Int J Hematol (2017) 105:440–444
DOI 10.1007/s12185-016-2147-3

ORIGINAL ARTICLE

Primary mediastinal large B-cell lymphoma in Japanese children and adolescents

Tomoo Osumi[1] · Fumiko Tanaka[2] · Tetsuya Mori[3] · Reiji Fukano[4] · Masahito Tsurusawa[5] · Koichi Oshima[6] · Atsuko Nakazawa[7] · Ryoji Kobayashi[8]

Received: 1 August 2016 / Revised: 13 November 2016 / Accepted: 13 November 2016 / Published online: 17 November 2016

Abstract This is the first case series to describe primary mediastinal large B-cell lymphoma (PMLBL) patients in children and adolescents in Asia. We retrospectively identified 17 PMLBL patients diagnosed between 1991 and 2014; in seven of these cases, the diagnosis was confirmed by central review, representing 1.0% of all NHL and 2.2% of all B-NHL cases registered. All patients were teenagers, including seven adolescents, with a median age of 14 years (range 12–18 years). Ten patients were male, and seven were female. The 5-year EFS and OS rates were 81.9 and 84.4%, respectively. All seven recent cases remain alive, of which three received rituximab combination therapy. Incidence, characteristics, and outcome varied considerably from those of Western populations. Further studies, including molecular analysis, are warranted.

Keywords Primary mediastinal large B-cell lymphoma · PMLBL · Children · Adolescents · Non-Hodgkin lymphoma

Abbreviations

PMLBL	Primary mediastinal large B-cell lymphoma
NHL	Non-Hodgkin lymphoma
DLBCL	Diffuse large B-cell lymphoma
B-NHL	B-Cell NHL
OS	Overall survival
EFS	Event-free survival
CR	Complete remission
SCT	Stem-cell transplantation
HL	Hodgkin lymphoma

Introduction

Primary mediastinal large B-cell lymphoma (PMLBL) is a rare subtype of non-Hodgkin lymphoma (NHL) in childhood arising from mature thymic B cells. In the World Health Organization classification, PMLBL was originally described as a subtype of diffuse large B-cell lymphoma (DLBCL), but is currently classified independently according to the results of recent analyses, including molecular genetics [1]. Clinically, PMLBL occurs in the mediastinum and invades aggressively, often causing superior vena cava syndrome. Reports from Western countries showed that it is predominant in adolescents and females [2, 3]. In addition, recent clinical trials of pediatric B-cell NHL (B-NHL) showed inferior outcome of pediatric PMLBL patients under standard therapy for pediatric B-NHL [4–7],

✉ Tomoo Osumi
osumi-t@ncchd.go.jp

1 Children's Cancer Center, National Center for Child Health and Development, 2-10-1, Okura, Setagaya-ku, Tokyo 157-0074, Japan

2 Department of Pediatrics, Saiseikai Yokohamashi Nanbu Hospital, Yokohama, Kanagawa, Japan

3 Department of Pediatrics, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan

4 Department of Pediatrics, National Kyushu Cancer Center, Fukuoka, Japan

5 Department of Pediatrics, Aichi Medical University, Nagakute, Aichi, Japan

6 Department of Pathology, Kurume University School of Medicine, Fukuoka, Japan

7 Department of Pathology, National Center for Child Health and Development, Tokyo, Japan

8 Department of Pediatrics, Sapporo Hokuyu Hospital, Sapporo, Hokkaido, Japan

Table 1 Reports of children and adolescents with PMLBL

Study Group	*n*	Frequency	Median age (range)	Sex ratio (M/F)	EFS/OS	References
JPLSG	17	1.0% of NHL 2.2% of B-NHL	14 (12–18)	1.4 (10/7)	82%/84%	Current study
COG	20	7.2% of LCL	12.5 (4–19)	1.1 (11/9)	75%/85%	Lones et al., JCO [12]
BFM	40	1.9% of NHL 3.3% of B-NHL	13.2 (1.4–17.9)	0.9 (19/21)	65%/NA	Burkhardt et al., Blood, [2]
FAB/LMB	42	3.8% of B-NHL	15.7 (12.6–19.7)	0.6 (16/26)	66%/73%	Gerrard et al., Blood, [3]

PMLBL, Primary mediastinal large B-cell lymphoma; M/F, male/female; EFS, event-free survival; OS, overall survival; JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group; COG, Children's Oncology Group; BFM, Berlin–Frankfurt–Münster; FAB/LMB, French–American–British/Lymphome Malins de Burkitt; NHL, non-Hodgkin lymphoma; LCL, Large-cell Lymphoma

therefore, stratified to the other treatment option. On the other hand, little is known about PMLBL of Asian children. Herein, we report a retrospective study of PMLBL in Japanese children and adolescents.

Methods

The clinical data of children and adolescents with PMLBL in this study consisted of two separate cohorts. Cohort 1 includes the patients (diagnosed between 1991 and 2004) from the registries of four local clinical study groups in Japan, the Tokyo Children's Cancer Study Group (TCCSG), the Japan Association of Childhood Leukemia Study (JACLS), the Children's Cancer and Leukemia Study Group (CCLSG), and the Kyushu Yamaguchi Children's Cancer Study Group (KYCCSG). The pathological diagnosis of patients in Cohort 1 was based on each institutional pathological review. Cohort 2 includes the patients (diagnosed between 2004 and 2014) from the nationwide central pathological review registration of the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), a national study group established in 2003 after merger of the 4 existing groups as mentioned before. Patients' data in Cohort 2 were collected as part of the retrospective study focusing on the rare subtype of pediatric NHL conducted by the JPLSG lymphoma committee. We combined the information, and analyzed their clinical characteristics, treatments received, and outcome. The current study was approved by the JPLSG and the ethics committee of the Sapporo Hokuyu Hospital in Hokkaido, Japan. Overall survival (OS) and event-free survival (EFS) rates were analyzed using the Kaplan–Meier method. SPSS 22.0 software (IBM SPSS, Inc. in Chicago, IL, USA) was used for analysis of data.

Results

We collected 17 PMLBL patients: 10 from Cohort 1 and seven from Cohort 2. According to the current nationwide registration data, PMLBL occupied 1.0% of NHL (7 out of 696 NHL patients) and 2.2% of B-NHL patients (7 of 314 B-NHL patients) (Table 1). Detailed characteristics of the 17 cases are shown in Table 2. All patients were teenagers, including seven adolescents, with median age of 14 years (range 12–18 years). Among them, 10 patients were male and seven were female. Regarding initial Murphy's staging, 15 were in stage III and 2 were in stage IV. Treatments for the patients were heterogeneous, especially in Cohort 1 [8–10]. In Cohort 2, three out of seven patients received NHL-BFM95 [5] and three received JPLSG B-NHL03 [11], which was the current nationwide clinical trial for B-NHL in Japan. Two patients who received B-NHL03 treatment switched to rituximab combination therapy after diagnosis because of the methotrexate-related toxicity in one patient and the residual tumor after chemotherapy in the other patient. One patient received R-CHOP (rituximab, cyclophosphamide, vincristine, and prednisolone) from the beginning. The best response achieved after the initial treatments was complete remission (CR) in 15 and induction failure in two. Among them, two patients received autologous peripheral blood stem-cell transplantation (SCT) in CR and one patient with Wiskott–Aldrich syndrome received cord blood transplantation to correct the underlying disease. Two patients who could not achieve CR received SCT but no detailed information was available. All the patients who could achieve first CR were alive, although one patient suffered from secondary leukemia. Both patients who could not achieve CR died of lymphoma in spite of receiving SCT without CR. The overall 5-year OS rate and EFS rates were 84.4 and 81.9%, respectively, with median follow-up period of 4.5 years (range 2.7–9.3 years) (Fig. 1).

Discussion

To the best of our knowledge, this is the first case series describing PMLBL in Asian children and adolescents. The reported pediatric case series of PMLBL in Western

Table 2 Characteristics, treatment, and outcome of Japanese children and adolescents with PMLBL

Patient	Age at diagnosis	Sex	Initial staging	Pathological review	LDH (IU/l)	Largest dimension of the tumor (cm)	Treatments	Response	HSCT	Outcome
1	14	M	3	No	244	9.5	CCLSG 960NLB [8]	CR	–	Alive
2	14	F	3	No	629	Unknown	CCLSG 960NLB [8]	CR	–	Alive
3	11	M	3	No	892	10	TCCSG B9604 [9]	CR	–	Alive
4	15	M	3	No	405	10.5	TCCSG B9604 [9]	CR	–	Alive[c]
5	14	F	3	No	8440	15	TCCSG B9604 [9]	CR	–	Alive
6	12	F	3	No	391	Unknown	JACLS NHL-98 [10]	CR	–	Alive
7	14	F	3	No	10,770	20	JACLS NHL-98 [10]	IF	HSCT[b]	DOD
8	15	M	4	No	1240	20	TCCSG 8801[a]	IF	HSCT[b]	DOD
9	12	M	3	No	315	6	Unknown	CR	Auto-PBSCT	Alive
10	14	M	4	No	Unknown	Unknown	Unknown	CR	Auto-PBSCT	Alive
11	14	F	3	Yes	626	8	NHL-BFM95 [5]	CR	–	Alive
12	16	F	3	Yes	257	16	NHL-BFM95 [5]	CR	–	Alive
13	18	M	3	Yes	422	8	NHL-BFM95 [5]	CR	–	Alive
14	14	M	3	Yes	891	Unknown	JPLSG B-NHL03 [12]	CR	–	Alive
15	15	M	3	Yes	630	Unknown	JPLSG B-NHL03 [12] → R-CHOP	CR	–	Alive
16	16	F	3	Yes	301	9	JPLSG B-NHL03 [12] → R-THP-COP	CR	–	Alive
17	15	M	3	Yes	396	5.5	R-CHOP	CR	CBT	Alive

LDH, lactate dehydrogenase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-THP-COP, rituximab, THP, doxorubicin, cyclophosphamide, vincristine, and prednisone; HSCT, hematopoietic stem-cell transplantation; auto-PBSCT, autologous peripheral blood stem-cell transplantation; CBT, cord blood transplantation

[a] Unpublished treatment, [b] No further information, [c] The patients suffered from secondary leukemia

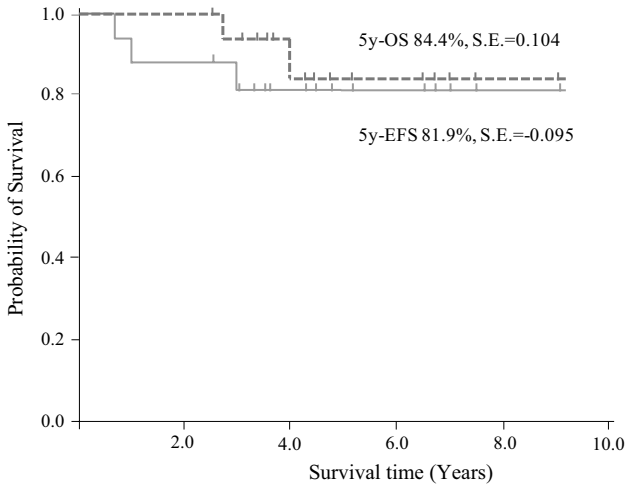

Fig. 1 Kaplan–Meier curve for probability of overall survival (OS) and event-free survival (EFS) in 17 patients enrolled in this study

countries was listed in Table 1 [2, 3, 12]. In our cohort, all cases were teenagers similar to previous series. On the other hand, female predominance was not observed in Japan. In addition, it seemed that the incidence of PMLBL in Japan was low. The same trend could be seen in the registration of the recent large clinical trials for pediatric B-NHL; JPLSG B-NHL03 included only 0.6% of PMLBL cases (two patients in 321 all enrolled cases), whereas NHL-BFM95 trial and FAB/LMB96 trial included 2.9% (15 patients in 515 all enrolled cases) and 3.8% (42 patients in 1111 enrolled cases) of PMLBL cases, respectively [3–5, 11].

It is well recognized that the incidence of certain subtypes of pediatric lymphomas is different between Japan and Western countries [11, 13, 14]. For example, higher frequency of DLBCL and fewer Hodgkin lymphoma (HL) is observed in Japan. From the analysis of gene expression profile, the features of PMLBL were completely different from those of DLBCL, but similar to those of HL [15, 16]. The rarity of PMLBL in Japan might be associated with that of HL.

In terms of the prognosis, PMLBL has been reported to have worse prognosis than other subtypes of pediatric B-NHL despite the improvement in the overall treatment results [5, 6]. Considering these results, PMLBL is separated and treated with another strategy, and dose adjusted (DA)-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in the Inter-B-NHL ritux 2010, which is the ongoing international clinical trial for pediatric B-NHL to investigate the effectiveness of rituximab combination therapy. Dunleavy et al. [17] reported that DA-EPOCH-R was effective for PMLBL in adults. Although confirmation in large clinical trials is necessary, DA-EPOCH-R regimen is expected to be a promising treatment even for pediatric cases [18]. In our cohort, about 90% of the patients who achieved CR after primary treatment survived with no relapse and two patients in Cohort 1 died with the refractory disease. On the other hand, all the seven recent cases in Cohort 2, whose diagnoses were confirmed at the central pathological review, were alive. As treatments in Cohort 1 were too heterogeneous, it is difficult for discussions on the reason of inferior outcome. However, with regard to Cohort 2, all the patients received modern intensive chemotherapy, of which three patients received rituximab combination therapy. Considering that the EFS and the OS rates were 87.4 and 92.7% of JPLSG B-NHL03 study [11], the prognosis of PMLBL patients of children and adolescents in Japan did not seem inferior compared with that of other B-NHL patients, especially in the recently diagnosed cohort. In addition, rituximab combination therapy might contribute to the good prognosis.

On the other hand, eight patients with primary mediastinal mass were registered on B-NHL03 protocol. Their diagnosis was BL in three patients, DLBCL in one, and the aggressive B-NHL with insufficient material in two, other than two patients with PMLBL. As one of two patients with ambiguous diagnosis suffered relapse and died of disease, the true diagnosis might impact on the prognosis of Japanese patients with PMLBL.

In conclusion, this is the first case series describing PMLBL patients in children and adolescent from Asia. The incidence, characteristics, and outcome varied considerably from those of Western populations. Further studies, including molecular analysis, will be needed.

Acknowledgements We would like to thank Dr. Daisuke Tomizawa of Children's Cancer Center and Dr. Julian Tang of the Department of Education for Clinical Research, National Center for Child Health and Development, for proofreading and editing this manuscript. This research is supported by the Practical Research for Innovative Cancer Control from the Japan Agency for Medical Research and Development, AMED.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition, World Health Organization, 2008 pp 251–252.
2. Burkhardt B, Oschlies I, Klapper W, Zimmermann M, Woessmann W, Meinhardt A, et al. Non-Hodgkin's lymphoma in adolescents: experiences in 378 adolescent NHL patients treated according to pediatric NHL-BFM protocols. Leukemia. 2011;25:153–60.

3. Gerrard M, Waxman IM, Sposto R, Auperin A, Perkins SL, Goldman S, et al. Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood. 2013;121:278–85.
4. Cairo MS, Sposto R, Gerrard M, Auperin A, Goldman SC, Harrison L, et al. Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age (≥15 years), are associated with an increased risk of treatment failure in children and adolescents with mature B-cell non-Hodgkin's lymphoma: results of the FAB LMB 96 study. J Clin Oncol. 2012;30:387–93.
5. Woessmann W, Seidemann K, Mann G, Zimmermann M, Burkhardt B, Oschlies I, et al. 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. 2005;105:948–58.
6. Patte C, Auperin A, Gerrard M, Michon J, Pinkerton R, Sposto R, 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;109:2773–80.
7. Cairo MS, Gerrard M, Sposto R, Auperin A, Pinkerton CR, Michon J, 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;109:2736–43.
8. Tsurusawa M, Katano N, Hirota T, Ito M, Yanase T, Asami K. et al [Studies of childhood non-Hodgkin's lymphoma–treatment results with the CCLSG NHL 960 protocol. Children's Cancer and Leukemia Study Group (CCLSG)]. Rinsho Ketsueki. 1998;39:1092–8.
9. Kikuchi A, Mori T, Fujimoto J, Kumagai M, Sunami S, Okimoto Y, 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;49:757–62.
10. Fujita N, Kobayashi R, Takimoto T, Nakagawa A, Ueda K, Horibe K. 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. 2011;52:223–9.
11. Tsurusawa M, Mori T, Kikuchi A, Mitsui T, Sunami S, Kobayashi R, et al. Improved treatment results of children with B-cell non-Hodgkin lymphoma: a report from the Japanese Pediatric Leukemia/Lymphoma Study Group B-NHL03 study. Pediatr Blood Cancer. 2014;61:1215–21.
12. Lones MA, Perkins SL, Sposto R, Kadin ME, Kjeldsberg CR, Wilson JF, et al. Large-cell lymphoma arising in the mediastinum in children and adolescents is associated with an excellent outcome: a Children's Cancer Group report. J Clin Oncol. 2000;18:3845–53.
13. Horibe K, Saito AM, Takimoto T, Tsuchida M, Manabe A, Shima M, 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.
14. Koga Y, Kumagai M, Takimoto T, Mimaya J, Nakazawa A, Horibe K, et al. Retrospective analysis of 157 patients with pediatric Hodgkin lymphoma in Japan: investigation by four pediatric cancer study groups. Rinsho Ketsueki. 2012;53:443–9.
15. Savage KJ, Monti S, Kutok JL, Cattoretti G, Neuberg D, De Leval L, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood. 2003;102:3871–9.
16. Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003;198:851–62.
17. Dunleavy K, Pittaluga S, Maeda LS, Advani R, Chen CC, Hessler J, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;368:1408–16.
18. Woessmann W, Lisfeld J, Burkhardt B. Therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;369:282.