Prognostic factors in paediatric anaplastic large cell lymphoma: role of ALK

Christine Damm-Welk¹,³, Marta Pillon², Wilhelm Woessmann¹,³, Lara Mussolin²,³

¹Dept. of Paediatric Haematology and Oncology and NHL-BFM Study Centre, Justus-Liebig-University, Feulgenstrasse 12, 35392 Giessen, Germany, ²Istituto di Ricerca Pediatrico Fondazione Città della Speranza, Corso Stati Uniti 4, 35127 Padova, Italy and Department of Paediatric Haematology and Oncology, University of Padova, Via Giustiniani 3, 35128 Padova, Italy, ³European Research Initiative on ALK-related malignancies (ERIA)

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Prognostic factors front-line
   3.1. Clinical risk factors
   3.2. Radiological risk factors
   3.3. Pathological risk factors
   3.4. Bone marrow involvement / disseminated disease, involvement of central nervous system
   3.5. ALK-related biological risk factors
   3.6. Other biological risk factors
4. Risk factors at relapse
5. Future directions
6. Acknowledgements
7. References

1. ABSTRACT

Event-free survival of children and adolescents with ALK-positive anaplastic large cell lymphoma (ALCL) reaches 65-75% with current chemotherapy regimen. Risk stratification of children with ALCL was, until now, based on clinical parameters. More recently, pathological and biological risk factors have been described in trials applying BFM-type chemotherapy. Histological subtypes containing small-cell or lymphohistiocytic components indicate a high risk of failure. Minimal disseminated disease (MDD) detected by qualitative RT-PCR for NPM-ALK in bone marrow or blood is associated with a relapse risk of 50%. Quantification of MDD and persistent minimal residual disease (MRD) characterize very high risk patients. Serum ALK-autoantibody titres inversely correlate with relapse risk. The combination of MDD and ALK-antibody titre separates both low and very high risk patients from those with standard risk. In relapse, the time of relapse/progression, central nervous system and bone marrow involvement are major risk factors. In conclusion, MDD, MRD, ALK-antibody titres and histological subtype are strong biological risk factors in childhood ALCL. The combination of MDD and ALK-antibody titre may serve for patient stratification in upcoming clinical trials.

2. INTRODUCTION

Anaplastic large cell lymphomas (ALCL) have first been described in 1985 by Stein and coworkers (1). ALCLs were separated from other large cell lymphomas by the large anaplastic cells with horseshoe-like nuclei, sinusoidal growth pattern and the expression of the surface marker Ki-1 (CD30). In the late 1980s several groups described an association of the specific translocation t(2;5)(p23;q35) with ALCL. Morris and coworkers reported the molecular basis of the translocation in 1994, the fusion of the genes for nucleophosmin (NPM) and anaplastic lymphoma kinase (ALK) (2). One next step in history of ALK-positive ALCL was the production of the ALK1 monoclonal antibody by Karen Pulford in 1997 which allowed for accurate diagnosis of the disease (3). Several groups unravelled the molecular pathogenesis of ALK-positive ALCL during the following 15 years by demonstrating that lymphoma pathogenesis and survival depends on activated ALK-kinase signaling and by describing its signaling pathways (Review: (4, 5). This allowed for the preclinical development of several new treatment targets. During the last years the detection of the immunogenicity of ALK fusion proteins led to the exploration of further possible therapeutic options (6-12). The short time of less than 25 years from the first pathological description of the disease to the understanding the molecular pathogenesis resulted in the incorporation of ALK-positive ALCL as distinct entity in the 2008 WHO-classification for hematologic malignancies (13).
ALK-positive ALCL is a disease of children and young adults (13). It accounts for 10-15% of paediatric and adolescent Non-Hodgkin Lymphomas (14). In contrast to adults, more than 90% of childhood ALCLs are ALK-positive (15-18). Almost 90% of ALK-positive ALCL carry the typical t(2;5) with NPM-ALK fusion (18, 19). Clinically, ALCL are characterized by a high incidence of B-symptoms (60%) and extranodal involvement (60%), particularly skin, lung, bone and soft tissue (15, 17, 20-23). ALCL in children and adolescents still has a relapse rate of 25-35% with current therapy strategies which often are based on short-pulse chemotherapy courses (15, 17, 20-23).

In light of new treatment options stringent prognostic factors are urgently needed for therapy stratification. Biomarkers detecting high risk patients would allow selecting patients for early clinical trials with new targeted therapies or allogeneic blood stem cell transplantation (SCT), whereas low risk patients could be treated less intensively or by immunostimulation. The evolution of a standard therapy for children with ALCL in Europe during the 1990s and 2000s provided the opportunity to test several pathological and biological markers for their prognostic value. The current standard strategy consists of six courses short-pulse chemotherapy given over a time period of five months (15, 20). Modifications of the chemotherapy courses have been modest over the last 25 years and were not accompanied by a change in relapse rate so that large cohorts of uniformly treated children and adolescents with ALCL are available for risk factor analyses.

3. PROGNOSTIC FACTORS FRONT-LINE

3.1. Clinical risk factors

Clinical characteristics were analysed for their prognostic value already in the first national trials on childhood ALCL. However, different factors turned out to be significantly associated with outcome in each trial, and low patient numbers did not allow drawing definitive conclusions (17, 20, 21, 24). 70% of patients present with advanced stage disease. Unlike mature B-NHL, the stage did not impact on the relapse risk in ALCL. A negative prognostic impact of skin involvement was described in the first Berlin-Frankfurt-Muenster (BFM)-group series (24). The French Society of Paediatric Oncology (SFOP) and UK Children’s Cancer and Study group (UKCCSG) – studies identified mediastinal and visceral involvement (liver, spleen, lung) as factors associated with a high risk of relapse (17, 21). None of these factors turned out to be of significant prognostic value in the BFM90 trial in which B-symptoms correlated with relapse risk (20). Analyses of cumulative data from European national studies from the 1990s identified mediastinal involvement, visceral involvement, and skin lesions as poor prognostic factors (25). 64% of the analysed 225 patients had at least one clinical risk factor. Progression-free survival (PFS) and overall survival (OS) were significantly lower for patients with at least one clinical risk factor (61% and 73%, respectively) compared to patients without (89% and 94%, respectively) (25). These factors have been used for patient stratification in the first randomised clinical trial of the European InterGroup for Childhood Non-Hodgkin lymphoma (eicnhl), ALCL99 (15, 26), leading to the expected patient distribution into standard and high risk groups (15). ALCL was complicated by haemophagocytosis in 12% of children and adolescents in a large single centre analysis without impacting on the outcome of the patients (27).

3.2. Radiological risk factors

Imaging is implicated in staging and definition of risk organ involvement in ALCL. Early treatment response has not been analysed for its prognostic value in clinical trials so far. The observation that even a residual mass at the end of treatment does not mean failure in ALCL suggests that early response should not be used for treatment modification before studying its impact on outcome. There are only few data on 18-Fluorodesoxyglucose (FDG)-positron emission tomography (PET)-(CT) in ALCL. These limited reports support the view that systemic ALCL usually are “PET-positive” (28-30). However, there are currently no data indicating that the addition of PET improves staging above conventional imaging. Furthermore, the available data do not allow connecting early PET-response with outcome in ALK-positive ALCL (28, 31). The potential role of PET-response in ALK-positive ALCL needs to be addressed in upcoming clinical trials.

3.3. Pathological risk factors

Histological subtypes of ALCL were defined during the 1990s. The current WHO classification distinguishes the common type ALCL from the small cell and the lymphohistiocytic variant, as well as the mixed type with more than one subtype in a biopsy (13). It was noted already early that certain histological subtypes might indicate a higher risk of relapse (17). The lymphohistiocytic subtype correlated with lower event-free survival (EFS) in univariate but not in multivariate analysis among 82 patients treated according to the subsequent trials HM89 and HM91 of the SFOP (17). In an analysis of 80 paediatric NPM-ALK-positive ALCL of the BFM group all “not common” histological subtypes (i.e., small cell, lymphohistiocytic, and mixed) were associated with a higher risk of relapse. In a Cox regression analysis with the co-variables minimal disseminated disease (MDD), histologic subtype and clinical risk features, MDD in bone marrow (BM) and “not common” histology remained independent prognostic factors with similar risk ratios (32). The strong prognostic impact of morphologic and phenotypic characteristics was confirmed among 375 patients with systemic ALK positive ALCL included in the ALCL 99 study of the eicnhl (16). 361 of the tumours were classifiable by the international pathologist panel.
Prognostic factors in paediatric ALK-positive ALCL

235 tumours (65%) were of common subtype, 114 showed “small cell or lymphohistiocytic components” (SC/LH, i.e. including cases with mixed subtype). SC/LH components could be shown to be significantly associated with the clinical risk factors skin lesions and mediastinal involvement, as well as with CD3 expression. A perivascular growth pattern was detected more often in ALCL with a SC/LH subtype (75/113, 66%) than in tumours without (72/244, 30%; P= .001). In multivariate analysis including the co-variables ALK staining pattern, perivascular pattern, clinical risk factors, CD3-positivity and SC/LH component, the SC/LH subtype as well as the perivascular pattern were significantly associated with the relapse risk (HR 2.0 and HR 1.7, respectively) (16). Despite the prognostic value of the subtypes a relatively high interobserver variability may hinder using the histological subtype for risk stratification in international clinical trials (16).

In ALCL, tumour cells often are surrounded by abundant lymphoid bystander cells, hindering the definition of the immunophenotype. Multi-colour-staining immunofluorescence and digital image analysis was used for more reliable determination of CD30, CD3, CD5, CD8, Ki67,CD56 and phosphorylated Stat3 expression of tumour cells in 124 cases of paediatric ALK-positive ALCL treated in BFM trials (33). CD56-positivity was observed rarely (7%) and was associated with poorer EFS in univariate analysis. This finding was not observed in a Children’s Oncology Group (COG) report but consistent with an earlier single centre analysis including ALK-positive as well as ALK-negative ALCL (34, 35). CD8 expression correlated with non-common histological subtype and clinical high risk features, and was associated with a significantly poorer outcome in univariate and multivariate analyses including the co-variables CD8-expression, histological subtype and clinical risk features (CD8-positive versus CD8-negative: EFS 29% versus 68%, OS 57% versus 84%, respectively) (33).

A few additional immune histology based prognostic factors were described in smaller case series usually including adults and children, ALK-positive as well as ALK-negative ALCL. A single centre analysis correlated survivin expression with outcome (36). More than 5% active caspase 3 expressing cells was associated with improved survival in an analysis of ALK-positive and -negative ALCL (37).

3.4. Bone marrow involvement / disseminated disease, involvement of central nervous system

Microscopic BM involvement is an uncommon event in ALCL. The frequency depends on the method used. It ranges from 5-10% by aspiration cytology to 10-15% by BM histology and more than 20% by immunohistochemistry with CD30 and EMA-staining (15, 17, 20-23, 38). Correspondingly, leukemic ALCL is exceedingly rare accounting for less than 3% of ALCL (39, 40). Microscopic BM infiltration detected by aspiration cytology was associated with a poor prognosis in one BFM-group analysis including patients from two consecutive trials but not in earlier national trials with lower patient numbers (17, 20-23,32). BM infiltration detected by immunohistology, also correlated with the risk of relapse (38). The fusion gene transcript NPM-ALK can be detected by a sensitive RT-PCR in about 50-60% of patients and implicates a significantly higher relapse risk compared to BM-PCR-negative patients (see below) (32, 41). Comparison of results of quantitative PCR for NPM-ALK in BM and correspondent aspiration cytology suggests that ALCL-cells might easily be missed by microscopy (32). Furthermore, comparison of both qualitative and quantitative PCR for NPM-ALK between BM and blood (PB) showed high concordance (32, 42). Slightly more patients were positive in PB, and positive patients tended to have higher NPM-ALK copy numbers in PB compared to BM suggesting that detection of disseminated ALCL cells is rather a sign of circulating tumour cells than true BM infiltration.

Only 1-3% of children with ALCL present with central nervous system (CNS)-disease. The low number of patients precludes a detailed analysis of a possible prognostic value. Allogether, children with CNS-involvement have a survival chance of 50-60% with intensive B-NHL-type CNS-directed therapy with or without cranial irradiation (43-44).

3.5. ALK-related biological risk factors

All ALCL-cells express ALK-fusion genes in ALK-positive ALCL. They are dependent on ALK-signaling. In addition, ALK normal tissue distribution is restricted to few neurons in the CNS. This allowed exploring ALK as minimal disease marker as well as the patients’ immune response against ALK as potential risk factor.

MDD represents a small numbers of tumour cells present in BM or PB of a patient at diagnosis, whereas minimal residual disease (MRD) defines tumour cells remaining detectable during treatment. Generally, MDD and MRD are measured by polymerase chain reaction, a highly sensitive technique, or flow cytometry. In ALCL, a Reverse Transcriptase (RT)-PCR for NPM-ALK mRNA allows detecting 1 tumour cell among 10^5 to 10^6 normal cells (32, 41). Flow cytometry for ALK and CD30 co-expressing cells was one log less sensitive in one series (45). The first data on the prognostic impact of MDD in BM studied by RT-PCR for NPM-ALK in 52 paediatric ALCL patients, was reported by the AIEOP (Italian Association of Paediatric Haematology and Oncology) in 2005 (41). 61% of patients had detectable NPM-ALK transcripts at diagnosis. Survival analysis demonstrated a 5-year PFS of 41% for patients with molecularly positive BM versus 100% for patients with negative BM (p=0.001). The high percentage and prognostic role of qualitative
Prognostic factors in paediatric ALK-positive ALCL

MDD was confirmed by the BFM-group on 80 patients with NPM-ALK-positive ALCL (32). BM involvement was detected in 47% of patients who showed a significantly poorer EFS and OS compared to BM-PCR-negative patients (EFS 38% vs 82%, p<0.001). Additionally, a quantitative real-time (RQ)-PCR approach and PB as MDD-medium were tested in this study (32). BM from 74 and PB from 51 ALCL patients could be analysed by the RQ-PCR. Qualitative and quantitative PCR findings in BM and PB strongly correlated. 16 patients had more than 10 normalized copy numbers (NCN) of NPM-ALK/10^4 ABL in BM, as detected by quantitative PCR, which was associated with a cumulative incidence of relapses (CI-R) of 71% compared with a CI-R of 18% for 59 patients with 10 or fewer NCN. However, although quantitative real-time PCR allowed the identification of a small very poor risk group of patients, the method is difficult to transfer to other laboratories with quality control, it is more expensive compared to qualitative RT-PCR, and patients with a low relapse risk could not be separated. Qualitative RT-PCR, on the other hand, is highly sensitive, easily reproducible and inexpensive. The AIEOP and BFM study groups performed collaborative MDD studies by RT-PCR in a large cohort of 180 uniformly treated children with ALCL (46, 47). MDD was detected in 57% (103/180) of the patients and correlated with clinical risk factors and non-common histology, thus confirming the earlier observations. The 5-year EFS was 51% for MDD-positive and 83% for MDD-negative patients, respectively (p<0.001).

The same RT-PCR method was used by the AIEOP- and BFM-groups to study the prognostic impact of early MRD measured before the second course of chemotherapy (47). The EFS of 52 MDD-positive patients was significantly higher for 26 MDD-positive/MRD-positive than for 26 MDD-positive/MRD-negative patients (19% versus 69%, p<0.01) (Figure 1) (47). The strong impact of MRD in multivariate analysis may allow early identification of patients with chemoresistant disease.

ALK over-expression induces a host immune reaction, giving rise to circulating autologous anti-ALK antibodies in more than 90% of patients (6-8, 46, 48). First data suggested that anti-ALK antibody titres inversely correlated with lymphoma dissemination and risk of relapse (8, 48). The prognostic value of the strength of the anti-ALK antibody response was analysed in detail in a common AIEOP – BFM-study including 128 NPM-ALK-positive ALCL patients (46). The 5-year PFS was 42% for 39 patients with low antibody titre (≤1/750) compared to 79% for 89 patients with high antibody titer (>1/750) (p<0.001).

This large group of uniformly treated children and adolescents with NPM-ALK-positive ALCL and availability of clinical data, histopathology, MDD and ALK-antibody titre allowed detailed analysis of the described risk factors (46) (Table 1). The combination of the parameters MDD and ALK-antibody titre for the first time allowed identifying not only a high-risk group of patients but also a very low-risk group amenable to therapy reduction (46). The following 3 subgroups of patients with different prognosis could be identified: 1) a biological high risk group (bHR) defined by MDD-positivity and antibody titre ≤1/750 (20% of patients); 2) a biological low risk group (bLR) defined by MDD negativity and an antibody titre >1/750 (31% of patients); 3) a biological intermediate risk group (bIR) including all other patients (48%; MDD negative/antibody titre ≤1/750 or MDD positive/antibody titre >1/750). PFS was 25% for bHR patients and 92% for bLR patients (p<0.001) (Figure 2A). The bIR group showed a 5-years PFS of 68% and was predominantly composed of patients with high antibody titre/MDD positivity (79%). The 5-years OS was 71% for bHR patients, 83% for bIR cases and 97% for bLR patients (p=0.02) (Figure 2B) In multivariate analysis including the co-variables stage (St Jude), peripheral lymph nodes, mediastinal involvement, visceral involvement, BM involvement, histological subtype, MDD, antibody titre and biological risk group, the biological high risk group (bHR) and a non-common histology remained independent prognostic factors (hazard ratio 4.98 and 2.7, respectively) (46).
Prognostic factors in paediatric ALK-positive ALCL

3.6. Other biological risk factors

Gene expression analysis of 25 ALK positive and 7 ALK negative ALCL tumours detected two different clusters of gene expression. The clusters corresponded with the common and non-common subtype. In the cluster enriched for non-common type ALCL, a statistical significant overexpression of genes involved in inflammatory and immune response was detected (49). BCL6, SerpinA1, PTPN12 and C7EBPbeta were highly discriminatory between ALK-positive and -negative cases (49). The role of soluble receptors (sCD30), chemokines and cytokines (sIL2R, IL10, TNFR1, IL8, IL17 and IL22) were analysed in few studies without clear prognostic value for ALK-positive ALCL so far (50-54).

The type of the ALK-fusion partner (NPM versus variant) has not been shown to be associated with outcome in molecular or immunohistological studies (16). Concurrent C-MYC translocation may indicate a highly aggressive phenotype of ALK positive ALCL. Three cases with dual translocations of ALK and C-MYC, all showing an aggressive clinical course, have been described (55-57).

4. RISK FACTORS AT RELAPSE

Patients with relapsed ALCL have a 30-60% chance to reach a second continuous remission (58-60). Cure can even be reached after several relapses. The analyses of prognostic factors in relapse are hampered by several factors: first, the available data are until now limited to three retrospective reports (58-60). Secondly, therapies at relapse were as different as maintenance treatment with vinblastine, autologous and allogeneic SCT (21, 58-63). However, considering the efficacy of these highly variable therapies, identification of risk factors for second relapse and death would allow for treatment stratification upon relapse.

The time from initial diagnosis to relapse or progression turned out as major risk factor for children and adolescents with relapsed ALCL (58, 60). 24 of 41 children with relapsed ALCL in the French series relapsed during the first 12 months after initial diagnosis. They had a significantly lower disease-free survival (DFS) of 28% compared patients with later relapses (DFS 68%, p=0.01) (58). Patients with disease progression or early relapse had a tendency towards lower OS among 26 relapse patients reported from Japan (59). Among 74 children with ALCL-relapse after comparable first-line therapy reported by the BFM-group, the prognostic impact of the time of relapse could be confirmed.

The relapse strategy recommended re-induction chemotherapy followed by autologous SCT. Only four of the 16 patients (25%) with progression during frontline therapy survived compared to 38 of the 58 patients with relapses after first line therapy (66%; p=0.02) (60). EFS and OS of the 40 patients relapsing after therapy but within 12 months from initial diagnosis were 50% and 57%, respectively, compared to 67% and 83% of the 18 patients with a relapse later than one year after initial diagnosis (p=0.14 for EFS and 0.06 for OS). About 15% of children and adolescents present with BM or CNS – involvement in relapse (58, 60) which correlated with reduced survival in one analysis (60) whereas the affection of new sites outside BM or CNS was without impact on outcome (59, 60).

Besides the major risk factor, time to failure, expression of the T-cell antigen CD3 was associated with a high risk of failure in patients consolidated by autologous SCT in the retrospective BFM-series. However, the possible prognostic value of CD3-positivity cannot readily be generalised currently due to low patient numbers and retrospective analysis with lack of a defined cut-off for CD3-positivity.
Table 1. Prognostic factors in children and adolescents with ALK-positive anaplastic large cell lymphoma (ALCL)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Definition/cut-off</th>
<th>Percentage of patients with risk factor</th>
<th>Prognostic impact</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical risk factors</td>
<td>Mediastinum, lung, liver, spleen, skin</td>
<td>60-65%</td>
<td>HR (EFS&gt;60%)</td>
<td>Simple, readily available</td>
<td>No VHR, no LR</td>
<td>(25)</td>
</tr>
<tr>
<td>Histological subtype</td>
<td>Common versus 'not common'/SCLH</td>
<td>35%</td>
<td>HR (EFS&gt;50%)</td>
<td>Paraffin, available from all patients</td>
<td>No VHR, no LR, interobserver variability</td>
<td>(16, 32, 46)</td>
</tr>
<tr>
<td>Qualitative MDD (RT-PCR for NPM-ALK in PB/BM)</td>
<td>Positive versus negative</td>
<td>50-60%</td>
<td>HR (EFS&gt;50%)</td>
<td>Simple, easy QC</td>
<td>No VHR, no LR</td>
<td>(32, 41, 46, 47)</td>
</tr>
<tr>
<td>MRD before course 2 (RT-PCR)</td>
<td>Positive versus negative</td>
<td>20%</td>
<td>VHR (EFS&lt;30%)</td>
<td>Simple, easy QC</td>
<td>Dependent on ALCL99-therapy</td>
<td>(47)</td>
</tr>
<tr>
<td>Quantitative MDD (RQ-PCR for NPM-ALK, control ABL)</td>
<td>&gt;10 copies NPM-ALK/10^4 copies ABL</td>
<td>25%</td>
<td>VHR (EFS 30%)</td>
<td>VHR at diagnosis</td>
<td>Difficult to transfer, QC, expensive, no LR</td>
<td>(32)</td>
</tr>
<tr>
<td>ALK antibody titre</td>
<td>≤1/750</td>
<td>30%</td>
<td>HR (EFS 40%)</td>
<td>Easy QC</td>
<td>No LR, no VHR, labor-intensive</td>
<td>(6, 46, 48)</td>
</tr>
<tr>
<td>Qualitative MDD+ histological subtype</td>
<td>No RF 30%</td>
<td>LR (&gt;90%)</td>
<td>Interobserver variability</td>
<td>LR+VHR</td>
<td>(32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 RF 50%</td>
<td>IR VHR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 RF 20%</td>
<td>VHR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qualitative MDD+ ALK antibody titre</td>
<td>No RF 30%</td>
<td>LR (&gt;90%)</td>
<td>Interobserver variability</td>
<td>LR+VHR, measurable from 1 EDTA blood sample</td>
<td>(46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 RF 50%</td>
<td>IR VHR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 RF 20%</td>
<td>VHR (&lt;30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Whether MDD or ALK-antibody titres at the time of relapse can identify patients at risk for further relapse or death is subject of an ongoing prospective analysis.

5. FUTURE DIRECTIONS

Brentuximab vedotin, crizotinib and other ALK-inhibitors are emerging as new targeted treatment options for CD30-positive and ALK-positive malignancies (64-67) with promising first clinical data on safety and response. However, long-term data on possible late effects especially in children are still missing. Weekly Vinblastine monotherapy has been shown to be effective in relapse almost without risk of late effects (61, 68). Risk stratified clinical trials are necessary to define the role of these new drugs or principles in the therapeutic strategy against ALK-positive ALCL. High-risk patients could be eligible for early phase clinical trials. Low-risk patients should not be objected to new drugs with unknown possible late effects but could be eligible to test a less toxic chemotherapy backbone. Currently, the combination of MDD and histological subtype or MDD and ALK-antibody titres allow separating a group of 30% very good risk and 20% very high risk patients from those with an intermediate risk. MDD and ALK-antibody titre can be determined within one to two weeks from a single EDTA blood sample before the start of therapy. These parameters have therefore been chosen to be used for risk stratification in the forthcoming ALCL-trial of the EICNHL.

6. ACKNOWLEDGMENTS

The present review was concerted inside the European Research Initiative of ALK-related malignancies (ERIA) (http://www.erialcl.net).

7. REFERENCES


Prognostic factors in paediatric ALK-positive ALCL

DOI: 10.1126/science.8122112


DOI: 10.1038/nrc2291

DOI: 10.1038/nrc3580


DOI: 10.1002/ijc.21410

DOI: 10.1182/blood-2009-11-251892

DOI: 10.1158/0008-5472.can-06-4427

DOI: 10.1038/nm1769

DOI: 10.1182/blood.V99.6.2100


DOI: 10.1111/j.1365-2141.2005.05735.x

DOI: 10.1200/JCO.2008.18.1487

DOI: 10.1200/JCO.2011.36.5411


28. X Cahu, C Bodet-Milin, E Brissot, H Maisonneuve, R Houot, N Morineau, P Solal-Celigny, P Godmer, T Gastinne, P Moreau, A Moreau, T Lamy, F Kraber-Bodere and S L Bouill: 18F-fluorodeoxyglucose-positron emission tomography before, during and after


55. X Liang, B Branchford, B Greffe, L McGavran, B Carstens, L Meltesen, E A Albano, R Quinones, B Cook and D K Graham: Dual


67. Y P Mosse, M S Lim, S D Voss, K Wilner, K Ruffner, J Laliberte, D Rolland, F M. Balis,


**Key Words:** Anaplastic Large Cell Lymphoma, ALCL, Children, ALK, Risk factor, Minimal disseminated disease, MRD, ALK antibody, Histological subtype, Review

**Send correspondence to:** Willi Woessmann, Justus-Liebig-University, Department of Pediatric Hematology and Oncology, Feulgenstr. 12, D-35392 Giessen, Germany, Tel: 49-641/99-43421, Fax: 49-641/99-43429, E-mail: wilhelm.woessmann@paediat.med.uni-giessen.de