR in ALK-positive anaplastic large cell lymphoma: a step towards risk stratification in international trials? Cancers 2022;14:1703.
[96] Quelen C, Grand D, Sarot E, Brugieres L, Sibon D, Pradines A, et al. Minimal residual disease monitoring using a 3'ALK universal probe assay in ALK-positive anaplastic large-cell lymphoma: ddPCR, an attractive alternative method to real-time quantitative PCR. J Mol Diagn 2021;23:131–9.