STATA® statistical analysis software (version 11.0; StataCorp LP, College Station, TX) was used for all computations.

RESULTS

Patients

The protocol was conducted in 112 hospitals of the JPLSG after approval by each institution's review board, and written informed consent was provided by patients or legal guardians before treatment. Between November 2004 and January 2011, 346 cases of newly diagnosed B-NHL were enrolled in this study. Of these, 25 cases were excluded: 14 due to ineligible pathology, 8 for late enrollment, 2 for ineligible clinical stage, and 1 for prior chemotherapy. A total of 321 cases of four treatment groups were analyzed (Fig. 2).

Patient characteristic are shown in Table II. There were few protocol deviations: 10 patients in the Group 3/4 skipped or postponed HDMTX therapy in the A course, 5 because of retention of ascites or pleural effusion, 2 because of renal dysfunction, 2 due to septic infection, and one for stomatitis.

EFS and OS

The follow-up time ranged from 0.8 to 88 months, with a median 47 months. For the 321 patients analyzed in this study, 4-year OS was 92.7% ± 1.4% and 4-year EFS was 87.3% ± 1.8% (Fig. 3A). There was no significant difference in outcome by gender (4-year EFS, male 87.5% ± 2.2% vs. female 87.0% ± 3.8%, $P = 0.864$). The 4-year OS and EFS according to treatment subgroup were 100% and 94.1% ± 5.7% for Group 1, 100% and 98.6% ± 1.4% for Group 2, 93.6% ± 2.3% and 83.6% ± 3.5% for Group 3, and 82.1% ± 4.1% and 77.8% ± 4.4% for Group 4 (Fig. 3B). The 4-year OS and EFS according to clinical stage were 100% and 97.7% ± 2.3% for stage I, 100% and 97.8% ± 2.0% for stage II, 92.0% ± 2.9% and 82.9% ± 4.0% for stage III, 84.6% ± 5.8% and 71.8% ± 7.2% for stage IV. The 4-year OS and EFS of B-ALL were 86.2% ± 4.0% and 83.6% ± 4.3%. The 4-year EFS by histology was 86.1% ± 2.6% for BL/BLL, 87.3% ± 3.5% for DLBCL, 92.1% ± 4.3% for others, and 100% for MLBCL ($P = 0.717$) (Fig. 3C). When we analyzed the outcome of patients who had BM or CNS disease, the 4-year EFS was 83.8% ± 4.3% for patients (n = 74) with BM involvement only (BM+/CNS−), 60.0% ± 1.5%

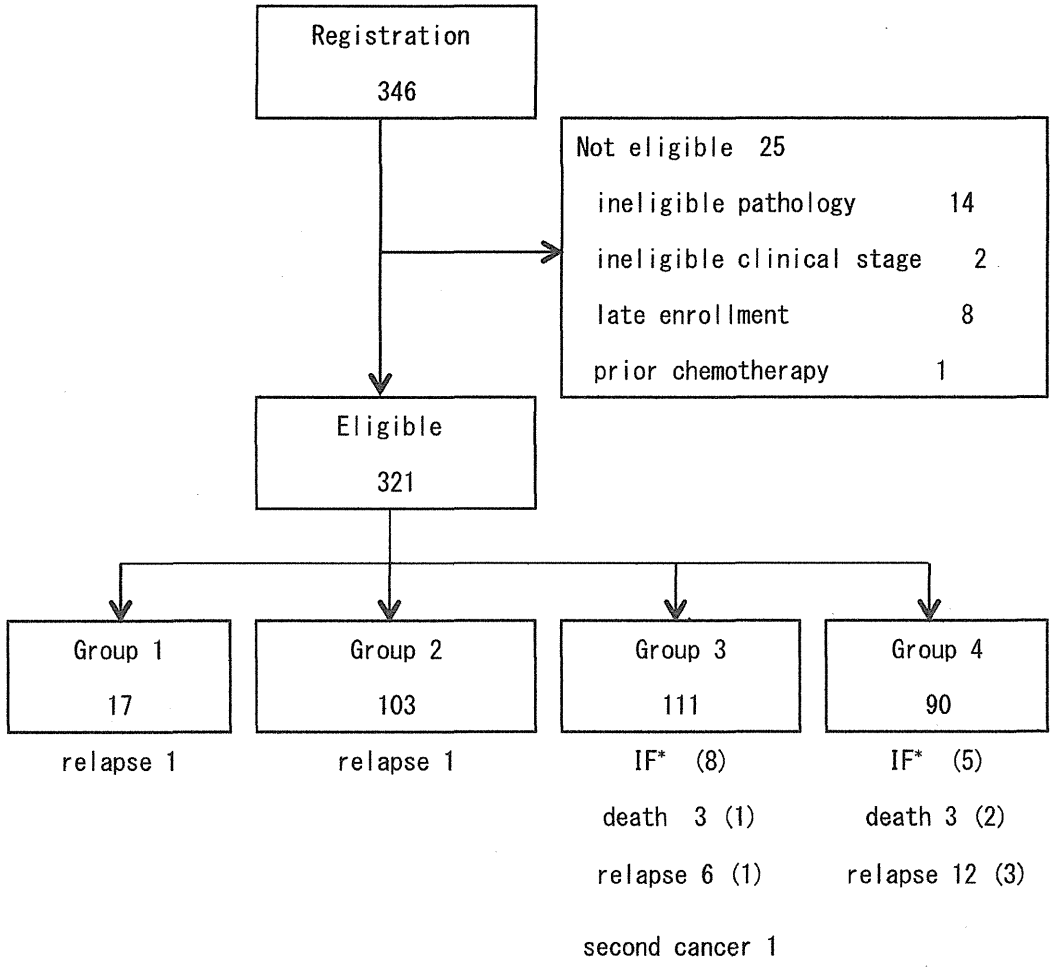

Fig. 2. Patient flow chart and events according to the treatment group. There were 40 events which consisted of each one in Group 1 and 2, 18 in Group 3, and 20 in Group 4. Number in parentheses indicates events occurred during protocol chemotherapy. Number in parenthesis indicates events occurred during protocol chemotherapy. *IF, induction failure defined as patients did not achieve complete remission or unconfirmed remission at the last evaluation time in group 3/4.

TABLE II. Patients Characteristics

Therapy groups	G1	G2	G3	G4	Total (%)
No. of patients	17	103	111	90	321
Sex					
Male	12	72	90	71	245 (76)
Female	5	31	21	19	76 (24)
Age					
0–4	2	12	18	16	48 (15)
5–9	3	45	42	39	129 (40)
10–14	8	42	42	27	119 (37)
15–	4	4	9	8	25 (8)
Histology					
BL/BLL/B-ALL	5	33	62	80	180 (56)
DLBCL	12	58	26	5	101 (31.4)
MLBCL	0	0	2	0	2 (0.6)
Others	0	12	21	5	38 (12)
Primary sites					
Thorax	5	30	7	1	43
Head & neck	5	39	12	2	58
Peripheral lymph nodes	0	3	3	0	6
Abdomen	7	29	75	11	122
Mediastinum	0	0	8	0	8
B-ALL	0	0	0	73	73
CNS	0	0	0	2	2
Other tumor site	0	2	5	0	7
Not specified	0	0	1	1	2
BM involvement	0	0	22	80	102 (32)
CNS involvement	0	0	0	38	38 (12)

BL, Burkitt lymphoma; BLL, Burkitt-like lymphoma; B-ALL, Burkitt leukemia; DLBCL, diffuse large B-cell lymphoma, MLBCL, mediastinal large.

for patients (n = 10) with CNS involvement only (BM−, CNS+), and 75.0% ± 8.2% for patients (n = 28) with BM and CNS involvements (BM+/CNS+), ($P = 0.102$) (Fig. 3D). Outcome by treatment response to initial A courses were as follows: The 4-year OS and EFS for patients who achieved CR (n = 236) or CRu (n = 54) at the last evaluation time were 95.7% ± 1.6% and 93.5% ± 1.6%, and 96.1% ± 2.7% and 86.9% ± 4.6%, respectively, while the 4-year OS and EFS for patients (n = 13) who did not achieve CR/CRu was 69.2% ± 12.8% and 15.4% ± 10.1% ($P < 0.001$), respectively.

Treatment Failure Events

Forty patients experienced an event and 25 have died (Fig. 2). The cause of death was tumor progression in 14, infection in 7, stem cell transplantation-related death in 3, and pulmonary bleeding in 1. The 40 events consisted of 13 induction failures, 6 deaths, 20 relapses, and one second cancer. Of the13 patients (6 in Group 3 and 7 in Group 4) who failed the initial treatment, 4 patients in Group 3 received salvage therapy and achieved CRu. At the time of the last analysis, 8 patients (4 in Group 3 and 4 in Group 4) were alive without tumor. Death in remission occurred in 3/321 (1%) patients: two died of infection and one died of pulmonary bleeding. The longest duration before relapse from the start of therapy was 38.9 months in DLBCL and 13.6 months in Burkitt histology. Relapse sites were 10 in local, 6 in BM, 2 in BM+CNS, one in local + CNS, and one in CNS. All CNS relapse occurred in patients with BL, but not with DLBCL. Thus, isolated CNS failure was only one among 38 patients with CNS involvement. Of the 20 relapsed patients, 11 died and 9 survived without tumor. A second cancer occurred among the patients who failed the initial treatment: a 12-year-old male with BL developed a secondary malignancy with acute myeloid leukemia (FAB M5) 17 months after the initial diagnosis.

Toxicity

Acute toxicity of treatment courses (A and B) was evaluated by the scale of NCI-CTC version 2.0., and rates of acute toxicity Grade 3 among patients in Groups 2, 3, and 4 are shown in Supplemental Table I. Anemia and neutropenia were the most frequent hematological toxicities with grade III or IV in all groups. In particular, grade IV neutropenia occurred in almost all patients (>98%) during A courses. In nonhematologic toxicity, infection was the single most frequent occurring with grade III or IV at least once in 70% of patients although the rate of grade IV infection was very small (<1%). Stomatitis and hepatotoxicity were also frequent, occurring with grade III or IV at least once in 20–35% and 24–38% of patients, respectively. The rate of renal toxicity grade III was very low. Leukoencephalopathy was reported in two patients of Group 3, and their MRI findings disappeared within 2 months without neurological symptoms. The overall incidence of renal insufficiency associated with tumor lysis syndrome was 2 out of 96 (2%) in Group 4, and these required assisted renal support with continuous hemodiafiltration.

DISCUSSION

During the last two decades, the survival outcome of children with B-NHL has been markedly improved through consecutive

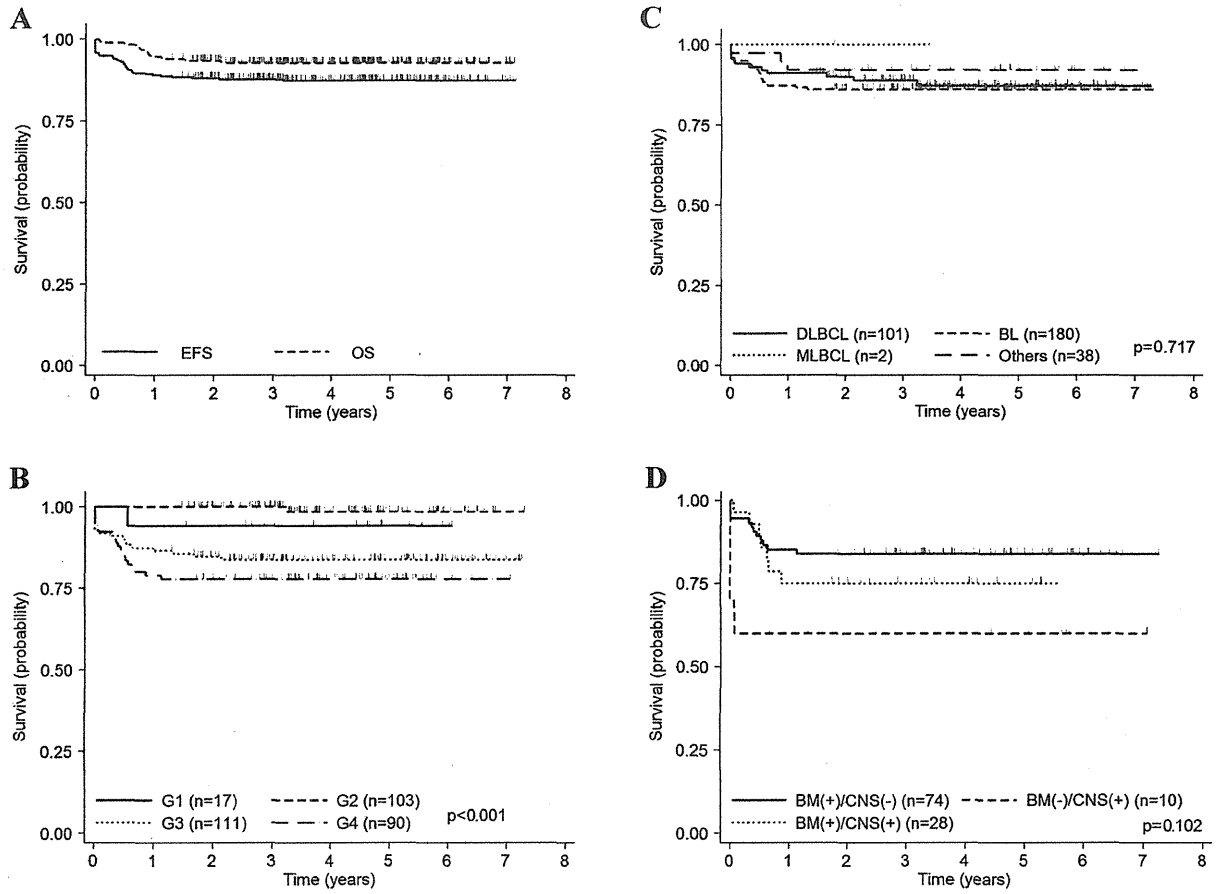

Fig. 3. Kaplan–Meier curves for OS and EFS of all patients (A). Kaplan–Meier curves for EFS according to treatment group (B), histology (C), and BM/CNS involvement (D).

clinical trials in large study groups, and the cure rate of childhood B-NHL has reached 90% [1–6]. In the present study, we showed an excellent survival outcome with 4-year OS 93% in children with B-NHL. In our study, the 4-year EFS 84% of Group 3 patients was considerably lower than the 4-year EFS 90% of intermediate risk group in the FAB/LMB96 study [5] or the 6-year EFS 88% of stage III patients in the BFM90 study [2], whereas, the 4-year EFS 78% of Group 4 patients compared favorably with the 4-year EFS 79% of high-risk group in the FAB/LMB96 study [5] and the 6-year EFS 74% of stage IV/B-ALL patients in the BFM90 study [2]. This outcome was obtained via the short-intensive chemotherapy regimen based on COPAD (CPM, VCR, PSL, and ADR) regimen plus the HDMTX of the lymphomas malin B (LMB) studies [3]. We omitted cranial irradiation for all patients, because recent studies have suggested the possibility of deleting radiotherapy in treating CNS diseases as well as CNS prophylaxis [2,3,5,9]. However, having no experience in administrating 8 g/m^2 HDMTX, we employed 5 g/m^2 HDMTX over 24 hour-infusion and not the 8 g/m^2 HDMTX over 4 hour-infusion in the LMB protocols for treating patients with CNS disease [3,5]. The treatment result for CNS disease was satisfactory, because CNS failure was only one of 38 patients with primary CNS disease in the present study.

This suggests that the 5 g/m^2 HDMTX over 24 hour-infusion is equally as effective to the CNS-positive disease as the aforementioned 8 g/m^2 HDMTX over 4 hours infusion, and reinforces the possibility that CNS irradiation could be omitted without jeopardizing the outcome of patients with CNS disease by using systemic and it MTX therapy [3,5,9].

The treatment of DLBCL as well as BL was another important focus of our study, because the incidence of DLBCL in childhood B-NHL is relatively more frequent than that of Western countries: the number of DLBCL was almost similar to that of BL (excluding B-ALL) in the present study and our recent national survey for childhood hematological malignancies has shown that the ratio of DLBCL to BL was 0.79 [14]. In our study, according to the strategy that DLBCL was treated by short-pulse chemotherapy as well as BL [15], we followed the same protocol, and achieved a favorable outcome of 4-year EFS with 87% for DLBCL which was not inferior to that of BL. This outcome can be partly explained by shared biological features, that is, that more than half of childhood DLBCL has the molecular subtypes of BL [16].

Several factors associated with poor outcome in the high-risk group in childhood B-NHL have been reported. Cairo et al. has shown a significantly inferior outcome (4-year EFS 61% ± 6%) of the subgroup of children with combined BM and CNS involvement at diagnosis as compared with children with BM or CNS only [5]. However, our results in Group 4 showed that the outcome (4-year EFS 75% ± 8%) of this subgroup with BM+/CNS+ was not significantly inferior than that of the subgroup with BM+ (83% ± 4%) or CNS+ (60% ± 1%). Failure to initial therapy is

also known to be a strong, unfavorable prognostic factor. Past studies in LMB 89/96 have shown that non-responders to pre-phase therapy (COP regimen) suffer a significantly inferior outcome as compared with responders or incomplete responders [3,5]. In our study, an appropriate evaluation of tumor regression just after pre-phase therapy was difficult for many patients, such that we compared the outcome according to response at the final evaluation time after two or three courses of therapy. These results showed that 4-year EFS of patients who did not achieve CR/CRu was only $15\% \pm 10\%$, which was as dismal as the outcome of poor-responders to COP regimen in the FAB/LMB 96 study [5]. To rescue the poor-responders in our study, we employed salvage therapy with high-dose Ara-C and VP16 to patients who did not achieve remission after 2 or 3 courses of therapy in Group 2 or 3, as in the BFM90 or FAB96 study [2,4]. As a result, 4 of 6 patients in Group 3 received salvage therapy and survived without tumor. This response rate was similar to that of FAB96 study, in which 10 out of 16 patients who received the second phase treatment intensification after the consolidation phase were alive. Thus, our results reconfirmed the efficacy of the salvage therapy.

Management of acute toxicity by short-pulse intensive chemotherapy is essential to successfully carry out the treatment protocol for childhood B-NHL. In our study, grade IV neutropenia occurred in almost all patients, but the rate of grade IV infection was quite low. Consequently, therapy-related death was less than 1% in all patients, and 2.1% in Group 4 patients. These results show the safety and feasibility of our treatment protocol. Anthracycline cardiotoxicity and secondary malignancy by alkylating agents are serious late events in pediatric cancer treatment [17,18]. To reduce the risk of cardiotoxicity, we employed THP-adriamycin (pirarubicin) instead of ADR. Pirarubicin is a derivative of ADR with reportedly less cardiotoxicity in adults [19–24]. Recently, we have reported that no significant cardiac dysfunction was detected in long-term survivors of children with acute lymphoblastic leukemia who received THP treatment [25–27]. In the present study, there were no patients with cardiac insufficiency or cardiac myopathy during the 7-year observation period. These results suggest that late-onset cardiotoxicity induced by pirarubicin is uncommon in childhood lymphoid malignancies, at least up to the cumulative dose of 240 mg/m^2. In our study, there was one male with a second cancer with acute myeloid leukemia, although the correlation between his second cancer and the protocol treatment is uncertain because he was resistant to the pre-phase followed by arbitrary treatment.

As shown above, chemotherapy-related toxicity of our protocol treatment was within acceptable range. However, a 6-course treatment for Group 3 seemed to be more intensive as compared with a 4-course treatment for intermediate risk group in the FAB96 study [4]. In order to reduce the total dose of cytotoxic drugs without impairing the survival outcome, new approaches including targeted monoclonal antibody therapy in combination with chemotherapy [28,29], are needed for children with an advanced or resistant disease in coming studies.

In conclusion, our nationwide study resulted in a cure rate above 90% with <1% toxic death in childhood B-NHL.

ACKNOWLEDGMENTS

We would like to thank all of the patients who enrolled in the B-NHL03 study and their families. This study was supported by Grants for Clinical Cancer Research from the Ministry of Health, Labor and Welfare of Japan; H14-Koka(Gan)-031, H15-Koka(Gan)-024, H16-GanRinsho-004, H17-GanRinsho-004, H20-GanRinsho-Ippan-017, H23-GanRinsho-Ippan-014.

REFERENCES

1. Reiter A, Schrappe M, Parwaresch R, et al. Non-Hodgkin's lymphomas of childhood and adolescence: Results of a treatment stratified for biologic subtypes and stage. A report of the Berlin Frankfurt-Münster Group. J Clin Oncol 1995;13:359–372.
2. Reiter A, Schrappe M, Tiemann M, et al. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: Reports of the Berlin–Frankfurt–Münster Group trial NHL–BFM 90. Blood 1999;94:3294–3306.
3. Patte C, Auperin A, Michon J, et al. The Société Française d'Oncologie Pédiatrique LMB89 protocol: Highly effective multiagent chemotherapy tailored to the tumor burden and response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 2001;97:3370–3379.
4. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents. It is possible to reduce treatment for the early responding patients. Blood 2007;109:2773–2780.
5. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109:2736–2743.
6. Gerrard M, Cairo MS, Weston C, et al. Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: Results of the FAB/LMB 96 international study. Br J Haematol 2008;141:840–847.
7. Shimizu H, Kikuchi M, Takaue Y, et al. Improved treatment results of non-Hodgkin's lymphoma in children: A report from the Children's Cancer and Leukemia Study Group of Japan. Int J Hematol 1995;61:85–96.
8. Horibe K, Akiyama Y, Kobayashi M, et al. Treatment outcome of AT-B88 regimen for B-cell non-Hodgkin's lymphoma and surface immunoglobulin-positive acute lymphoblastic leukemia in children. Int J Hematol 1997;66:89–98.
9. Tsurusawa M, Taga T, Horikoshi Y, et al. Favourable outcomes in children with diffuse large B-cell lymphoma treated by a short-term ALL-like regimen: A report on the NHL960 study from the Japanese Childhood Cancer and Leukemia Study Group. Leuk Lymphoma 2008;49:734–739.
10. Kikuchi A, Mori T, Fujimoto J, et al. Outcome of childhood B-cell non-Hodgkin lymphoma and B-cell acute lymphoblastic leukemia treated with the Tokyo Children's Cancer Study Group NHL B9604 protocol. Leuk Lymphoma 2008;49:757–762.
11. Lee SH, Yoo KH, Sung KW, et al. Should children with non-Hodgkin lymphoma be treated with different protocols according to histopathologic subtype? Pediatr Blood Cancer 2013;60:1842–1847.
12. Jaffe ES, Harris NL, Stein H, et al., editors. WHO classification of tumors, pathology and genetics of tumors of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001.
13. Murphy SB. Classification, staging and results of treatment of childhood NHL, dissimilarities from lymphoma in adults. Seminars in Oncology 1980;7:332–339.
14. Horibe K, Saito AM, Takimoto T, et al. Incidence and survival rates of hematological malignancies in Japanese children and adolescents (2006-2010): Based on registry data from the Japanese Society of Pediatric Hematology. Int J hematol 2013;98:74–88.
15. Reiter A, Klapper W. Recent advances in the understanding and management of diffuse large B-cell lymphoma in children. Br J Haematol 2008;142:329–347.
16. Klapper W, Szczepanowski M, Burkhardt B, et al. Molecular profiling of pediatric mature B-cell lymphoma treated in population-based prospective clinical trials. Blood 2008;112:1374–1381.
17. Sorensen K, Levitt GA, Bull C, et al. Late anthracycline cardiotoxicity after childhood cancer: A prospective longitudinal study. Cancer 2003;97:1991–1998.
18. Davies SM. Subsequent malignant neoplasms in survivors of childhood cancer: Childhood Cancer Survivor Study (CCSS) studies. Pediatric Blood Cancer 2007;48:727–730.
19. Umezawa H, Takahashi Y, Kinoshita M, et al. Tetrahydropyranyl derivatives of daunomycin and adriamycin. J Antibiot 1979;32:1082–1084.
20. Takagi T, Sakai C, Oguro M. Combination chemotherapy with pirarubicin (THP), cyclophosphamide, vincristine, and prednisolone (VEP-THP therapy) in the treatment of non-Hodgkins lymphoma. Oncology 1990;47:25–28.
21. Niitsu N, Umeda M. Biweekly THP-COPBLM (pirarubicin, cyclophosphamide, vincristine, prednisone, bleomycin and procarbazine) regimen combined with granulocyte colony-stimulating factor (G-CSF) for intermediate- and high-grade non-Hodgkins's lymphoma. Leukemia 1998;12:1457–1460.
22. Niitsu N, Umeda M. Response and adverse drug reactions to combination chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma: Comparison of CHOP, COP-BLAM, COP-BLAM III, and THP-COPBLM. Eur J Haematol 1999;63:337–344.
23. Tsurumi H, Yamada T, Sawada M, et al. Biweekly CHOP or THP-COP regimens in the treatment of newly diagnosed aggressive non-Hodgkin's lymphoma. A comparison of doxorubicin and pirarubicin: A randomized phase II study. J Cancer Res Clin Oncol 2004;130:107–113.
24. Zhai L, Guo C, Cao Y, et al. Long-term results of pirarubicin versus doxorubicin in combination chemotherapy for aggressive non-Hodgkin's lymphoma: Single center, 15-year experience. Int J Hematol 2010;91:78–86.
25. Tsurusawa M, Shimomura Y, Asami K, et al. Long-term results of the Japanese Childhood Cancer and Leukemia Study Group studies 811, 874 and 911 on childhood acute lymphoblastic leukemia. Leukemia 2010;24:335–344.
26. Yamaji K, Okamoto T, Yokota S, et al. Minimal residual disease-based augmented therapy in childhood acute lymphoblastic leukemia: A report from the Japanese Childhood Cancer and Leukemia Study Group Study. Pediatr Blood Cancer 2010;55:1287–1295.
27. Shimomura Y, Baba R, Watanabe A, et al. Japanese Childhood Cancer and Leukemia Study Group (JCCLSG). Assessment of late cardiotoxicity of pirarubicin (THP) in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2011;57:461–466.
28. Meinhardt A, Burkhardt B, Zimmermann M, et al. Phase II window study on rituximab in newly diagnosed pediatric mature B-cell non-Hodgkin's lymphoma and Burkitt leukemia. J Clin Oncol 2010;28:3115–3121.
29. Barth MJ, Goldman S, Smith L, et al. Rituximab pharmacokinetics in children and adolescents with de novo intermediate and advanced mature B-cell lymphoma/leukaemia: A Children's Oncology Group report. Br J Haematol 2013;162:678–683.

Ann Hematol (2013) 92:1537–1541
DOI 10.1007/s00277-013-1785-2

ORIGINAL ARTICLE

Children and adolescents with follicular lymphoma have an excellent prognosis with either limited chemotherapy or with a "watch and wait" strategy after complete resection

Andishe Attarbaschi · Auke Beishuizen · Georg Mann · Angelo Rosolen · Tetsuya Mori · Anne Uyttebroeck · Felix Niggli · Monika Csoka · Zdenka Krenova · Karin Mellgren · Edita Kabickova · Alan KS Chiang · Alfred Reiter · Denise Williams · Birgit Burkhardt · on behalf of the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Study Group

Received: 20 February 2013 / Accepted: 2 May 2013 / Published online: 12 May 2013

Abstract Data on clinical features and outcome in pediatric follicular lymphoma (pFL) are scarce. The aim of this retrospective study including 13 EICNHL and/or i-BFM study group members was to assess clinical characteristics and course in a series of 63 pFL patients. pFL was found to be associated with male gender (3:1), older age (72 % ≥10 years old), low serum LDH levels (<500 U/l in 75 %), grade 3 histology (in 88 %), and limited disease (87 % stage I/II disease), mostly involving the peripheral lymph nodes. Forty-four out of sixty-three patients received any polychemotherapy and 1/63 rituximab only, while 17/63 underwent a "watch and wait" strategy. Of 36 stage I patients, 30 had complete resections. Only one patient relapsed; 2-year event-free survival and overall survival were 94±5 and 100 %, respectively, after a median follow-up of 2.2 years. Conclusively, treatment outcome in pFL

A. Attarbaschi (✉) · G. Mann
Pediatric Hematology and Oncology, St. Anna Children's Hospital, Kinderspitalgasse 6,
1090 Vienna, Austria
e-mail: andishe.attarbaschi@stanna.at

A. Beishuizen
Pediatric Hematology and Oncology, Erasmus MC—Sophia Children's Hospital, Rotterdam, The Netherlands

A. Rosolen
Pediatric Hematology and Oncology, University of Padova, Padova, Italy

T. Mori
National Hospital Organization Nagoya Medical Center, Aichi, Japan

A. Uyttebroeck
Pediatric Hematology and Oncology, University of Leuven, Leuven, Belgium

F. Niggli
Pediatric Hematology and Oncology, University Hospital, Zurich, Switzerland

M. Csoka
Pediatric Hematology and Oncology, Semmelweis University, Budapest, Hungary

Z. Krenova
Pediatric Hematology and Oncology, University Hospital, Brno, Czech Republic

K. Mellgren
Pediatric Hematology and Oncology, The Queen Silvia's Hospital for Children and Adolescents, University of Gothenburg, Gothenburg, Sweden

E. Kabickova
Pediatric Hematology and Oncology, University Hospital, Prague, Czech Republic

A. K. Chiang
Department of Pediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong

A. Reiter · B. Burkhardt
Pediatric Hematology and Oncology, Justus Liebig University, Giessen, Germany

D. Williams
Pediatric Hematology and Oncology, Cambridge University Hospitals Foundation Trust, Addenbrooke's Hospital, Cambridge, UK

B. Burkhardt
Pediatric Hematology and Oncology, University of Münster, Münster, Germany

seems to be excellent with risk-adapted chemotherapy or after complete resection and an observational strategy only.

Keywords Follicular lymphoma · Complete resection · "Watch and wait" · Outcome

Introduction

While follicular lymphoma (FL) accounts for 25 % of non-Hodgkin's lymphomas (NHL) in adulthood, it rarely occurs in children and adolescents (<2 % of cases) [1–4]. FL is recognized as a unique histopathological entity in the pediatric age group, with a high proportion, having grade 3 morphology, and no *BCL2*-rearrangement [1, 3, 5]. Moreover, while most adult patients present with disseminated disease at initial diagnosis, children usually present with localized disease often confined to the peripheral lymph nodes only [1, 3, 6, 7]. Optimal treatment of pediatric FL (pFL) has not yet been defined, and therapeutic strategies differ considerably with some groups applying intensive B cell NHL-type chemotherapy according to the stage of disease, others relying on CHOP-like cycles±rituximab and others favoring a "watch and wait" strategy after complete resection for at least *BCL2*–negative pFL [3, 6–12]. Regardless of the type of therapy, cure rates approach 90 % [3, 6, 8–10, 12]. Nevertheless, systematic data are scarce regarding clinical, biological, and outcome data in children and adolescents with FL. Thus, the two largest consortia in childhood NHL, the European Intergroup for Childhood NHL (EICNHL) and the international Berlin–Frankfurt–Münster (i-BFM) group, designed a retrospective multinational study on this rare B cell NHL. Herein, we report on the characteristics and outcome of 63 patients with pFL included in this analysis.

Patients and methods

Between May and December 2011, we performed an international survey of pFL, including only patients with nationally centrally reviewed histopathology from 13 EICNHL and/or i-BFM study group members. The survey included questions on demographics and disease (age, gender, sites of involvement, stage of disease, pretherapeutic lactate dehydrogenase (LDH) level) as well as on treatment (surgery, chemotherapy, radiotherapy) and outcome (date of remission, relapse, death, last follow-up). After 2000, a total of 63 children and adolescents up to 18 years old diagnosed with pFL were identified in the respective countries. The diagnosis was based on morphological and immunophenotypic criteria according to the World Health Organization classification [13]. Staging procedures as well as therapy protocols applied to the patients are described in detail elsewhere [3, 11, 14–19]. Most, if not all, patients were treated according to national treatment guidelines. All patients were treated, with informed consent from the patients, patient's parents, or legal guardians. Studies were conducted in accordance with the Declaration of Helsinki, and approval was delivered by the ethic committees. Event-free survival (EFS) and overall survival (OS) were estimated with Kaplan–Meier curves.

Results and discussion

Among the 63 patients, the male to female ratio was 3:1, and median age was 13.0 years (range 1.4–17.1 years), with 45/63 patients (72 %) ≥10 years old. The median pretherapeutic serum LDH level was 252 U/l (range 93–550 U/l), with 47/63 patients (75 %) having levels <500 U/l. Thirty-six out of sixty-three (57 %) had stage I (30 (83 %) with initial complete resection), 19 (30 %) stage II (2 (11 %) with initial complete resection), six (10 %) stage III, and two (3 %) children had stage IV disease, according to the St. Jude staging system, resulting in 54/63 patients (87 %) with limited stage I/II disease [19]. Details on patient characteristics and sites of involvement are summarized in Table 1, showing that 50/63 patients (79 %) had peripheral lymph node involvement. Histopathological grading was available in 48/63 patients (76 %), demonstrating grade 1 or 2 morphology in 6/48 (12.5 %) and grade 3 morphology in 42/48 patients (87.5 %). Nine out of forty-two patients (21 %) with grade 3 pFL had components of diffuse large B cell lymphoma (DLBCL).

Forty-four out of sixty-three patients (70 %) received any polychemotherapy and one (2 %) rituximab only, while 17 (26 %) underwent a "watch and wait" strategy (all with initial complete resection) (Table 1). In one patient (2 %), the type of therapy received could not be retrieved. Of the 38/44 patients with available information, all but two patients received low or intermediate risk B cell NHL-type therapy (Table 1). Only 1/63 patients (2 %) relapsed (after "watch and wait"), and none of the patients died from the disease itself or therapy-related toxicity. The 2-year EFS and OS rates were 94±5 and 100 % (Fig. 1), respectively, after a median follow-up of 2.2 years (range 0.19–8.71 years).

To our knowledge, this report including 63 patients with centrally reviewed pFL covering a time period >10 years represents by far the largest series of pFL in childhood and adolescence reported to date. Although the analysis has been conducted retrospectively, was not population-based, and patients were not treated according to a common protocol or strategy, it allows several insights into the clinical presentation and outcome of pFL patients and thus may have important implications on the future management of this

Table 1 Clinical, laboratory, and treatment characteristics as well as outcome of the 63 patients with pediatric follicular lymphoma

Variable	No. of pts.
Gender	
Male	47 (75 %)
Female	16 (25 %)
Age (y)	
Median	13.0
Range	1.4–17.7
<10	18 (28 %)
≥10–15	25 (40 %)
≥15	20 (32 %)
sLDH level (U/l)	
Median	252
Range	93–550
<500	47 (75 %)
≥500	5 (8 %)
n.a.	11 (17 %)
Stage of disease	
Stage I	36 (57 %)
Stage II	19 (30 %)
Stage III	6 (10 %)
Stage IV	2 (3 %)
Histological grading	
Grade 1	4 (6 %)
Grade 2	1 (2 %)
Grade 3[a]	27 (43 %)
Grade 1+2	1 (2 %)
Grade 1+3a	1 (2 %)
Grade 1+2+3a+MZL	1 (2 %)
Grade 2+3a	2 (3 %)
Grade 3+DLBCL[b]	9 (14 %)
Grade 3a+MZL	2 (3 %)
n.a.	15 (24 %)
Sites of involvement[c]	
Peripheral lymph nodes*	50 (79 %)
Head and neck (extranodal)	1 (2 %)
Tonsils	4 (6 %)
Ear–nose–throat	4 (6 %)
Mediastinum	0
Abdomen	9 (14 %)
Bone marrow	2 (3 %)
Central nervous system	0
Testis	2 (3 %)
Skin	1 (2 %)
Bone	1 (2 %)
Resection status	
Incomplete/biopsy	26 (41 %)
Complete	32 (51 %)
n.a.	5 (8 %)
Treatment	
Chemotherapy[e]	44 (70 %)
Rituximab only	1 (2 %)
"Watch and wait"	17 (26 %)
n.a.	1 (2 %)
Complete resection	
"Watch and wait"	17 (53 %)
Chemotherapy	15 (47 %)
Resection acc. to stage	
Stage I	36
Stage I-R	30 (83 %)
Stage I-NR	4 (11 %)
Stage I-n.a.	2 (6 %)
Stage II	19
Stage II-R	2 (10 %)
Stage II-NR	14 (74 %)
Stage II-n.a.	3 (16 %)
Stage III/IV-NR	8 (100 %)
Radiotherapy	
Yes	1 (2 %)
No	61 (96 %)
n.a.	1 (2 %)
Outcome	
Relapse	1 (2 %)
Death	0
2-year EFS	94±5 %
2-year OS	100 %
Follow-up (y)	
Median	2.2
Range	0.2–8.7
Lost to follow-up	1 (2 %)[f]

No. of pts number of patients, *y* years, *sLDH* serum lactate dehydrogenase, *n.a.* not available, *MCL*, marginal zone lymphoma, *DLBCL* diffuse large B cell lymphoma, *acc.* according, *R* complete resection, *NR* no complete resection, *CCR* complete continuous remission, *EFS* event-free survival, *OS* overall survival

[a] 13/27 with grade 3a, 10/27 with grade 3b, and 3/27 patients with no information on the 3a/3b variant; [b] 3/9 with grade 3a and 6/9 patients with grade 3b morphology, [c] 27/63 patients suffered from stage II, III, or IV disease and thus had >1 site of involvement. [d] corresponding to cervical (submandibular), supra- and infraclavicular, pre- and retroauricular, nuchal, parotical, axillary, and inguinal lymph node regions, [e] according to protocols of the NHL-BFM (n=27), AIEOP (n=3), LMB (n=2), JACLS (n=5), and UKCCSG (n=1) studies; CHOP (n=5), CVP (n=1). [f] This patient was lost to follow-up immediately after the primary operation

indolent disease. Our data convincingly show that pFL is usually associated with male gender (3:1), older age (40 % 10–15 years, 32 % ≥15 years old), low serum LDH levels (<500 U/l in 75 %), and limited disease (87 % with stage I/II

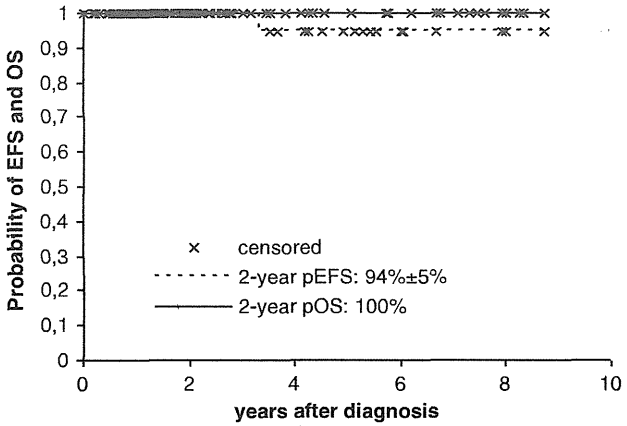

Fig. 1 Two-year event-free and overall survival of the 63 patients with pediatric follicular lymphoma

disease), mostly involving the peripheral lymph nodes. However, as we identified stage III/IV patients, initial diagnostic work-up should always follow the St. Jude staging system [19]. Due to its rarity, only few case reports and series on pFL have been published so far with patient numbers ranging from 4–25 [3, 6, 8–10, 12]. Most of the reports demonstrated similar findings concerning the initial clinical and laboratory features of pFL [1, 3, 6, 8–10, 12].

Nonetheless, we demonstrated that in contrast to FL in adults which is usually of low-grade morphology and not curable with diverse treatment approaches, pFL is frequently associated with grade 3 morphology and has a very good outcome after limited chemotherapy or complete resection followed by a "watch and wait" strategy [3, 11, 20]. Chemotherapy was performed according to stage-adapted protocols of the NHL-BFM (n=27), AIEOP (n=3), LMB (n=2), JACLS (n=5), and UKCCSG (n=1) studies and with CHOP (n=5) and CVP (n=1) cycles, respectively [6, 15–18, 21, 22].

Importantly, neither higher histological grading nor initial components of DLBCL were associated with an unfavorable prognosis. In addition, of the 32 patients with initial complete resection (including 30/36 stage I patients), 17 (53 %) children had no further treatment with only one relapse (local), suggesting no systemic disease in localized pFL. The excellent overall outcome of our cohort of FL patients is comparable to the results published in the literature, showing that pediatric stage-adapted B cell NHL-type chemotherapy and CHOP-like cycles±rituximab are effective in (in)completely resectable disease [1, 3, 6, 8–10, 12, 22]. However, the exact role of complete resection and observation has not been validated until yet. Thus, future clinical trials should aim to establish the least amount of effective (chemo) therapy necessary for cure of pFL. As almost all cycles of chemotherapy used for pediatric B cell NHL include anthracyclines, alkylating agents, and intrathecal therapy, low intensity chemotherapy for pFL should be ideally free of the latter components usually carrying the risk for acute and long-term toxicity [16–18, 23]. A recent study in pediatric early-stage nodular lymphocyte predominant Hodgkin's lymphoma may serve as a paradigm, as it has shown that low intensity chemotherapy is successful in noncompletely resectable disease, while more toxic treatment blocks applied for classic Hodgkin's lymphoma can be reserved for relapse [24].

Notably, there are several limitations when analyzing data from a multinational retrospective survey on a very rare lymphoma subtype, all of which necessitate further evaluation in well-defined prospective trials. As such, we were unable to report on genetic studies, minimal residual disease screening, and in particular on how and why the decision was taken by the responsible physicians to follow a "watch and wait strategy" or chemotherapy in completely resected disease.

Nevertheless, based on the data gained from our unique survey on pFL, we concluded that in the case of complete resections in carefully evaluated stage I patients a "watch and wait" strategy might be possible. However, we suggest that patients are only candidates for complete surgical resection if the operation can be performed easily and safely, and, most importantly, without any functional impairment. In all other patients, initial surgery should include the least invasive procedure to establish the diagnosis followed by limited chemotherapy. Given the difficulties in differentiating pFL from reactive lymphadenopathy, evaluation by an experienced hematopathologist is highly recommended before starting any therapy [13]. As children with nonresectable pFL had an excellent outcome with multidrug chemotherapy, which is associated with acute and long-term toxicity, multinational controlled trials have to be performed, taking genetics (*BCL2*, *BCL6*, *IGH*, *C-MYC*) into account, to clearly establish not only that no chemotherapy is a safe approach in stage I patients with complete resection, but low intensity chemotherapy ± monoclonal antibodies is sufficient for patients with noncompletely resectable disease [7, 21–23, 25, 26].

Acknowledgments We thank all participating institutions and physicians for their support of the study. This EICNHL and i-BFM paper was written on behalf of the Berlin–Frankfurt–Münster (BFM) study group (Austria, Germany, Switzerland, Czech Republic), Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), UK Children's Cancer and Leukemia study group (CCLG), Nordic Society of Pediatric Hematology and Oncology (NOPHO), Belgian Society of Pediatric Hematology and Oncology, Dutch Childhood Oncology Group (DCOG), Hungarian Pediatric Oncology Network, Japanese Pediatric Leukemia/Lymphoma study group (JPLSG), and Hong Kong Pediatric Hematology and Oncology study group (HKPHOSG). This work was supported by the Cancer Research UK, the Forschungshilfe Station Peiper (BFM Germany), the St. Anna Kinderkrebsforschung (BFM Austria), the Czech Ministry of Health supported projects for conceptual

development of research organization 00064203 and 65269705 (BFM Czech Republic), the Associazione Italiana Contro le Leucemie and Fondazione Citta della Speranza (AIEOP), and the Ministry of Health, Labor, and Welfare of Japan (JPLSG).

Conflicts of interest The authors declare no competing financial interests.

References

1. Agrawal R, Wang J (2009) Pediatric follicular lymphoma: a rare clinicopathologic entity. Arch Pathol Lab Med 133:142–146
2. Anderson JR, Armitage JO, Weisenburger DD (1998) Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's lymphoma classification project. Ann Oncol 9:717–720
3. Oschlies I, Salaverria I, Mahn F, Meinhardt A, Zimmermann M, Woessmann W, Burkhardt B, Gesk S, Krams M, Reiter A, Siebert R, Klapper W (2010) Pediatric follicular lymphoma—a clinicopathological study of a population-based series of patients treated within the non-Hodgkin's lymphoma-Berlin–Frankfurt–Munster (NHL-BFM) multicenter trials. Haematologica 95:253–259
4. Kansal R, Singleton TP, Ross CW, Finn WG, Padmore RF, Schnitzer B (2002) Follicular Hodgkin lymphoma: a histopathologic study. Am J Clin Pathol 117:29–35
5. Louissaint A Jr, Ackerman AM, Dias-Santagata D, Ferry JA, Hochberg EP, Huang MS, Iafrate AJ, Lara DO, Pinkus GS, Salaverria I, Siddiquee Z, Siebert R, Weinstein HJ, Zukerberg LR, Harris NL, Hasserjian RP (2012) Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood 120:2395–2404
6. Atra A, Meller ST, Stevens RS, Hobson R, Grundy R, Carter RL, Pinkerton CR (1998) Conservative management of follicular non-Hodgkin's lymphoma in childhood. Br J Haematol 103:220–223
7. Kumar R, Galardy PJ, Dogan A, Rodriguez V, Khan SP (2011) Rituximab in combination with multiagent chemotherapy for pediatric follicular lymphoma. Pediatr Blood Cancer 57:317–320
8. Finn LS, Viswanatha DS, Belasco JB, Snyder H, Huebner D, Sorbara L, Raffeld M, Jaffe ES, Salhany KE (1999) Primary follicular lymphoma of the testis in childhood. Cancer 85:1626–1635
9. Lones MA, Raphael M, McCarthy K, Wotherspoon A, Terrier-Lacombe MJ, Ramsay AD, Maclennan K, Cairo MS, Gerrard M, Michon J, Patte C, Pinkerton R, Sender L, Auperin A, Sposto R, Weston C, Heerema NA, Sanger WG, von Allmen D, Perkins SL (2012) Primary follicular lymphoma of the testis in children and adolescents. J Pediatr Hematol Oncol 34:68–71
10. Lorsbach RB, Shay-Seymore D, Moore J, Banks PM, Hasserjian RP, Sandlund JT, Behm FG (2002) Clinicopathologic analysis of follicular lymphoma occurring in children. Blood 99:1959–1964
11. McNamara C, Davies J, Dyer M, Hoskin P, Illidge T, Lyttelton M, Marcus R, Montoto S, Ramsay A, Wong WL, Ardeshna K (2012) Guidelines on the investigation and management of follicular lymphoma. Br J Haematol 156:446–467
12. Pinto A, Hutchison RE, Grant LH, Trevenen CL, Berard CW (1990) Follicular lymphomas in pediatric patients. Mod Pathol 3:308–313
13. Murphy SB, Fairclough DL, Hutchison RE, Berard CW (1989) Non-Hodgkin's lymphomas of childhood: an analysis of the histology, staging, and response to treatment of 338 cases at a single institution. J Clin Oncol 7:186–193
14. Amos Burke GA, Imeson J, Hobson R, Gerrard M (2003) Localized non-Hodgkin's lymphoma with B cell histology: cure without cyclophosphamide? A report of the United Kingdom Children's Cancer Study Group on studies NHL 8501 and NHL 9001 (1985–1996). Br J Haematol 121:586–591
15. Fujita N, Kobayashi R, Takimoto T, Nakagawa A, Ueda K, Horibe K (2011) Results of the Japan Association of Childhood Leukemia Study (JACLS) NHL-98 protocol for the treatment of B cell non-Hodgkin lymphoma and mature B cell acute lymphoblastic leukemia in childhood. Leuk Lymphoma 52:223–229
16. Gerrard M, Cairo MS, Weston C, Auperin A, Pinkerton R, Lambilliote A, Sposto R, McCarthy K, Lacombe MJ, Perkins SL, Patte C (2008) Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B cell non-Hodgkin's lymphoma: results of the FAB/LMB 96 international study. Br J Haematol 141:840–847
17. Pillon M, Di Tullio MT, Garaventa A, Cesaro S, Putti MC, Favre C, Lippi A, Surico G, Di Cataldo A, D'Amore E, Zanesco L, Rosolen A (2004) Long-term results of the first Italian Association of Pediatric Hematology and Oncology protocol for the treatment of pediatric B cell non-Hodgkin lymphoma (AIEOP LNH92). Cancer 101:385–394
18. Woessmann W, Seidemann K, Mann G, Zimmermann M, Burkhardt B, Oschlies I, Ludwig WD, Klingebiel T, Graf N, Gruhn B, Juergens H, Niggli F, Parwaresch R, Gadner H, Riehm H, Schrappe M, Reiter A (2005) The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B cell neoplasms: a report of the BFM Group Study NHL-BFM95. Blood 105:948–958
19. Murphy SB (1980) Classification, staging, and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol 7:332–339
20. Kridel R, Sehn LH, Gascoyne RD (2012) Pathogenesis of follicular lymphoma. J Clin Invest 122:3424–3431
21. Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, Offner FC, Gomez-Codina J, Belch A, Cunningham D, Wassner-Fritsch E, Stein G (2008) Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 26:4579–4586
22. Perkins SL, Gross TG (2011) Pediatric indolent lymphoma–would less be better? Pediatr Blood Cancer 57:189–190
23. Goldman S, Smith L, Anderson JR, Perkins S, Harrison L, Geyer MB, Gross TG, Weinstein H, Bergeron S, Shiramizu B, Sanger W, Barth M, Zhi J, Cairo MS (2012) Rituximab and FAB/LMB 96 chemotherapy in children with Stage III/IV B-cell non-Hodgkin lymphoma: a Children's Oncology Group report. Leukemia
24. Shankar A, Hall GW, Gorde-Grosjean S, Hasenclever D, Leblanc T, Hayward J, Lambilliotte A, Daw S, Perel Y, McCarthy K, Lejars O, Coulomb A, Oberlin WO, Wallace WH, Landman-Parker J (2012) Treatment outcome after low intensity chemotherapy (CVP) in children and adolescents with early stage nodular lymphocyte predominant Hodgkin's lymphoma—an Anglo–French collaborative report. Eur J Cancer 48:1700–1706
25. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, Solal-Celigny P, Offner F, Walewski J, Raposo J, Jack A, Smith P (2005) CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 105:1417–1423
26. Meinhardt A, Burkhardt B, Zimmermann M, Borkhardt A, Kontny U, Klingebiel T, Berthold F, Janka-Schaub G, Klein C, Kabickova E, Klapper W, Attarbaschi A, Schrappe M, Reiter A (2010) Phase II window study on rituximab in newly diagnosed pediatric mature B cell non-Hodgkin's lymphoma and Burkitt leukemia. J Clin Oncol 28:3115–3121

Pediatr Blood Cancer 2013;60:E118–E121

BRIEF REPORT

Central Nervous System Involvement in Anaplastic Large Cell Lymphoma in Childhood: Results From a Multicentre European and Japanese Study

Denise Williams, MB Bch,[1]* Tetsuya Mori, MD PhD,[2] Alfred Reiter, MD,[3] Wilhelm Woessman, MD,[3] Angelo Rosolen, MD,[4] Grazyna Wrobel, MD,[5] Jozsef Zsiros, MD PhD,[6] Anne Uyttebroeck, MD PhD,[7] Ildiko Marky, MD,[8] Marie-Cécile Le Deley, MD PhD,[9,10] Laurence Brugières, MD,[11] and for the European Intergroup for Childhood Non-Hodgkin Lymphoma, the Japanese Pediatric Leukemia/Lymphoma Study Group

In an international study of systemic childhood ALCL, 12/463 patients had CNS involvement, three of which had isolated CNS disease. Comparative analysis of CNS positive and negative patients showed no difference in ALK positivity, immunophenotype, presence of B symptoms or other sites of disease. The lymphohistiocytic variant was over represented in the CNS positive group (36% vs. 5%). With multi-agent chemotherapy, including high dose methotrexate, Ara-C and intrathecal treatment, the event free and overall survival of the CNS positive group at 5 years were 50% (95%CI, 25–75%) and 74% (45–91%), respectively with a median follow up of 4.1 years. Pediatr Blood Cancer 2013;60:E118–E121. © 2013 Wiley Periodicals, Inc.

Key words: anaplastic large cell lymphoma; childhood; CNS disease; lymphohistiocytic; non-Hodgkin lymphoma

INTRODUCTION

Central nervous system (CNS) involvement in anaplastic large cell lymphoma (ALCL) is rare at diagnosis and relapse and there are few published data. Most publications report collectively on CNS disease in childhood NHL, of which ALCL constitutes small numbers [1], or are single case reports [2,3]. In 1999, the European Intergroup for Childhood NHL (EICNHL) designed a prospective multinational study for treatment of childhood ALCL (ALCL99). We report the incidence, clinical pattern and outcome of CNS disease in this study.

PATIENTS AND METHODS

Between 1999 and 2006, 463 children with systemic ALCL from 10 study groups and 12 countries were registered with informed consent on the ALCL99 study. The study involved registration of all children with ALCL and a randomised treatment trial according to risk factors defined by the previously reported prognostic factor study [4]. Patients with CNS disease were registered but were excluded from the treatment trial.

ALCL diagnosis was based on histopathology and immunohistochemistry according to the revised European American classification of lymphoid malignancies. Pathological review was performed in 96% of registered patients, including all patients with CNS involvement [5].

Staging was performed as described within the protocol [6,7]. A cerebrospinal fluid (CSF) examination was performed at diagnosis in all patients and cranial imaging, CT or MRI, recommended in patients with neurological symptoms. CNS involvement was defined as the presence of lymphoma cells in the CSF, demonstration of the t(2;5) translocation in the CSF, presence of a cranial nerve palsy (CNP) not explained by a lesion outside the CNS or an intracerebral (ICM) or spinal lesion on imaging.

Patients with CNS disease were treated according to the preference of the treating national group with protocols designed for B-NHL with CNS involvement, either the Berlin-Frankfurt-Münster (BFM) group BFM 90 protocol branch K3 [8] or the LMB 96/2001 of the French Society of Paediatric Oncology (SFCE) [9,10]. Some patients, though ineligible, were treated on the ALCL 99 protocol [6]. Cranial radiotherapy was recommended depending on age and response to chemotherapy.

Clinical and pathological characteristics were compared between the CNS-positive and CNS-negative patients using Fisher's exact tests. Event-free and overall survival were estimated with Kaplan–Meier curves and comparisons performed with log-rank tests.

DOI 10.1002/pbc.24591
Published online 29 May 2013 in Wiley Online Library (wileyonlinelibrary.com).

[1]Department of Pediatric Oncology, Cambridge University Hospital NHS Trust, Cambridge, United Kingdom; [2]Department of Paediatrics, National Center for Child Health and Development, Tokyo, Japan; [3]Non-Hodgkin Lymphoma–Berlin-Frankfurt-Muenster Study Centre, Department of Pediatric Hematology and Oncology, Justus-Liebig-University, Giessen, Germany; [4]Department of Pediatrics, University Hospital, Padova, Italy; [5]Department of Bone Marrow Transplantation, Children Oncology and Hematology, Medical University, Wroclaw, Poland; [6]Department of Pediatric Oncology, Emma Kinderziekenhuis, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [7]Department of Pediatric Hematology/Oncology, University Hospital, Leuven, Belgium; [8]Department of Pediatrics, Göteborg University, Göteborg, Sweden; [9]Biostatistics and Epidemiology Unit, Institut Gustave-Roussy, Villejuif, France; [10]Paris-Sud University, Le Kremlin-Bicetre, France; [11]Department of Pediatric Oncology, Institut Gustave-Roussy, Villejuif, France

Authorship contributions: L.B., M.L.D. and A.R. (Reiter), D.W. and A. Rosolen designed and planned the study; D.W., T.M., L.B. and M.L.D. wrote the manuscript; M.L.D. was in charge of data pooling, data checking and statistical analysis; all other authors (A.U., I.M., W.W., G. W., J.Z.) as well as L.B., A.R. (Reiter) and D.W. were principal or co-investigators in their study groups and institutions, coordinated the study in their countries, provided study materials and recruited patients. All authors read and approved the final version of the manuscript.

Conflict of interest: Nothing to declare.

*Correspondence to: Dr. Denise Williams, Department of Pediatric Oncology, Cambridge University Hospital NHS Trust, Cambridge CB2 0QQ, UK. E-mail: denise.williams@addenbrookes.nhs.uk

Received 8 January 2013; Accepted 11 April 2013

TABLE I. Tweleve Patients With Anaplastic Large Cell Lymphoma With Central Nervous System (CNS) Disease: Pattern of CNS Disease, Sites of Disease, Treatment and Response to Treatment

Patient	CNS disease CNP/ICM/LCCSF	Other sites of disease	Histologic subtype/ immunophenotype	Chemotherapy protocol	RT Y/N dose	CR	Relapse	Site of disease at relapse	Outcome: Alive (A)/dead (D) median follow up of 4.1 yrs (range 2.3–7.4)
1	LCCSF	Nodes, skin	LH/T cell	BFM NHL 90 K3	N but planned	Y	Y	Skin, spleen, nodes	D (TRM after further relapse)
2	LCCSF	Nodes, liver, skin, BM	LH/T cell	ALCL 99	N	N			D
3	LCCSF/ICM	None	Unclassified/T cell	BFM NHL 90 K3	Y 24Gy	Y			A
4	CNP/ICM	None	LH/T cell	BFM NHL 90 K3	Y 24Gy	Y			A
5	ICM	Nodes, mediastinum, lung, liver, spleen	LH/T cell	ALCL 99	N	Y			A
6	LCCSF	Nodes, sinuses, ENT	Common type/null cell	BFM NHL 90 K3	N but planned	N			A
7	ICM	Lung	Mixed/T cell	LMB96 Group C	N but planned	N			D
8	LCCSF	Nodes, skin	Common type/T cell	LMB96 Group C	N	Y	Y	CNS	D (TRM after further relapse)
9	CNP/ICM/LCCSF	Nodes, mediastinum, lung, liver, spleen	Common type/T cell	LMB96 Group C	Y 24Gy	Y			A
10	CNP/ICM	Nodes, spleen, bone	Common type/T cell	LMB 2001 group C	Y 18Gy	Y			A
11	LCCSF	Nodes, mediastinum, lung, liver, skin	Common type/T cell	LMB 2001 group C	N	Y			A
12	CNP/ICM	None	Common type/T cell	ALCL 99	N	Y	Y	CNS	A

CNS, central nervous system; CNP, cranial nerve palsy; ICM, intracerebral mass; LCCSF, lymphoma cells in the CSF; LH, lymphohistiocytic; RT, radiotherapy; CR, complete remission; TRM, treatment related mortality.

RESULTS

CNS involvement at diagnosis occurred in 12/463 (2.6%) patients registered in ALCL99 study (Table I). Lymphoma cells in the CSF alone were found in 5/12 (range 56–570 cells/mm^3), an ICM alone in 5/12, and 2/12 showed the presence of both. All four patients with a cranial nerve palsy also had an ICM. Isolated CNS involvement occurred in 3/12 patients, all with an ICM.

Comparative analysis of CNS positive and negative patients revealed no significant difference in the incidence of ALK positivity, immunophenotype, presence of B symptoms or other sites of disease. However, presence of a lymphohistiocytic (LH) histological component was significantly higher in the CNS positive patients, 4/11 (36%) compared to 23/423 (5%) of the CNS negative group ($P = 0.003$) (Table II). One CNS positive patient, though confirmed ALCL at review did not have a subtype allocated.

In patients with CNS and systemic disease, there appeared to be an association with other clinical risk factors; 8/9 patients having high risk features, skin, mediastinal, liver, spleen or lung involvement [4].

All 12 patients were treated with chemotherapy according to BFM 90 protocol branch K3 (n = 4) or LMB 96/2001 protocol (n = 5) and three with ALCL 99 protocol [6]: three did not achieve remission, two of them died and the third progressed but achieved complete remission (CR) with second line therapy (Table I). Among the 9/12 patients (75%) who achieved remission with initial therapy, six are alive in 1st CR and three relapsed systemically (one also in the CNS). Two died of toxicity during treatment after a further relapse and one patient achieved a second CR. Overall, 8/12 patients remain alive in first (n = 6) or second CR (n = 2). Four patients died, two of treatment related toxicity, and two of disease. Cranial radiotherapy (18–24 Gy) was planned in seven patients and performed in only four as three patients relapsed/progressed before radiotherapy. All 4 patients who received cranial irradiation as part of first line therapy remain in complete remission, whereas the five patients where the intention was to treat with chemotherapy alone, two patients relapsed in the CNS alone at 2 and 7 months off treatment. All four patients treated with radiotherapy had ICM's, two of them associated with systemic disease. With a median follow

TABLE II. Clinical and Pathological Characteristics of 463 Patients With Systemic ALCL, According to the CNS Involvement

	CNS negative n = 451		CNS positive n = 12		
Characteristics	N	%	N	%	*P*-value Fisher exact
Review					0.21
None	20	4	0	0	
National only	47	10	3	25	
International +/− National	384	85	9	75	
Sub-type (MD = 29a)					0.06
Common type	271	64	6	55	
Giant cell	8	2	0	0	
Small cell	24	6	0	0	
Lymphohistiocytic	11	3	3	27	
Hodgkin's like	9	2	0	0	
Mixed	98	23	2	18	
Other	2	<1	0	0	
Lymphohistiocytic component (MD = 29a)	23	5	4	36	0.003
ALK negative	20	4	1	8	0.43
Immunophenotype					>0.99
Null	55	12	1	8	
T-cell	396	88	11	92	
B-symptom	252	57	7	58	>0.99
Lymph nodes	392	87	7	58	0.02
Mediastinal involvement	208	46	4	33	0.56
Spleen involvement	77	17	5	42	0.04
Liver involvement	68	15	4	33	0.10
Lung involvement	91	20	5	42	0.08
Spleen, liver or lung involvement	149	33	7	58	0.12
Visceral involvement	215	48	7	58	0.56
Bone lesion	76	17	1	8	0.70
Skin lesion	85	19	3	25	0.71
High risk (involvement of spleen or liver or lung or mediastinal involvement or skin lesion)	283	63	8	67	>0.99
Bone marrow involvement	44	10	3	25	0.11
Ann Arbor staging (MD = 2)					$<10^{-3}$
St 1	42	9	0	0	
St 2	133	29	0	0	
St 3	137	30	0	0	
St 4	139	31	12	100	

[a]MD, missing data. The histological subtype was defined for 423 CNS negative and 12 CNS positive patients.

up of 4.1 years, the 5-year pEFS and OS of the CNS positive group were 50% (95%CI, 25–75%) and 74% (45–91%) (range 2.3–7.4), respectively.

DISCUSSION

The incidence of CNS disease reported here is similar to previous reports, which range from 0% to 22% [1,8,9,11–13]. This variation may be the result of small numbers, or varying definitions of CNS involvement [3]. The lymphohistiocytic variant seen in this study to be over represented in the CNS + ve group has been reported in case reports of patients with ALCL and CNS disease [2] and also to be associated with a poorer prognosis in systemic ALCL [9,14].

In patients with CNS and systemic disease, there appeared to be an association with other clinical risk factors with 8/9 patients having high risk features [4] supporting the findings of CNS disease in children with NHL being associated with high stage disease [1].

The inferior progression free survival of CNS positive as compared with CNS negative patients may be related to advanced stage disease, or poor risk histological variants, but appears to be an independent prognostic variable in this study [15].

Even though this series of ALCL with CNS involvement is the largest published to date, the number of patients is too small to allow comparison of the efficacy of chemotherapy regimens. Protocols including high dose MTX, Ara-C and intrathecal treatment seem to be effective in this population of patients since a CR could be obtained in 75% of the cases.

As cranial radiotherapy was only planned as part of initial treatment for 7/12 patients, its role is difficult to assess. It was performed more frequently in patients with ICM than in patients with tumour cells in the CSF. It is noteworthy that 5/7 patients with an ICM, who remain alive, had cranial radiotherapy as part of first or second line treatment and of 2/5 patients in whom radiotherapy was not planned suffered a CNS relapse. Though we cannot prove that radiotherapy is necessary to obtain long-term survival, these data support the recommendation of cranial radiotherapy for patients with ALCL and CNS involvement.

There are new promising approaches to the management of ALCL. Vinblastine has been shown to induce complete remission in patients with systemic ALCL even after multiple relapses [16] and is known to cross the blood–brain barrier. Its dual therapeutic effect with a direct killing of tumour cells and ability to boost host immunity [17] may be important in ALCL where the importance of an immune response to the ALK protein has been demonstrated [18]. Additionally, a number of new agents are being evaluated for systemic ALCL. These include brentuximab vedotin and the ALK inhibitor crizotinib [19]. Their role in CNS disease may be limited, crizotinib being shown to have poor CSF penetrance [20] but in combination with standard therapy may improve the outlook in this disease.

ACKNOWLEDGEMENTS

We would like to thank all participating institutions for their support of the study and Nathalie Bouvet-Forteau for the data management of the international database. This EICNHL paper was written on behalf of the Société Francaise de Lutte contre les Cancers et Leucémies de l'enfants, Berlin-Frankfurt-Münster (BFM) Study Group, Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP), United Kingdom Children's Cancer and Leukaemia Group (UK CCLG), Nordic Society of Pediatric Hematology and Oncology (NOPHO), Polish Pediatric Leukemia and Lymphoma Study Group (PPLLSG), Belgian Society of Pediatric Hematology and Oncology, Dutch Childhood Oncology Group (DCOG) and Japanese Pediatric Leukemia and Lymphoma Study Group (JPLLSG). This work was support**ed by the Association Cent Pour Sang la Vie and Institute Gustave-Roussy, Cancer Research United Kingdom, the Forschungshilfe Station Peiper (BFM Germany), the St. Anna Kinderkrebsforschung (BFM Austria), the Associazione Italiana Contro le Leucemie and Fondazione Citta della Speranza (AIEOP), and the Japanese Ministry of Health, Labor and Welfare.

REFERENCES

1. Salzburg J, Burkhardt B, Zimmermann M, et al. Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: A Berlin-Frankfurt-Munster Group Report. J Clin Oncol 2007;25:3915–3922.
2. Ponzoni M, Terreni MR, Ciceri F, et al. Primary brain CD30+ ALK1+ anaplastic large cell lymphoma ('ALKoma'): The first case with a combination of 'not common' variants. Ann Oncol 2002;13:1827–1832.
3. Karikari IO, Thomas KK, Lagoo A, et al. Primary cerebral ALK-1-positive anaplastic large cell lymphoma in a child case report and literature review. Pediatr Neurosurg 2007;43:516–521.
4. Le Deley MC, Reiter A, Williams D, et al. Prognostic factors in childhood anaplastic large cell lymphoma: Results of a large European intergroup study. Blood 2008;111:1560–1566.
5. Harris NL, Jaffe ES, Stein H, et al. A revised European–American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 1994;84:1361–1392.
6. Brugieres L, Le Deley MC, Rosolen A, 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.
7. Le Deley MC, Rosolen A, Williams DM, 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;28:3987–3993.
8. Seidemann K, Tiemann M, Schrappe M, 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;97:3699–3706.
9. Brugieres L, Deley MC, Pacquement H, 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;92:3591–3598.
10. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109:2736–2743.
11. Laver JH, Kraveka JM, Hutchison RE, 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;23:541–547.
12. Williams DM, Hobson R, Imeson J, et al. 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;117:812–820.
13. Pillon M, Gregucci F, Lombardi A, et al. Results of AIEO P LNH-97 protocol for the treatment of anaplastic large cell lymphoma of childhood. Pediatr Blood Cancer 2012;59:828–833.
14. Lamant L, McCarthy K, D'Amore E, 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;29:4669–4676.
15. Le Deley MC, Rosolen A, Williams D, et al. Prognostic factors in childhood anaplastic lymphoma (ALCL): Results of the ALCL99 study. [Abstract 83. Third International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma, Frankfurt 2009]. 2009.
16. Brugieres L, Pacquement H, Le Deley MC, 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;27:5056–5061.
17. Tanaka H, Matsushima H, Nishibu A, et al. Dual therapeutic efficacy of vinblastine as a unique chemotherapeutic agent capable of inducing dendritic cell maturation. Cancer Res 2009;69:6987–6994.
18. Ait-Tahar K, Cerundolo V, Banham AH, et al. B and CTL responses to the ALK protein in patients with ALK-positive ALCL. Int J Cancer 2006;118:688–695.
19. Foyil KV, Bartlett NL. Brentuximab vedotin crizotinib in anaplastic large-cell lymphoma. Cancer J 2012;18:450–456.
20. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. J Clin Oncol 2011;29:e443–e445.

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

Ilske Oschlies,[1] Jasmin Lisfeld,[2] Laurence Lamant,[3] Atsuko Nakazawa,[4] Emanuele S. G. d'Amore,[5] Ulrika Hansson,[6] Konnie Hebeda,[7] Ingrid Simonitsch-Klupp,[8] Jadwiga Maldyk,[9] Leonhard Müllauer,[8] Marianne Tinguely,[10] Markus Stücker,[11] Marie-Cecile LeDeley,[12] Reiner Siebert,[13] Alfred Reiter,[2] Laurence Brugières,[14] Wolfram Klapper,[1] and Wilhelm Woessmann[2]

[1]Department of Pathology, Hematopathology Section and Lymph Node Registry, Christian-Albrechts-University Kiel and University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [2]NHL-BFM Study Center, Department of Pediatric Hematology and Oncology, Justus-Liebig University, Giessen, Germany; [3]Laboratoire Anatomie Pathologique, Centre Hospitalier Universitaire Purpan, Toulouse, France; [4]Department of Pathology, National Center for Child Health and Development, Tokyo, Japan; [5]UO di Anatomia Patologica, Ospedale San Bortolo, Vicenza, Italy; [6]Avdehingen foer patologi, Sahlgrenska Universitetssjukhuset, Gothenburg, Sweden; [7]Radbound University Nijmegen Medical Centre, Department of Pathology, Nijmegen, The Netherlands; [8]Institute of Pathology, Medical University Vienna, Vienna, Austria; [9]Department of Pathology, Childrens Hospital, Warsaw, Poland; [10]Institute of Surgical Pathology, University Hospital Zurich, Zurich, Switzerland; [11]Department of Dermatology and Allergology, Ruhr University Bochum, St. Joseph, Germany; [12]Department of Biostatistics, Institut Gustave Roussy, Villejuif, France; [13]Institute of Human Genetics, Christian-Albrechts-University Kiel and University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany, and [14]Department of Pediatric Oncology, Institut Gustave Roussy, Villejuif, France

ABSTRACT

Anaplastic large cell lymphomas are peripheral T-cell lymphomas that are characterized by a proliferation of large anaplastic blasts expressing CD30. In children, systemic anaplastic large cell lymphomas often present at advanced clinical stage and harbor translocations involving the anaplastic lymphoma kinase (*ALK*) gene leading to the expression of chimeric anaplastic lymphoma kinase (ALK)-fusion proteins. Primary cutaneous anaplastic large cell lymphoma is regarded as an ALK-negative variant confined to the skin and is part of the spectrum of primary cutaneous CD30-positive T-cell lymphoproliferative disorders. Thirty-three of 487 pediatric patients registered within the Anaplastic Large Cell Lymphoma-99 trial (1999 to 2006) presented with a skin limited CD30-positive lymphoproliferative disorder. In 23 of the 33 patients, material for international histopathological review was available, and the cases were studied for histopathological, immunophenotypical and clinical features as well as for breaks within the *ALK* gene. Five of 23 cases and one additional case (identified after closure of the trial) expressed ALK-protein. Complete staging excluded any other organ involvement in all children. Expression of ALK proteins was demonstrated by immunohistochemistry in all cases and the presence of breaks of the *ALK* gene was genetically confirmed in 5 evaluable cases. The histopathological and clinical picture of these skin-restricted ALK-positive lymphomas was indistinguishable from that of cutaneous anaplastic large cell lymphoma. Five children presented with a single skin lesion that was completely resected in 4 and incompletely resected in one. Three of these patients received no further therapy, 2 additional local radiotherapy, and one chemotherapy. All children remain in complete remission with a median follow up of seven years (range 1-8 years). We present 6 pediatric cases of ALK-positive primary cutaneous anaplastic large cell lymphomas. After thorough exclusion of systemic involvement, therapy confined to local measures seems to be sufficient to induce cure.

 doi:10.3324/haematol.2012.065664

Introduction

Anaplastic lymphoma kinase-positive (ALK-positive) anaplastic large cell lymphoma (ALCL) is characterized by a neoplastic proliferation of large pleomorphic (*anaplastic*) CD30-positive ($CD30^+$) T cells with typical translocations involving the *ALK* gene and subsequent expression of chimeric ALK protein.[1] This lymphoma accounts for approximately 15% of childhood non-Hodgkin's lymphomas, but is rare in adulthood.[2,3] ALK-positive (ALK^+) ALCL is usually a systemic disease that frequently involves extranodal sites. In children, 18-25% of systemic ALCLs develop skin manifestations during the course of the disease and this is a poor prognostic factor.[4-9] Systemic ALK-negative (ALK^-) ALCL is included in the updated WHO classification as a separate preliminary entity.[1] ALK-negative ALCL accounts for less than 5% of pediatric systemic ALCLs.[5,10] However, both ALK-positive and ALK-negative ALCLs are considered potentially disseminated diseases.[1]

Primary cutaneous ALCL (cALCL) is regarded by the WHO as a separate disease entity and belongs to the spectrum of

Manuscript received on March 15, 2012. Revised version arrived on June 27, 2012. Manuscript accepted on July 2, 2012.
Correspondence: Ilske Oschlies. E-mail: ioschlies@path.uni-kiel.de

primary cutaneous CD30-positive lymphoproliferations (CD30⁺LPD), a group that also includes lymphomatoid papulosis (LyP).[1] CD30⁺ LPDs share with systemic ALCL the presence of neoplastic CD30⁺ large T cells, but lack *ALK* translocations and protein expression. cALCLs remain confined to the skin, virtually never disseminate beyond local lymph nodes, and show an excellent prognosis after surgical resection without systemic therapy. Most cases of cALCL present as solitary skin lesions, but multiple skin nodules are also found. In contrast to systemic ALCL, cALCL is only rarely found in children and young adults.[11-13] Recently published recommendations for the diagnosis of CD30⁺LPD state that immunohistochemical detection of ALK expression should be considered highly suspicious of a cutaneous manifestation of underlying systemic ALCL.[13] In contrast, *IRF4* translocations have been reported in cALCL and in ALK⁻ ALCLs but not in ALK⁺ ALCL.[14,15] In the international multicenter trial ALCL99, children included with localized skin disease were not to receive systemic chemotherapy based on the assumption that their disease would be CD30⁺LPD. We describe a series of 6 pediatric ALCLs that clinically and histologically resembled cALCL but expressed ALK fusion proteins. These localized cutaneous ALK⁺ ALCL followed the typical benign clinical course of a CD30⁺LPD.

Design and Methods

Identification of cases and histopathological review

In the ALCL99 multicenter study, 487 children and young adults with the diagnosis of ALCL were registered from 1999 to 2006, including 33 patients with a CD30⁺ lymphoproliferative disorder limited to the skin. Patients with isolated skin lesions diagnosed by complete staging procedures were to be followed after resection by 'watchful waiting' without further systemic therapy regardless of the Alk status. For 23 of these, skin limited lymphoma material was available for an international histopathological review. One additional case reported here was identified after completion of registration in 2006. The histological review of the cases was performed by members of the international pediatric lymphoma pathology panel (*IO, LL, AN, EdA, UH, KH, ISK, JM, LM, MT*) using hematoxylin and eosin (H&E) stained slides as well as slides stained immunohistochemically in various laboratories (*see below*). The registered clinical data from the study center were reviewed and additional details were obtained by contacting the attending pediatric oncologist. The study was part of the scientific projects accompanying the ALCL99 study, for which informed consent was obtained. The study was carried out according to the local ethical guidelines and in accordance with the ethical guidelines of the studies in which the patients were treated.

Immunohistochemistry and fluorescence in situ hybridization

All immunohistochemical stainings were performed on whole tissue sections. The stainings were scored semiquantitatively as negative, weak (<30% positive tumor cells or all tumor cells weakly positive), positive (>30% positive tumor cells) or not interpretable. The minimal staining panel for each lymphoma included CD20, CD3, CD30, and ALK. Additional stainings for granzyme B, perforin, TIA1, EMA, CD2, and CD5 were available for individual cases. Due to the retrospective nature of the study, the staining procedures and antibody sources for these markers varied between the participating countries but had been previously established within the group as part of the ALCL99 study.[16] Fluorescence *in situ* hybridization (FISH) for chromosomal breaks in the *ALK* gene or at the *IRF4/DUSP22* locus was performed as previously described.[17,18]

Results

Identification of the 6 ALK-positive cases limited to the skin

Among the 23 cases with ALCL or CD30⁺ lymphoproliferations confined to the skin registered into the ALCL99 study and available for international histopathological review, 5 patients with expression of ALK protein were identified. During the preparation of the manuscript, another case of ALK⁺ ALCL limited to the skin was identified by the NHL-BFM study center and included in this series.

Table 1. Histopathological and immunohistochemical features of 6 pediatric cases of ALK-positive primary cutaneous anaplastic large cell lymphoma.

	Histopathological features					Immunohistochemistry					
Case n.	Epidermal change	Epidermotropism of tumor cells	Dermal involvement*	Involvement of subcutis	Admixed inflammatory cells	CD30 (pattern)	ALK	ALK staining pattern	ALK⁻ small cell component	EMA	CD3
1	hyperplastic, ulceration	+	+	ni	–	++ (sheets)	++	n+cyt	+	++	–
2	ni	ni	ni	+	neutrophils	++ (sheets)	++	n+cyt	–	ni	–
3	normal	–	+	+	lymphohistiocytic	+ (single)	+	n+cyt	+	++	+
4	normal	–	+	+	–	++ (sheets)	++	n+cyt	+	++	–
5	hyperplastic	+	+	+	–	++ (sheets)	++	cyt	–	++	–
6	hyperplastic	–	+	+	lymphohistiocytic	++ (sheets)	++	n+cyt	+	++	+

*Scoring of histopathological features: +: present; -: absent; ni: not interpretable. Scoring of immunohistochemistry: -: negative staining; +: weak staining or <30% of cells moderate to strong staining; ++: moderate to strong staining in >30% cells; n+cyt: nuclear and cytoplasmic staining; cyt: cytoplasmic staining only. *In all evaluable cases dermal involvement was superficial and deep.*

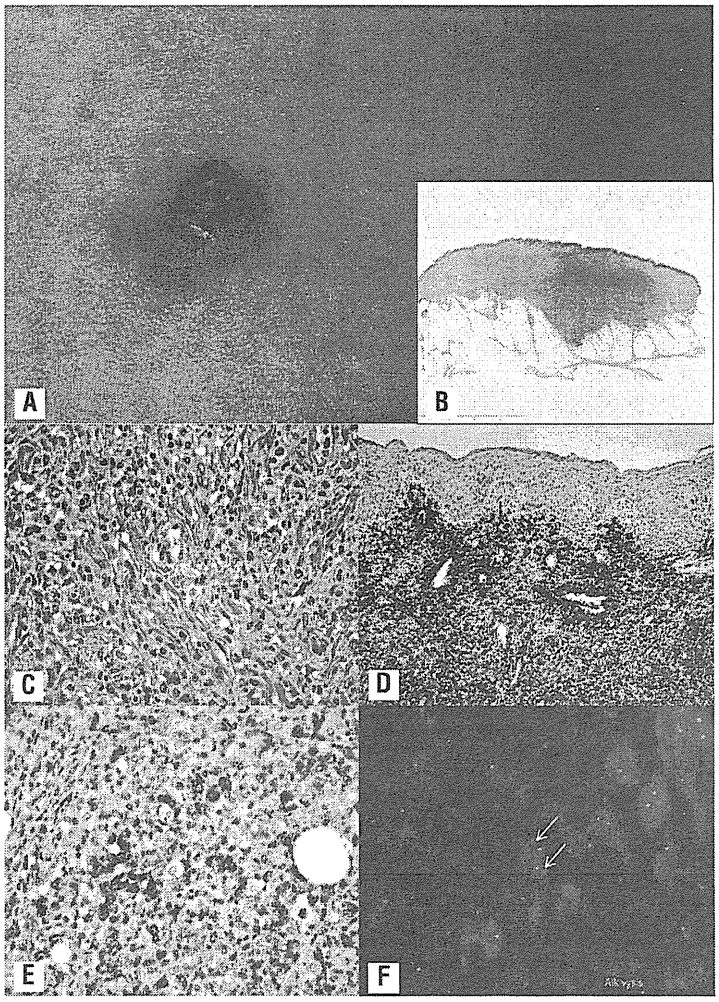

Figure 1. Clinical and histological features of one representative example of ALK-positive ALCL confined to the skin (case 6, see Tables 1 and 2). This is a nodular lesion on the thigh, approximately 2 cm in largest diameter (case 6). The black ink marks the area that had initially been planned for resection; it was later decided to resect the lesion completely (A). At low magnification deep extension of the lesion with a dense dermal infiltration as well as reactive epidermal hyperplasia is observed (B) (Hematoxylin & Eosin staining). Cytologically, histiocytes, a few lymphocytes and intermingled atypical large cells are seen (C) (Hematoxylin & Eosin staining). Large cells in clusters with a perivascular pattern are observed. There is no epidermotropism (D, CD30). Large cells show nuclear and cytoplasmic ALK staining; intermingled with some smaller cells with nuclear ALK (E, ALK). Fluorescence *in situ* hybridization using the LSI ALK BAP probe (Abbott) indicates a chromosomal breakpoint in the *ALK* gene (arrows)(F).

Histological and immunohistochemical features

The main histological and immunohistochemical features of the 6 cases are summarized in Table 1. In most cases, a superficial and deep cutaneous infiltration extending into the subcutis was observed (3 of 4 cases in which all skin layers were included in the biopsy specimen). The lesions were rather poorly demarcated. In one case, an isolated subcutaneous nodule without dermal involvement was seen. In 5 cases, the epidermis was included in the specimen and was either normal in appearance (n=2), showed hyperplastic changes (n=2), or hyperplastic changes with additional focal superficial erosion (n=1). A large number of $CD30^+$ neoplastic blasts forming cohesive sheets were detectable in 5 of 6 cases. However, one case displayed only scattered blasts. In 3 of 6 lesions, the growth pattern of the blasts was perivascular. Reactive inflammatory bystander cells were composed of a moderate number of neutrophils (1 of 6) or lymphohistiocytic cells (2 of 6). No inflammatory bystander cells were detectable in 3 of 6 lymphomas. Figure 1 shows one representative example of an ALK^+ ALCL confined to the skin.

ALK expression was immunohistochemically detectable in all cases with nuclear and cytoplasmic staining in 5 of 6 cases, indicating an underlying *NPM-ALK* fusion due to a t(2;5) translocation. In one lymphoma, diffuse cytoplasmic ALK staining without nuclear positivity was noted. Interestingly, in 4 of 6 lymphomas, a small cell component was detectable, as indicated by predominately nuclear staining of small lymphoma cells (Figure 2). All 5 cases tested for epithelial membrane antigen (EMA) were strongly positive. CD3 was negative (4 of 6) or weakly expressed (2 of 6). All lymphomas expressed at least one cytotoxic protein, such as granzyme B, TIA1 or perforin with the characteristic granular staining pattern (*data not shown*).

Fluorescence in situ hybridization

Material for fluorescence *in situ* hybridization was available for 4 lymphomas. Breaks in the *ALK* gene were detectable in all 4 analyzed cases (Figure 1). In the additional patient with multilocular skin disease *NPM-ALK*-transcripts were detected in the bone marrow and blood by polymerase chain reaction (*data not shown*) so that the ALK-translocation was confirmed molecularely in 5 of 6 patients. In contrast, breaks affecting the *IRF4/DUSP22* locus in 6p25 recurrently involved in cALCL were not detectable in the 3 cases studied.

Clinical characteristics, therapy and outcome

Table 2 summarizes the clinical characteristics of the patients reported in this series. Median age was 10.8 years

(range 7.5-13.8 years). Three patients were male and 3 female. None of the children had a clinically documented history of lymphomatoid papulosis (LyP) or mycosis fungoides. The lymphomas presented clinically as papulonodular skin lesions (5 of 6) and/or subcutaneous nodules (3 of 6). One patient displayed multiple skin lesions (case 4) which were described as multiple *pink nodules* on the trunk, arms and neck. The isolated lesions in the other 5 patients involved the thigh (n=3), neck (n=1) or knee (n=1). Figure 1 shows the clinical presentation of one case with a solitary lesion on the thigh (case 6). None of the children suffered from B symptoms. All patients underwent a complete initial staging procedure to exclude systemic disease according to the ALCL99 protocol, including imaging of the abdomen and thorax, full blood cell count and bone marrow cytology. Lumbar puncture was performed in 5 of the 6 patients. In one patient, minimal disseminated disease (MDD) was detectable, measured by polymerase chain reaction for *NPM-ALK* transcripts[19] in the bone marrow and blood (case 4, Table 2 and *data not shown*). The single skin lesion was surgically completely resected in 4 of the 5 patients. One patient received addi-

Table 2. Clinical features of 6 pediatric cases of ALK-positive primary cutaneous anaplastic large cell lymphoma.

Case n.	Age (years)	Clinical characteristics at diagnosis: Maculopapular lesions	Subcutaneous nodules	Multiple skin lesions	Location	B symptoms	Staging*	Complete resection	Therapy: Chemo/ radiation	Relapse	Outcome: Follow up (years)
1	9.1	+	–	–	ventral thigh, approx. 2 cm in diameter	–	+	+	–	-	8
2	7.5	+	+	–	neck, approx. 3 cm in diameter	–	+	+	–	-	2.3
3	10	+	–	–	thigh, small red lesion	n.e.	+	+	–	-	8
4	11	+	+	+	anterior wall of thorax, neck, back: pink nodules	– arms,	+ (MDD+ BM and pB)[1]	–	chemo[2]	-	8
5	11.9	–	+	–	right knee	–	+	–	radiation	-	5.2
6	13.8	+	–	–	left thigh	–	+ (no CSF)	+	radiation	-	1

[1]MDD: minimal disseminated disease assessed by RT-PCR for t(2;5) (NPM;ALK) in the bone marrow (BM) and peripheral blood (pB) was positive; [2]chemotherapy according to ALCL99 was pre-phase, 3xA, 3xB, complete remission after A1. CSF: cerebrospinal fluid; n.e.: not evaluated; staging: +: complete clinical staging was performed and remained negative.*

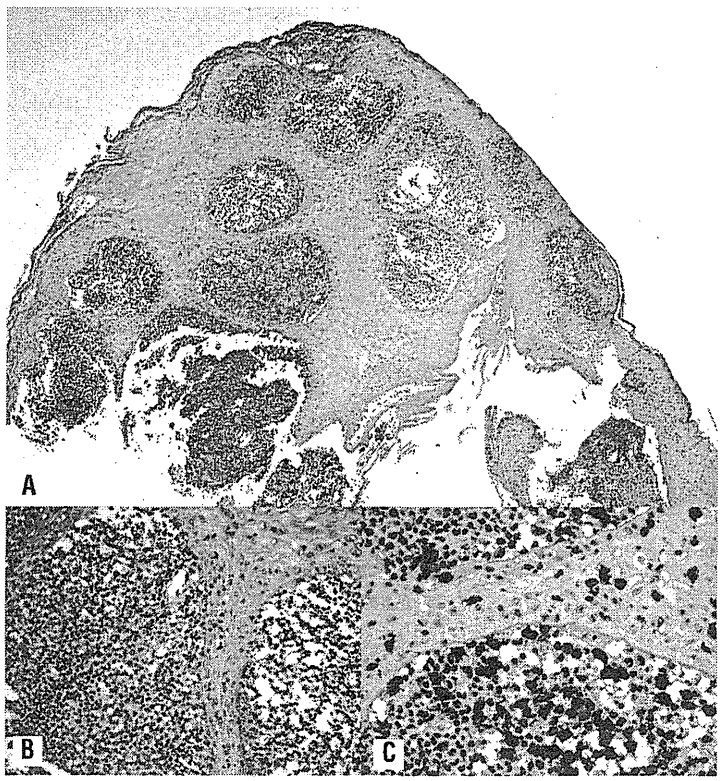

Figure 2. An example of ALK-positive ALCL (case 1, see Table 1) with epidermotropism of lymphoma cells and a subepithelial small cell tumor component. (A and B) Hematoxylin & Eosin staining. (C) ALK1).

Table 3. Literature review of reported ALK-positive cutaneous anaplastic large cell lymphomas and findings in this series.

	Age	Gender	Localization	ALK expression pattern	Therapy of first lesion	Local recurrence	Distant cutaneous recurrence	Number of recurrences reported	Treatment of recurrent lesions	Systemic dissemination	Outcome	Observation period in months
Chan *et al.*[10]	33	m	multiple: trunk, head, leg	nuclear and cytoplasmic	6 cycles of chemotherapy[1]	no	yes	2	excision, chemotherapy	systemic relapse 2 years after diagnosis	CCR	31
Kadin *et al.*[36]	57	m	single lesion leg	cytoplasmic[2]	surgical excision	no	yes	6	surgical excision and radiotherapy	no	CCR	156
Sasaki *et al.*[37] and Hosoi *et al.*[39]	57	f	single lesion forehead	cytoplasmic	spontaneous regression without treatment	no	yes	several	total excision and radiotherapy; 3 years later systemic relapse and DOD	systemic relapse 2.5 years after diagnosis,	DOD	71
Beylot-Barry[33]		1/26 reported primary cutaneous CD30+ lymphomas[3]		nuclear and cytoplasmic	not known	not known	not known	not known	not known	no	not known	at least 6
Su *et al.*[38]	57	f	multiple lesions: trunk	cytoplasmic	6 cycles CHOP[4]	no	no	0	no	no	CCR	13
This series n=6	mean age: 10.7 (range 7-13)	3 m and 3 f	5 patients: single lesions at leg or neck; 1 patient: multiple	5 cases with nuclear and cytoplasmic and 1 case with cytoplasmic	3 cases: surgical excision, 2 cases: excision and local radiotherapy, 1 case chemotherapy	0/6	0/6	0/6	no	no	all CCR	mean: 65 (range 12-96)

[1]*Cyclophosphamide, vincrestine, prednisolon, hydroxydoxorubicine.* [2]*Molecular findings: phosphorylated cytoplasmic ALK protein; FISH: no ALK break.* [3]*Clinical details were not described.* [4]*Cyclophosphamide, adriamycine, vincristine, prednisone. CCR: complete clinical remission; DOD: death of disease.*

tional local radiotherapy after complete excision and in one case an incomplete resection of the skin lesion was followed by local radiotherapy. The patient with multiple skin nodules and MDD in the bone marrow and peripheral blood (case 4, Table 1) received 6 courses of chemotherapy according to the protocol ALCL99 in the high-risk arm.[20] None of the other patients received chemotherapy. All patients reached a complete remission and remained disease-free with a median follow up of seven years (range 1-8 years).

Discussion

We report here 6 cases of ALK+ ALCL limited to the skin. These lymphomas mimicked primary cutaneous CD30+LPD in their histopathology, clinical presentation and response to therapy.

CD30+LPD comprise a spectrum of diseases confined to the skin, including LyP and cALCL, which show overlapping histological features. Both diseases are characterized by a neoplastic infiltrate of anaplastic CD30+ T cells with a variable admixture of reactive inflammatory cells. Single nodular skin lesion or, less frequently, multiple nodules that do not undergo spontaneous regression are the typical presentation of cALCL.[1,13] Distinguishing a primary cutaneous CD30+LPD, such as LyP and cALCL, from secondary involvement of the skin by systemic ALCL is clinically relevant. Treatment of systemic ALCL consists of risk-adapted polychemotherapy. Secondary skin involvement is regarded as a clinical risk factor, often utilized to stratify patients to a more aggressive treatment regimen.[21,22] In contrast, primary cutaneous CD30+LPD, which is limited to the skin and rarely disseminates, usually either resolves spontaneously or is treated locally, e.g. by surgical excision.[13]

All of our cases fulfilled the clinical and histological criteria of a primary cutaneous anaplastic large cell lymphoma with predominantly solitary skin lesions, no history of LyP, no extracutaneous dissemination and response to local therapy,[13] but all cases were ALK+. Given the higher incidence of cALCL in adults, most published series analyzing ALK expression have included predominately adult patients.[23] There have been only single case reports and small series of pediatric cALCL, and in these ALK staining was inconsistently performed.[24-28] We assume that our series is not population-based as cutaneous CD30+LPD are diagnosed and treated either by dermatologists or pediatric oncologists. Nevertheless, our data suggest that ALK+ cALCL might be more frequent than anticipated within the pediatric population, and recommend that all CD30+LPD of the skin in children should be carefully analyzed for ALK expression.

Lamant *et al.*[29] recently reported 5 children with systemic ALK+ ALCL that presented as skin lesions at the site of preceding insect bites, often with involvement of the draining local lymphnode. Thus, the skin might not only present a preferred microenvironment for ALK+ ALCL but might even be the primary site of lymphomagenesis. At the moment, no reliable histopathological features are known to distinguish secondary skin involvement by a systemic ALCL from primary cutaneous CD30+LPD. EMA has been reported to be positive in most systemic ALK+ and ALK- ALCLs[30] but negative in cALCL.[13,31] ALK protein expression, as well as the underlying *ALK*-gene translocation, are considered indicative of systemic ALK+ ALCL and are seen in nearly all pediatric systemic ALCL cases.[10,20] In contrast, cALCL is considered ALK- both at the molecular and the protein level.[32-35] Our cases were ALK and EMA

positive on the one hand but localized and limited to the skin on the other. They, therefore, presented as and thus could be named as *primary cutaneous ALK-positive ALCL*. One could discuss whether the child with multiple skin lesions and positive MDD should have been classified as *child with systemic type ALCL*. Nevertheless, for the moment, staging is determined by clinical imaging as well as by the evaluation of bone marrow cytology, and all these investigations were negative in this child, indicating isolated skin disease. In practical terms, the child was treated with systemic chemotherapy despite the isolated skin involvement, and we would support this treatment decision, especially since positive MDD has been shown to be an adverse prognostic factor in systemic ALCL.[19] To the best of our knowledge, skin-confined variants of ALK$^+$ ALCL have previously been published in 5 cases only. Table 3 shows a summary of the literature[33,36-40] and the cases presented here. However, the published cases differ from our series in two main points. First, all previously published cases were adult patients (Table 2). Second, 2 of 5 previously published cases developed systemic disease years after the initial primary skin disease; a feature that was absent in our cohort (Table 2). Just recently, at the joint workshop of the Society for Hematopathology and the European Association for Hematopathology (SH/EAHP) on cutaneous lymphomas held in Los Angeles in October 2011,[41] 5 new cases of ALK$^+$ ALCLs confined to the skin were presented as case reports. Four of these occurred in adults with variable clinical scenarios, ALK-staining-patterns and histomorphological features, and only one ALK$^+$ ALCL confined to the skin was described in a child with a very unusual mycosis fungoides as clinical and histological presentation. Therefore, more attention to ALK-staining in cutaneous T-cell lymphoproliferations seems justified.

Interesting histological features of the lymphomas reported here were the presence of a small cell component in 4 of the 6 cases, and a perivascular growth pattern in 3. The presence of a small cell component and a perivascular growth pattern have recently been reported to be associated with a poorer outcome in systemic ALK$^+$ ALCL.[16] However, there was no relapse among the 5 patients with exclusive local therapy reported in our series. This emphasizes again that ALK-positive ALCL limited to the skin may represent a specific subgroup of ALK$^+$ ALCL for which prognostic parameters established in systemic ALK$^+$ ALCL do not apply.

In summary, our cases illustrate that ALK$^+$ ALCL can present as a localized skin-limited disease. Localized treatment with careful follow up seems justified after thorough exclusion of systemic disease in this rare variant. Understanding the biology of ALK$^+$ ALCLs that are confined to the skin might influence therapy strategies for ALK$^+$ ALCL also in other locations.

Funding

This work was supported by the José-Carreras-Foundation (DJCLS R08/09). RS and WK are supported by the Kinderkrebs Initiative Buchholz, Holm-Seppensen, Germany. The ALCL99 study was supported by the Forschungshilfe Peiper and the Association Cent pour Sang la Vie, France. None of the authors reported any other potential conflicts of interest.

Acknowledgments

The authors are indebted to all the children and parents who participated in this study, to Nathalie Bouvet, Institut Gustave-Roussy, Villejuif, France, for database management, and Oliviera Batic, Dimitry Abramov and Reina Zühlke-Jenisch for their technical assistance.

Authorship and Disclosures

Information on authorship, contributions, and financial and other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Swerdlow SH, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al. WHO Classification of Tumors of the Haematopoietic and Lymphoid Tissues. Lyon: IARC; 2008.
2. Burkhardt B, Zimmermann M, Oschlies I, Niggli F, Mann G, Parwaresch R, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol. 2005;131(1):39-49.
3. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-30.
4. 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(12):3699-706.
5. 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(6):897-903.
6. 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(3):1560-6.
7. Reiter A, Schrappe M, Parwaresch R, Henze G, Muller-Weihrich S, Sauter S, et al. Non-Hodgkin's lymphomas of childhood and adolescence: results of a treatment stratified for biologic subtypes and stage--a report of the Berlin-Frankfurt-Munster Group. J Clin Oncol. 1995;13(2):359-72.
8. 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(4):812-20.
9. 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(10):3591-8.
10. 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(3):306-9.
11. Bekkenk MW, Geelen FA, van Voorst Vader PC, Heule F, Geerts ML, van Vloten WA, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood. 2000; 95(12):3653-61.
12. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105(10):3768-85.
13. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011; 118(15):4024-35.

14. Wada DA, Law ME, Hsi ED, Dicaudo DJ, Ma L, Lim MS, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. Mod Pathol. 2011;24(4):596-605.
15. Feldman AL, Dogan A, Smith DI, Law ME, Ansell SM, Johnson SH, et al. Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing. Blood. 2011;117(3):915-9.
16. 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. 201;29(35):4669-76.
17. Salaverria I, Philipp C, Oschlies I, Kohler CW, Kreuz M, Szczepanowski M, et al. Translocations activating IRF4 identify a subtype of germinal center-derived B-cell lymphoma affecting predominantly children and young adults. Blood. 2011; 118(1):139-47.
18. Ventura RA, Martin-Subero JI, Jones M, McParland J, Gesk S, Mason DY, et al. FISH analysis for the detection of lymphoma-associated chromosomal abnormalities in routine paraffin-embedded tissue. J Mol Diagn. 2006;8(2):141-51.
19. 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(2):670-7.
20. 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(6):897-903.
21. 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(25):3987-93.
22. 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(5):899-908.
23. Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol. 2009;145(12):1399-404.
24. Tomaszewski MM, Moad JC, Lupton GP. Primary cutaneous Ki-1(CD30) positive anaplastic large cell lymphoma in childhood. J Am Acad Dermatol. 1999;40(5 Pt 2):857-61.
25. Fink-Puches R, Chott A, Ardigo M, Simonitsch I, Ferrara G, Kerl H, et al. The spectrum of cutaneous lymphomas in patients less than 20 years of age. Pediatr Dermatol. 2004;21(5):525-33.
26. Kumar S, Pittaluga S, Raffeld M, Guerrera M, Seibel NL, Jaffe ES. Primary cutaneous CD30-positive anaplastic large cell lymphoma in childhood: report of 4 cases and review of the literature. Pediatr Dev Pathol. 2005;8(1):52-60.
27. Santiago-et-Sanchez-Mateos D, Hernandez-Martin A, Colmenero I, Mediero IG, Leon A, Torrelo A. Primary cutaneous anaplastic large cell lymphoma of the nasal tip in a child. Pediatr Dermatol. 2011;28(5):570-5.
28. Hung TY, Lin YC, Sun HL, Liu MC. Primary cutaneous anaplastic large cell lymphoma in a young child. Eur J Pediatr. 2008;167(1):111-3.
29. Lamant L, Pileri S, Sabattini E, Brugieres L, Jaffe ES, Delsol G. Cutaneous presentation of ALK-positive anaplastic large cell lymphoma following insect bites: evidence for an association in five cases. Haematologica. 2010;95(3):449-55.
30. Benharroch D, Meguerian-Bedoyan Z, Lamant L, Amin C, Brugieres L, Terrier-Lacombe MJ, et al. ALK-positive lymphoma: a single disease with a broad spectrum of morphology. Blood. 1998; 91(6):2076-84.
31. ten Berge RL, Oudejans JJ, Dukers DF, Meijer CJ. Anaplastic large cell lymphoma: what's in a name? J Clin Pathol. 2001; 54(6):494-5.
32. ten Berge RL, Oudejans JJ, Ossenkoppele GJ, Pulford K, Willemze R, Falini B, et al. ALK expression in extranodal anaplastic large cell lymphoma favours systemic disease with (primary) nodal involvement and a good prognosis and occurs before dissemination. J Clin Pathol. 2000;53(6):445-50.
33. Beylot-Barry M, Groppi A, Vergier B, Pulford K, Merlio JP. Characterization of t(2;5) reciprocal transcripts and genomic breakpoints in CD30+ cutaneous lymphoproliferations. Blood. 1998;91(12):4668-76.
34. Herbst H, Sander C, Tronnier M, Kutzner H, Hugel H, Kaudewitz P. Absence of anaplastic lymphoma kinase (ALK) and Epstein-Barr virus gene products in primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis. Br J Dermatol. 1997;137(5):680-6.
35. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol. 2003; 49(6):1049-58.
36. Kadin ME, Pinkus JL, Pinkus GS, Duran IH, Fuller CE, Onciu M, et al. Primary cutaneous ALCL with phosphorylated/activated cytoplasmic ALK and novel phenotype: EMA/MUC1+, cutaneous lymphocyte antigen negative. Am J Surg Pathol. 2008; 32(9):1421-6.
37. Sasaki K, Sugaya M, Fujita H, Takeuchi K, Torii H, Asahina A, et al. A case of primary cutaneous anaplastic large cell lymphoma with variant anaplastic lymphoma kinase translocation. Br J Dermatol. 2004; 150(6):1202-7.
38. Su LD, Schnitzer B, Ross CW, Vasef M, Mori S, Shiota M, et al. The t(2;5)-associated p80 NPM/ALK fusion protein in nodal and cutaneous CD30+ lymphoproliferative disorders. J Cutan Pathol. 1997;24(10):597-603.
39. Hosoi M, Ichikawa M, Imai Y, Kurokawa M. A case of anaplastic large cell lymphoma, ALK positive, primary presented in the skin and relapsed with systemic involvement and leukocytosis after years of follow-up period. Int J Hematol. 2010; 92(4):667-8.
40. Chan DV, Summers P, Tuttle M, Cooper KD, Cooper B, Koon H, et al. Anaplastic lymphoma kinase expression in a recurrent primary cutaneous anaplastic large cell lymphoma with eventual systemic involvement. J Am Acad Dermatol. 2011; 65(3):671-3.
41. Workshop of the Society for Hematopathology and the European Association for Hematopathology (SH/EAHP) on Cutaneous Lymphomas and Their Mimics. 2011. Proceedings.