J Clin Immunol (2016) 36:667–676
DOI 10.1007/s10875-016-0324-z

ORIGINAL ARTICLE

Lymphoma Secondary to Congenital and Acquired Immunodeficiency Syndromes at a Turkish Pediatric Oncology Center

Hikmet G. Tanyildiz[1] · Handan Dincaslan[1] · Gulsan Yavuz[1] · Emel Unal[1] · Aydan Ikinciogulları[2] · Figen Dogu[2] · Nurdan Tacyildiz[1]

Received: 20 January 2016 / Accepted: 26 July 2016 / Published online: 4 August 2016

Abstract The prevalence of lymphoma in primary immunodeficiency cases and autoimmune diseases, as well as on a background of immunodeficiency following organ transplants, is increasing. The lymphoma treatment success rate is known to be a low prognosis. Our study aimed to emphasize the low survival rates in immunodeficient vs. immunocompetent lymphoma patients and also to investigate the effect of rituximab in patients with ataxia telangiectasia and other immunodeficiencies. We summarized the clinical characteristics and treatment results of 17 cases with primary immunodeficiency that developed non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) retrospectively. Seven patients were diagnosed with ataxia-telangiectasia, two with common variable immunodeficiency, two with selective IgA deficiency, one with X-related lymphoproliferative syndrome, one with Wiskott-Aldrich syndrome, one with Epstein-Barr virus-related lymphoproliferative syndrome, one with interleukin-2-inducible T-cell kinase (ITK) deficiency, and one with lymphoma developing after autoimmune lymphoproliferative syndrome (ALPS). One patient underwent a renal transplant. Of the nine males and eight females (aged 3–12 years, median = 7) that developed lymphoma, seven were diagnosed with HL and ten with NHL (seven B-cell, three T-cell). The NHL patients were started on the Berlin-Frankfurt-Münster, POG9317, LMB-96, or R-CHOP treatment protocols with reduced chemotherapy dosages. HL cases were started on the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and/or cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) protocol, also with modified dosages. Importantly, all seven cases of HL are alive and in remission, while six of the ten NHL patients have died. Primary immunodeficiency is a strong predisposing factor for developing lymphoma. Low treatment success rates relative to other lymphomas and difficulties encountered during treatment indicate that new treatment agents are needed. While some success has been achieved by combining rituximab with lymphoma treatment protocols in B-NHL cases with primary immunodeficiency, the need for new treatment approaches for these patients remains critical.

Keywords Primary immunodeficiency · Lymphoma · Childhood

Introduction

The duration of survival in patients with primary immunodeficiency has increased following improvements in treatment and the prevention of opportunistic infections, but this has also led to an increase in disease-related lymphoproliferative complications and secondary malignancies as the most common reason for death at an early age [1, 2]. The prevalence of cancer in these patients is reportedly 4 %, approximately 10,000 times the prevalence in normal healthy people, and the most common cancers in this group are lymphomas [3–8]. For example, the incidence of lymphoma in cases of immunodeficiency related to chromosome breakage (e.g., ataxia telangiectasia, Nijmegen breakage) shows a relative 250-fold increase [9–13]. The prevalence of non-Hodgkin lymphoma (NHL) is reported to be 60 %, with 40–50 % of these patients diagnosed with diffuse large B-cell lymphoma

✉ Hikmet G. Tanyildiz
g_oktay4910@yahoo.com

[1] Department of Pediatric Oncology, Ankara University Faculty of Medicine, Ankara, Turkey

[2] Department of Pediatric Immunology, Ankara University Faculty of Medicine, Ankara, Turkey

(DLBCL). Ataxia telangiectasia is an autosomal recessive multisystem disease characterized by progressive cerebellar dysfunction, oculocutaneous telangiectasia, combined cellular and humoral immunodeficiency, and an increased incidence of malignancy. The ataxia telangiectasia (AT) immunodeficiency state emerges due to a functional loss in the DNA repair gene ataxia telangiectasia-mutated kinase (ATM), which results in the cells being unable to efficiently induce a number of cell-signaling pathways following DNA damage, including breakage from exposure to ionizing radiation and chemotherapeutics [14]. The incidence of hematopoietic malignancies, especially leukemia and lymphoma, is increased in AT patients, and the incidence of childhood lymphoma increases 70- to 250-fold. The disorder has no known cure, and the patients usually die at an early age from the complications of chronic lung disease that develops in a background of bronchiectasis or malignancy and infection [12, 13, 15]. Their susceptibility to cancer is very high due to the problems with DNA repair, and they have a greater sensitivity to treatment methods such as chemotherapy and radiotherapy, with increased risks of toxicity. The patients can therefore die due to drug toxicity in the first few cycles. Reducing the chemotherapy dosages and avoiding radiotherapy can prevent the deaths due to drug toxicity [16]. However, there are reports of tumors becoming biologically refractory in AT patients following treatment with reduced dosages, which can affect treatment success. It is thought that the mutation in the ATM gene disrupts the perception of signals in the apoptotic pathway, causing the cancers that develop in an AT background to have an aggressive biological course [17].

Although the reasons for the increased lymphoproliferative disease incidence in immunodeficient patients are not fully understood, deterioration in immunoregulation, chronic antigenic stimulation, and tumor suppressor system dysregulation are thought to be the main factors [18, 19]. The clinical characteristics of lymphomas developing secondary to immunodeficiency can differ from those in primary lymphomas. For example, NHL in cases of primary immunodeficiency is seen at a younger age, and the origin is usually B-cells. It is more commonly seen in males, and extranodal involvement is the most frequent finding [20, 21]. The most important problem in cases with lymphoma developing on a background of immunodeficiency is the increased incidence of infection, mucositis, and bone marrow suppression due to chemotherapy sensitivity [8, 22]. These side effects due to drug toxicity can be prevented by reducing the chemotherapy dosages. With the exception of alkaline agents and epipodophyllotoxins, many clinicians report using the full dose of chemotherapy agents, as they believe that the survival rates are otherwise low [22]. However, there is no clear consensus regarding the choice of treatment agents to implement due to the chemotherapy sensitivity and the increased number of infections encountered in these patients. Successful treatment results have been reported with the R-CHOP protocol, especially in cases of NHL [22–24].

In this article, we present the treatment results of 17 cases that developed either NHL or Hodgkin lymphoma (HL) in a background of immunodeficiency. Our primary aim was to compare the survival of lymphoma patients with and without immunodeficiency, while the secondary aim was to investigate the effect of rituximab in patients with AT vs. other immunodeficiencies.

Patients and Methods

Patients

A total of 100 childhood lymphoma cases were followed up at our clinic between January 2002 and June 2014 (57 NHL, 43 HL). Seventeen (17 %) of these patients (aged 3–12 years; median follow-up duration of 42 months) had primary immunodeficiency and developed lymphoma secondarily. The median age was 6 years (3–16) at diagnosis, and the median follow-up duration was 95 months (1–168) in the lymphoma patients without immunodeficiency. In our lymphoma cases diagnosed on a background of immunodeficiency, the incidence of NHL was 59 % (10/17), and there were four patients with Burkitt lymphoma (BL), one with DLBCL, one with aggressive B-cell lymphoma, one with B-cell lymphoblastic lymphoma, and three with T-cell NHL. There were also fewer NHL cases in males (four) than in females (six). The rate of immunodeficiency was 17.5 % (10/57) in our NHL patients and 16.2 % (7/43) in those with HL. We retrospectively reviewed the charts of these 17 patients for clinical characteristics, treatment approaches used, and survival. The diagnoses included AT (seven), common variable immunodeficiency (CVID; two), selective IgA deficiency (two), autoimmune lymphoproliferative syndrome (ALPS; one), Wiskott-Aldrich syndrome (WAS; one), interleukin-2-inducible T-cell kinase (ITK) deficiency (one), X-linked lymphoproliferative syndrome (XLPS; one), and Epstein-Barr virus (EBV)-associated lymphoproliferative syndrome (LPS; one). Lymphoma also developed after kidney transplantation in one patient. The characteristics of these patients are summarized in Tables 1 and 2.

Diagnosis of Lymphoma

Laboratory investigations such as blood counts, peripheral smears, sedimentation rate, C-reactive protein, AST, ALT, LDH, urea, creatinine, ferritin, and radiologic imaging (chest X-ray, ultrasonography, computed tomography, magnetic resonance, and positron-emission tomography) were conducted for the immunodeficient patients who had B symptoms (e.g., fever, sweating, weight loss) or lymph node growths.

Table 1 Characteristics and overall survival of the patients who developed lymphoma in a background of ataxia telangiectasia

No.	Age at diag.	Gender	Type of PID	Lymphoma type	Stage	Treatment	Overall survival (months)	Response	Follow-up duration (months)	Outcome
1	10	M	AT	T-NHL	III	BFM non-B	6	CR	6	Discontinued follow-up
2	9	F	AT	B-LBL	III	LMB-96	66	PD with LMB-96, PR with R-CHOP	66	Alive
						Rituximab-CHOP				
3	6	F	AT	DLBCL	III	**Rituximab**-LMB	36	CR	36	Alive
4	5	F	AT	BL	III	POG9317	6	PD	6	Deceased
5	7	F	AT	BL	III	POG9317	6	PD	6	Deceased
6	7	M	AT	HL	IIB	ABVD	96	CR	96	Alive
7	9	M	AT	HL	III	ABVD	78	CR	78	Alive

Bold font represents a targeted molecular treatment agent

AT ataxia telangiectasia, *B-LBL* B-cell lymphoblastic lymphoma, *BFM* Berlin-Frankfurt-Münster, *CR* complete remission, *DLBCL* diffuse large B-cell lymphoma, *F* female, *HL* Hodgkin lymphoma, *M* male, *PD* progressive disease, *PID* primary immunodeficiency, *PR* partial remission, *T-NHL* T-cell non-Hodgkin lymphoma

Ultrasonography or magnetic resonance was preferred over X-ray and computed tomography in patients with ataxia telangiectasia. Excisional biopsy was obtained from the cervical, mediastinal, intra-abdominal, or inguinal lymph nodes with pathological growth. Lymphoma was diagnosed histopathologically.

Staging

We used the Ann Arbor staging system for HL and the St. Jude staging system for NHL, taking the location and distribution of growing lymph nodes, the number and size of the involved lymph nodes, and whether there was additional organ involvement into consideration [25, 26]. B symptoms (fever, sweating, weight loss), which have prognostic importance, were queried. A cerebral spinal fluid (CSF) evaluation and bone marrow aspiration and biopsy were performed to exclude possible bone marrow and central nervous system involvement in the patients at stage III–IV or with B symptoms. None of the patients had bulky disease, defined as tumors invading more than a third of the mediastinum or lymph nodes enlarged more than 10 cm.

Immunohistochemical Evaluation and Anti-CD20 Treatment

For the lymphoma patients with primary immunodeficiency, immunohistochemistry was used to determine the CD20 and CD30 expression in the lymph node tissues at the time of diagnosis or recurrence. Those who were positive received monoclonal antibody treatment. Rituximab was administered as a first-line treatment in the patients with DLBCL or Burkitt lymphoma (BL) in an AT or RT background and in the relapse protocol for the BL cases in an EBV-associated LP disease background and the B-cell lymphoblastic lymphoma cases in an AT background. Two BL patients and one T-cell-rich B-cell lymphoma patient died due to rapid progression, leaving no opportunity to add rituximab. Rituximab was not administered to the T-NHL and aggressive B-cell lymphoma patients, as they were CD20-negative.

Patient Stratification

The AT patients were evaluated separately from the immunodeficiency patients, because their lymphoma susceptibility and incidence, treatment sensitivity-related toxicity risk, and long-term survival characteristics differ from the others (see Tables 1 and 2).

Treatment

The Berlin-Frankfurt-Münster (dexamethasone, cyclophosphamide, ifosfamide, cytarabine, doxorubicin), POG9317

Table 2 Characteristics and overall survival of the patients who developed lymphoma in immunodeficiency backgrounds other than ataxia telangiectasia

No.	Age at diag.	Gender	Type of PID	Lymphoma type	Stage	Treatment	Overall survival (months)	Response	Follow-up duration (months)	Outcome
1	4	M	ALPS	T-NHL	IV	BFM non-B	9	PD	9	Deceased
2	12	F	CVID	T-cell-rich B-cell lymphoma	IV	BFM non-B	2	PD	2	Deceased
3	5	M	RT	BL	IV	**Rituximab** Steroid, CTX	1	PD	1	Deceased
4	12	M	WAS	Aggressive B-cell lymphoma	III	POG9317	61	PD	61	Deceased 1 month after relapse
5	11	F	EBV-associated LPS	BL	III	LMB-96 **Rituximab**-CHOP	30	PD	30	Alive
6	11	F	CVID	HL	III	COPP-ABVD **Rituximab**	156	CR	156	Alive
7	14	M	XLPS	HL	IVB	COPP	168	CR	168	Alive
8	7	M	Selective IgA deficiency	HL	III	ABVD Vinorelbine Gemcitabine **Rituximab** **Brentuximab** Autologous transplant	60	PD after 3 years and PR	60	Alive
9	3	M	Selective IgA Deficiency	HL	III	COPP After relapse: ABVD + COPP	84	PD after 2 years and CR	84	Alive
10	4	F	ITK Deficiency	HL	III	ABVD + **Rituximab**	12	CR	12	Alive

Bold font represents a targeted molecular treatment agent

ALPS autoimmune lymphoproliferative syndrome, *BFM* Berlin-Frankfurt-Münster, *BL* Burkitt lymphoma, *CR* complete remission, *CVID* common variable immunodeficiency, *Diag* diagnosis, *EBV* Epstein-Barr virus, *F* female, *HL* Hodgkin lymphoma, *ITK* interleukin-2-inducible T-cell kinase, *LPS* lymphoproliferative syndrome, *M* male, *PD* progressive disease, *PID* primary immunodeficiency, *PR* partial remission, *RT* renal transplant, *T-NHL* T-cell non-Hodgkin lymphoma, *WAS* Wiskott-Aldrich syndrome, *XLPS* X-linked lymphoproliferative syndrome

(doxorubicin, prednisone, vincristine, methotrexate, high-dose cytarabine), LMB-96 (vincristine, prednisone, methotrexate, doxorubicin), and R-CHOP (rituximab, cyclophosphamide, prednisolone, vincristine, doxorubicin) treatment regimens were used in the NHL cases, while the HL cases were treated with the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) regimen. All drug dosages were modified by decreasing them by 25 %.

Results

Treatment and Survival of Immunodeficient Lymphoma Patients

CD20 was positive in seven NHL patients, and rituximab was used in four of them. One achieved complete remission, and two are still on follow-up with partial remission, which was attained by combining rituximab with the CHOP protocol. The patient with lymphoproliferative disease following a renal transplant received the added rituximab, but he died in a short time from disease progression in a short time. The characteristic common to the three living NHL cases in remission was that they received chemotherapy combined with the targeted molecular treatment rituximab. The other NHL cases ($n = 5$), which were not treated with targeted agents such as rituximab, died due to progressive/relapsed disease.

In cases diagnosed with HL, rituximab was used concomitant with ABVD and COPP at the beginning of each cycle when the patient was CD20-positive at the time of diagnosis. CD20 was found in the diagnostic tissue (CVID and ITK deficiency) of two HL patients. A relapse was observed in two patients diagnosed with HL. Anti-CD30 and anti-CD20 agents were combined with gemcitabine and vinorelbine as a relapse protocol for the first relapse case, whereas ABVD and COPP were used for the second relapse case. No radiotherapy was administered in the HL cases. All HL cases entered remission after 2 cycles of the initial chemotherapy. The probability of general survival results of the immunodeficient patients who developed lymphoma with a background of immunodeficiency was significantly less favorable ($p = 0.001$) (Fig. 1).

Effect of Rituximab on Immunodeficient Lymphoma Patient Survival

Lymphoma in Ataxia Telangiectasia (Table 1)

Seven AT patients (3 male, 4 female) with a median age of 7 (5–10) and median follow-up duration of 36 months (6–96) developed lymphoma, five NHL (4 B-cell, 1 T-cell), and two HL. All patients had stage III disease with the exception of one

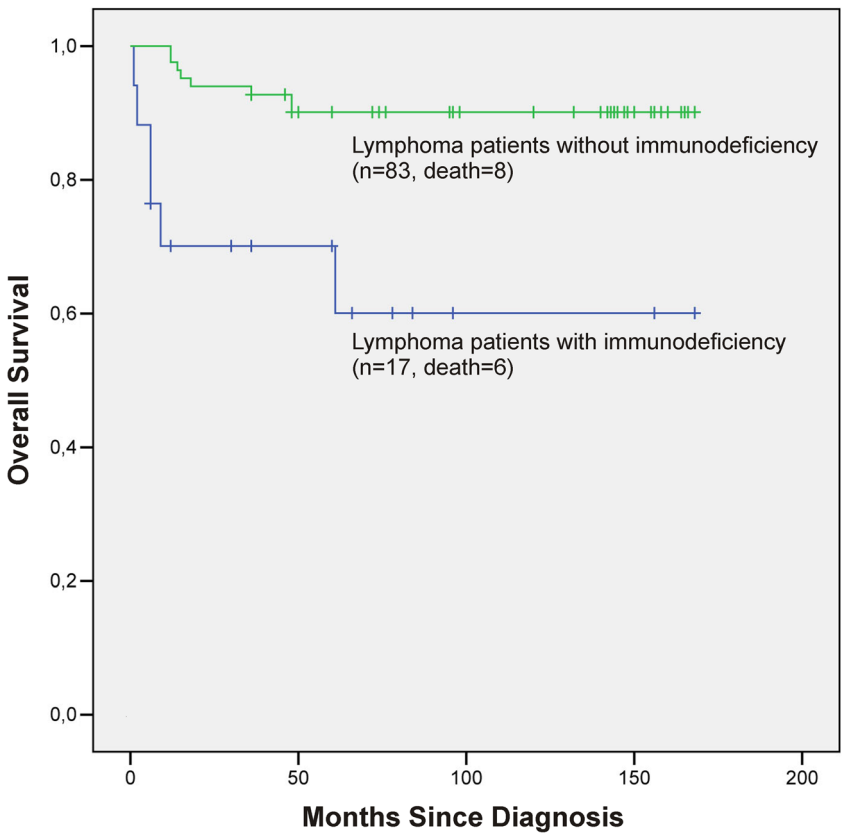

Fig. 1 Overall survival of the lymphoma patients with and without primary immunodeficiency

at stage IIB. The AT patients that developed lymphoma and received rituximab (2) are still living. Full remission was obtained when rituximab was added (at the 36-month follow-up) to the LMB treatment of one patient with DLBCL, and partial remission was achieved with the R-CHOP regimen used as a relapse protocol in the recurrent B-cell lymphoblastic lymphoma case (follow-up at 66 months). Two of the three NHL patients in whom rituximab was not used died. Two patients with stage III BL died at 6 months of treatment without rituximab due to progressive disease. At the patient's request, one T-cell NHL case in remission left follow-up after 6 months. The positive effect of the rituximab on survival was not statistically significant, possibly due to the low number of patients ($p = 0.327$).

The ABVD regimen (modified dosage) was also used for two cases of HL in the AT background. In contrast to the standard HL treatment approach, radiotherapy was not administered to the involved area. These two patients have been followed up for 78 and 96 months without disease.

Lymphoma in Other Immunodeficiencies (Table 2)

Ten patients (six male, four female) with other immunodeficiency diagnoses and a median follow-up duration of 45 months developed lymphoma, five NHL and five HL. B symptoms were seen in one case (XLPS-HL). The three patients who developed T-cell NHL in an ALPS background, aggressive B-cell lymphoma in a WAS background, and T-cell-rich B-cell lymphoma in a CVID background died due to progressive disease. One patient developed BL following kidney transplantation. Decreased steroid and cyclophosphamide dosages together with rituximab were initially used in this CD20-positive patient, but the patient died in the first month due to progression and multiorgan failure. One patient with BL in an EBV-related LPS background initially achieved full remission with the LMB-96 treatment, but recurrence emerged during follow-up. This treatment-refractory patient was continued with the R-CHOP combination, which controlled the disease.

Targeted treatment agents were also used in the HL patients with other immunodeficiency backgrounds. The COPP or ABVD regimen (reduced dosage) was used without local radiotherapy, and monoclonal antibody treatments were added when indicated. The survival rate for these HL cases with primary immunodeficiency was 100 %. The disease recurred only in two cases with selective IgA deficiency. Full remission was obtained in one of these cases with alternating ABVD and COPP regimens. Weak CD20 and CD30 expression was found in the recurrent tumor tissue of the other patient, and a treatment combination of rituximab, brentuximab vedotin, vinorelbine, and gemcitabine was started. When the disease was under control, an autologous bone marrow transplantation was performed and the patient has been followed up for 60 months. The tumors of the patients who developed HL in the CVID and ITK deficiency backgrounds were CD20-positive at diagnosis, and rituximab was used from the first cycle. Control was achieved in the XLPS case diagnosed with advanced stage HL in only two cycles of the modified COPP treatment, and the patient has been followed up in full remission for 168 months.

Rituximab was also used in five lymphoma patients with other immunodeficiencies. Only one of these patients died, while three of the five patients treated without rituximab have died. Although rituximab had a positive effect on the survival of this group, it was not statistically significant ($p = 0.473$), perhaps because of the low number of patients.

Discussion

Most of our immunodeficiency patients who developed lymphoma had AT (41 %). Although there is no consensus on the optimal treatment in hematopoietic malignancies in an AT background, reduced intensity treatment is generally recommended [27–30]. Since a conservative approach is more appropriate in the AT patients with mortality risks from complications, we modified their chemotherapy dosages and added rituximab to the first-line treatment of the CD20-positive patients, who were mostly older patients. This approach produced positive results because of rituximab's lower toxicity, which allowed the systemic chemotherapy dosages to also be reduced. Together, they increased the treatment success and provided long-term disease control by preventing the tumor from becoming refractory to treatment. The lack of any previously reported toxicity related to rituximab in AT patients also encouraged us at the treatment stage.

The AT patients who developed NHL and received rituximab have survived, while those who did not have died. Although the rituximab positively affected survival when it was added to the treatment regimen of the recurrent NHL patients or at an early stage before the disease had irreversibly progressed to its advanced stage, our results were not statistically significant due to the low number of patients ($p = 0.327$). The median survival duration of AT patients (36 months) was still less than that of the patients who were either not immunodeficient (95 months) or developed their lymphoma in a background of another immunodeficiency (45 months). However, given the positive effects of the rituximab shown here, the survival rate would be expected to rise with the use of such targeted treatment agents, especially for NHL (Fig. 2).

The incidence of lymphoma increases in WAS cases due to the dysfunction of the WAS protein gene in B lymphocytes [31–34]. Bone marrow transplantation, the main form of treatment, decreases the incidence of malignancy in advanced WAS stages. Aggressive B-cell lymphoma (stage III) developed in our patient diagnosed with WAS, and the POG9317

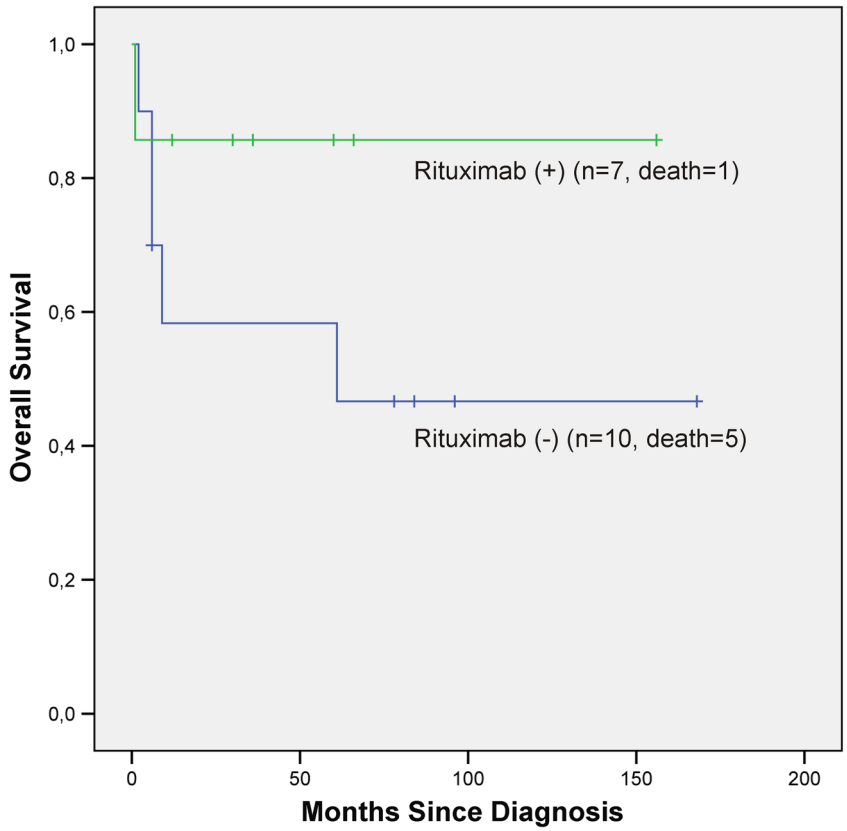

Fig. 2 Overall survival of the lymphoma patients with immunodeficiency treated with and without rituximab

treatment protocol was used at a decreased dosage (25 %) to achieve remission. However, the patient died due to disease progression after relapsing 48 months into follow-up. Successful treatment in WAS cases depends on the ability to use aggressive chemotherapy, as well as preventing the infections and toxicity that may occur [35, 36]. The decreased chemotherapeutic dosage may have been an important factor in the recurrence of this secondary diagnosis of aggressive B-cell lymphoma.

In common variable immunodeficiency (CVID) cases, the risk of developing lymphoma, particularly NHL, increases with increasing age. When viral infections, especially with EBV, result in T-cell dysfunction in an immunodeficiency background, a predisposition to T-cell lymphoma is created [37, 38]. In our case, T-cell-rich B-cell lymphoma (stage IV) developed in the CVID background. The reduced dosage (25 %) BFM non-B-cell treatment protocol was administered without rituximab, but the patient died with progression 2 months later.

The risks of NHL and HL increase 14- and 50-fold, respectively, when autoimmune lymphoproliferative disease (ALPS) is present. Rituximab (anti-CD20) and fansidar—the current approaches to treating the apoptosis pathway disturbance caused by the Fas antigen (FAS), FAS ligand, and caspase-8 gene defects in ALPS—are thought to prevent the development of lymphadenopathy as well as lymphoma. Administering anti-CD20 before hematopoietic stem cell transplantation (HSCT), the treatment option most likely to provide a cure, is becoming popular [39–43]. In our case, the patient died from disease progression after 9 months of follow-up, before HSCT could be performed.

The prevalence of NHL after solid organ transplantation is 0.6 %; after bone marrow transplantation, the prevalence of NHL and HL are 4 and 1.5 %, respectively [44–49]. Our case developed Burkitt lymphoma (stage IV) after a kidney transplant and was started on anti-CD20 combined with cyclophosphamide and steroids (25 % decreased dosage), but died in the first month due to multiple organ failure and disease progression.

Hodgkin lymphoma makes up 10 % of all malignancies emerging in a background of primary immunodeficiency, and these cases are diagnosed at an earlier age than primary HL [50]. In our study, a diagnosis of HL was made in 41 % (7/17) of the immunodeficiency patients. Five of these seven cases were classified as stage III, one as stage IIB, and the other as IVB. B symptoms, which are important indicators of poor prognosis, can accompany 25–40 % of HL cases [51]. However, our HL patients had a low incidence of B symptoms, which positively contributed to their treatment results. We obtained successful results in the two patients with B symptoms using ABVD and COPP at reduced dosages and did not require an aggressive treatment approach; there has been no recurrence on follow-up. The other HL cases were also

treated with ABVD or COPP at the 25 % decreased dosage, and rituximab was added to the treatment of the three patients who were CD20-positive. Brentuximab vedotin was combined with gemcitabine and vinorelbine as a targeted molecular treatment approach in one patient when CD30 positivity occurred after relapse. An autologous stem cell transplant was performed for this case, and partial remission was achieved. Although treatment options are considered limited and the prognosis poor when HL develops in an immunodeficiency background [52, 53], all of our HL patients are alive, including those who experienced a recurrence. Using rituximab or brentuximab vedotin as first-line or salvage treatments allowed for implementing the chemotherapy at decreased dosages and still effectively controlling the disease [54].

Conventional immunologic analyses before the start of chemotherapy found decreased serum IgA levels in two of our newly diagnosed HL patients who had experienced frequent sinopulmonary infections. We found no secondary immunodeficiencies due to steroid, immunosuppressive, or anti-convulsant drug use, and there was no intestinal or renal protein loss in these patients. After cellular immunodeficiency diagnoses were excluded, a primary antibody deficiency with delayed diagnosis was considered, because lymphoma or autoimmune diseases can accompany the clinical presentation of primary antibody deficiencies. Selective IgA deficiency commonly accompanies certain autoimmune diseases, such as celiac disease, immune thrombocytopenic purpura, and glomerulonephritis, as well as malignancy [55, 56], as in our cases. Simultaneous selective IgA deficiency has also been reported in cases diagnosed with primary cutaneous marginal zone lymphoma, T-cell NHL, and pleuropulmonary blastoma [57–59]. A possible increase in the incidence of malignancies such as adenocarcinoma, squamous cell carcinoma, and thymoma has also been reported in the IgA deficiency background. Because both of our patients with selective IgA deficiency had a prolonged severe febrile neutropenia attack following the first cycle of chemotherapy, the drug dosages were modified, allowing treatment to continue unhindered. Regular immunoglobulin replacement treatment was also administered. Long-term close follow-up of patients with selective IgA deficiency is very important, as panhypogammaglobulinemia can develop or the disorder can transform into CVID.

In recent years, ITK deficiency associated with hypogammaglobulinemia, diffuse lymphopenia, and progressive CD4+ T-cell loss has been reported. The recommended treatment approach is based on patient information, and the B-cell decrease with the use of rituximab may provide a temporary improvement in the clinical picture [60]. Although there are not yet any definite treatment recommendations, it has been reported that some approaches using HSCT may provide a definite solution [60, 61]. Our patient with HL in an ITK deficiency background responded positively to the reduced dosage ABVD in combination with rituximab. We continue to make preparations for HSCT for this patient, who is fully compatible with an HLA-matched unrelated donor.

X-linked lymphoproliferative disease, also known as Duncan disease, is a rare immunodeficiency disease that is characterized by severe immune dysregulation. Although controversial, allogeneic stem cell transplantation is recommended as the only curative option after controlling the symptoms of the disease. Myeloablative or reduced intensity allogeneic HSCT targets activated CD8+ T-cells and corrects the underlying immune defect. Allogeneic HSCT is especially suggested for those who have developed hemophagocytic lymphohistiocytosis (HLH) or lymphoma during follow-up when an HLA-matched and related donor is found [62, 63]. Our lymphoma patient in an XLPS background is still being monitored as the case with the longest survival duration.

The most important limitations of our study are its retrospective nature with a low number of patients and a mixture of different types of lymphomas; therefore, it is very difficult to draw any conclusions on survival and treatment response. More comprehensive prospective studies are needed to verify our results.

The successful treatment of infections in immunodeficient patients is currently achieved through treatment approaches such as HSCT and supportive treatment. However, the most significant problem in these patients is still the treatment of the hematologic malignancies that occur. These patients are very sensitive to the effects of chemotherapy and radiotherapy, and the treatment must be meticulously managed. Although success in treating HL in an immunodeficiency background is reportedly low, modifying the dosages and avoiding radiotherapy provided good results in our HL cases.

The prognosis of NHL cases developing in a background of immunodeficiency is also still poor, despite well-organized treatment protocols; therefore, less toxic and more effective treatments, and especially targeted treatments such as anti-CD20, are required. While a conservative approach is preferred in AT patients as they are more sensitive to the effects of chemotherapy and radiotherapy, the drug dosages can be slowly increased in other immunodeficiencies if the patient can tolerate it, especially in those who develop NHL to improve the treatment success.

Authors' Contributions HGT and NT designed the project. HGT wrote the manuscript. AI, FD, and NT reviewed the manuscript. The remaining authors provided clinical samples and data.

Compliance with Ethical Standard

Conflicts of Interest The authors declare that they have no conflicts of interest.

References

1. Filipovich AH, Heinitz KJ, Robison LL, Frizzera G. The immunodeficiency cancer registry. A research resource. Am J Pediatr Hematol Oncol. 1987;9:183–4.
2. Elenitoba-Johnson KS, Jaffe ES. Lymphoproliferative disorders associated with congenital immunodeficiencies. Semin Diagn Pathol. 1997;14:35–47.
3. Filipovich AH, Mathur A, Kamat D, Kersey JH, Shapiro RS. Lymphoproliferative disorders and other tumors complicating immunodeficiency. Immunodeficiency. 1994;5:91–112.
4. Morrell D, Cromartie E, Swift M. Mortality and cancer incidence in 236 patients with ataxia telangiectasia. J Natl Cancer Inst. 1986;77:89–92.
5. Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S, Lieberman P. Incidence of cancer in 98 patients with common variable immunodeficiency. J Clin Immunol. 1987;7:294–301.
6. Taylor AMR, Metcalfe JA, Thick J, Mak YF. Leukemia and lymphoma in ataxia telangiectasia. Blood. 1996;87:423–38.
7. Turvey SE, Bonilla FA, Junker AK. Primary immunodeficiency diseases: a practical guide for clinicians. Postgrad Med J. 2009;85:660–6.
8. Tran H, Nourse J, Hall S, Green M, Griffiths L, Gandhi MK. Immunodeficiency-associated lymphomas. Blood Rev. 2008;22:261–81.
9. Meyn MS. Chromosome instability syndromes: lessons for carcinogenesis. In Kaston MB, editor. Genetic instability and tumorigenesis. Current topics in microbiology and immunology; 1997. pp. 71–148.
10. Green AJ, Yates JR, Taylor AM, Biggs P, McGuire GM, McConville CM, et al. Severe microcephaly with normal intellectual development: the Nijmegen breakage syndrome. Arch Dis Child. 1995;73:431–4.
11. Overberg-Schmidt U, Wegner RD, Baumgarten E, Günther A, Ebell W, Stein H, et al. Low-grade non-Hodgkin's lymphoma after high-grade non-Hodgkin's lymphoma in a child with ataxia telangiectasia. Cancer. 1994;73:1522–5.
12. Janic D, Dokmanovic L, Jovanovic N, Lazic J. T-cell acute lymphoblastic leukemia in a child with ataxia-telangiectasia: case report. J Pediatr Hematol Oncol. 2007;29:713–5.
13. Sharma LM, Kashyap R, Gupta S, Bhargava M. B-cell acute lymphoblastic leukemia in a child with ataxia-telangiectasia. Pediatr Hematol Oncol. 2008;5:473–6.
14. Kastan MB. DNA damage responses: mechanisms and roles in human disease: 2007 G.H.A Clowes Memorial Award Lecture. Mol Cancer Res. 2008;6:517–24.
15. Hecht F, Hecht BK. Chromosome changes connect immunodeficiency and cancer in ataxia-telangiectasia. Am J Pediatr Hematol Oncol. 1987;9:185–8.
16. Seidemann K, Henze G, Beck JD, Sauerbrey A, Kühl J, Mann G, et al. Non-Hodgkin's lymphoma in pediatric patients with chromosomal breakage syndromes (AT and NBS): experience from the BFM trials. Ann Oncol. 2000;11:141–5.
17. Maclean KH, Kastan MB, Cleveland JL. Atm deficiency affects both apoptosis and proliferation to augment Myc-induced lymphomagenesis. Mol Cancer Res. 2007;5:705–11.
18. Shield JPH, Strobel S, Levinsky RJ, Morgan G. Immunodeficiency presenting as hypergammaglobulinemia with IgG2 subclass deficiency. Lancet. 1992;340:448–51.
19. Buckley RH. Breakthroughs in the understanding and therapy of primary immunodeficiency. Pediatr Clin North Am. 1994;41:665–90.
20. Seemayer TA, Gross TG, Egeler RM, Pirruccello SJ, Davis JR, Kelly CM, et al. X-linked lymphoproliferative disease: twenty-five years after the discovery. Pediatr Res. 1995;38:471–8.
21. Sumegi J, Huang D, Lanyi A, Davis JD, Seemayer TA, Maeda A, et al. Correlation of mutations of the SH2D1A gene and Epstein-Barr virus infection with clinical phenotype and outcome in X-linked lymphoproliferative disease. Blood. 2000;96:3118–25.
22. Seidemann K, Tiemann M, Henze G, Sauerbrey A, Müller S, Reiter A. Therapy for non-Hodgkin lymphoma in children with primary immunodeficiency: analysis of 19 patients from the BFM trials. Med Pediatr Oncol. 1999;33:536–44.
23. Sandoval C, Swift M. Treatment of lymphoid malignancies in patients with ataxia telangiectasia. Med Pediatr Oncol. 1998;31:491–7.
24. Shabbat S, Aharoni J, Sarid L, Ben-Harush M, Kapelushnik J. Rituximab as monotherapy and in addition to reduced CHOP in children with primary immunodeficiency and non-Hodgkin lymphoma. Pediatr Blood Cancer. 2009;52:664–6.
25. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. Cancer Res. 1971;31:1860–1.
26. Murphy SB. Classification, staging and results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol. 1980;7:332–9.
27. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235–42.
28. Kropshofer G, Wehl G, Klein-Franke A, Herbrecht R, Tilly H, Bouabdallah R, et al. B-cell lymphoma in a girl with ataxia telangiectasia (A-T) treated with rituximab monotherapy. Pediatr Blood Cancer. 2006;46:528–9.
29. Rossi G, Zecca M, Marchi A, de Stefano P, Sammarchi L, Locatelli F. Modified CHOP-chemotherapy plus rituximab for diffuse large B-cell lymphoma complicating ataxia-telangiectasia. Br J Haematol. 2003;120:369–71.
30. Sandlund JT, Hudson MM, Kennedy W, Onciu M, Kastan MB. Pilot study of modified LMB-based therapy for children with ataxia-telangiectasia and advanced stage high grade mature B-cell malignancies. Pediatr Blood Cancer. 2014;61:360–2.
31. Perry III GS, Spector BD, Schuman LM, Mandel JS, Anderson VE, McHugh RB, et al. The Wiskott-Aldrich syndrome in the United States and Canada (1892–1979). J Pediatr. 1980;97:72–8.
32. Derry JM, Ochs HD, Francke U. Isolation of a novel gene mutated in Wiskott-Aldrich syndrome. Cell. 1994;78:635–44.
33. Bosticardo M, Marangoni F, Aiuti A, Villa A, Grazia RM. Recent advances in understanding the pathophysiology of Wiskott-Aldrich syndrome. Blood. 2009;113:6288–95.
34. Staub E, Groene J, Heinze M, Mennerich D, Roepcke S, Klaman I, et al. An expression module of WIPF1-coexpressed genes identifies patients with favorable prognosis in three tumor types. J Mol Med. 2009;87:633–44.
35. Du S, Scuderi R, Malicki DM, Willert J, Bastian J, Weidner N. Hodgkin's and non-Hodgkin's lymphomas occurring in two brothers with Wiskott-Aldrich syndrome and review of the literature. Pediatr Dev Pathol. 2011;14:64–70.
36. Pasic S, Vujic D, Djuricic S, Jevtic D, Grujic B. Burkitt lymphoma-induced ileocolic intussusceptions in Wiskott-Aldrich syndrome. J Pediatr Hematol Oncol. 2006;28:48–50.
37. Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S, Lieberman P. Incidence of cancer in 98 patients with common varied immunodeficiency. J Clin Immunol. 1987;7:294–9.
38. Emir S, Vezir E, Azkur D, Demir HA, Metin A. Characteristics of children with non-Hodgkin lymphoma associated with primary immune deficiency diseases: descriptions of five patients. Pediatr Hematol Oncol. 2013;30:544–53.
39. Riex-Laucat F, Le Deist F, Hivroz C, Roberts IA, Debatin KM, Fischer A, et al. Mutations in Fas associated with human

lymphoproliferative syndrome and autoimmunity. Science. 1995;268:1347–9.
40. Bleesing JJ. Autoimmune lymphoproliferative syndrome (ALPS). Curr Pharm Des. 2003;9:265–78.
41. Clementi R, Dagna L, Dianzani U, Dupré L, Dianzani I, Ponzoni M, et al. Inherited perforin and Fas mutations in a patient with autoimmune lymphoproliferative syndrome and lymphoma. N Engl J Med. 2004;351:1419–24.
42. Poppema S, Maggio E, van den Berg A. Development of lymphoma in autoimmune lymphoproliferative syndrome (ALPS) and its relationship to Fas gene mutations. Leuk Lymphoma. 2004;45: 423–31.
43. Rao VK, Straus SE. Causes and consequences of the autoimmune lymphoproliferative syndrome. Hematology. 2006;11:15–23.
44. Harris NL, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: summary of Society for Hematopathology Workshop. Semin Diagn Pathol. 1997;14:8–14.
45. Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. J Clin Oncol. 2003;21:1352–8.
46. Gross TG, Steinbuch M, DeFor T, Shapiro RS, McGlave P, Ramsay NK, et al. B-cell lymphoproliferative disorders following hematopoietic stem cell transplantation: risk factors, treatment and outcome. Bone Marrow Transpl. 1999;23:251–8.
47. Bhatia S, Ramsay NK, Steinbuch M, Dusenbery KE, Shapiro RS, Weisdorf DJ, et al. Malignant neoplasms following bone marrow transplantation. Blood. 1996;87:3633–9.
48. Curtis RE, Travis LB, Rowlings PA, Socié G, Kingma DW, Banks PM, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood. 1999;94:2208–16.
49. Socie G, Curtis RE, Deeg HJ, Sobocinski KA, Filipovich AH, Travis LB, et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. J Clin Oncol. 2000;18:348–57.
50. Robison LL, Stoker V, Frizzera G, Heinitz K, Meadows AT, Filipovich AH. Hodgkin's disease in pediatric patients with naturally occurring immunodeficiency. Am J Pediatr Hematol Oncol. 1987;9:189–92.
51. Crnkovich MJ, Leopold K, Hoppe RT, Mauch PM. Stage I to IIB Hodgkin's disease: the combined experience at Stanford University and the Joint Center for Radiation Therapy. J Clin Oncol. 1987;5:1041–9.
52. Sandoval C, Swift M. Hodgkin disease in ataxia-telangiectasia patients with poor outcomes. Med Pediatr Oncol. 2003;40:162–6.
53. Niehues T, Schellong G, Dörffel W, Bucsky P, Mann G, Körholz D, et al. Immunodeficiency and Hodgkin's disease: treatment and outcome in the DAL HD78-90 and GPOH HD95 studies. Klin Padiatr. 2003;215:315–20.
54. Meister MT, Voss S, Schwabe D. Treatment of EBV-associated nodular sclerosing Hodgkin lymphoma in a patient with ataxia telangiectasia with brentuximab vedotin and reduced COPP plus rituximab. Pediatr Blood Cancer. 2015;62:2018–20.
55. Duraisingham SS, Buckland M, Dempster J, Lorenzo L, Grigoriadou S, Longhurst HJ. Primary vs. secondary antibody deficiency: clinical features and infection outcomes of immunoglobulin replacement. PLoS One. 2014;9:e100324.
56. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br J Haematol. 2009;145:709–27.
57. Wobser M, Kerstan A, Kneitz H, Goebeler M, Kunzmann V, Rosenwald A, et al. Primary cutaneous marginal zone lymphoma with sequential development of nodal marginal zone lymphoma in a patient with selective immunoglobulin A deficiency. J Cutan Pathol. 2013;40:1035–41.
58. Ott MM, Ott G, Klinker H, Trunk MJ, Katzenberger T, Müller-Hermelink HK. Abdominal T-cell non-Hodgkin's lymphoma of the gamma/delta type in a patient with selective immunoglobulin A deficiency. Am J Surg Pathol. 1998;22:500–6.
59. Chen Y, Jin M, Zhao W, Li S, Wang X, Cai S, et al. DICER1-negative pleuropulmonary blastoma in a patient with selective IgA deficiency. Pediatr Blood Cancer. 2016;63:757–8.
60. Ghosh S, Bienemann K, Boztug K, Borkhardt A. Interleukin-2-inducible T-cell kinase (ITK) deficiency—clinical and molecular aspects. J Clin Immunol. 2014;34:892–9.
61. Gross TG, Filipovich AH, Conley ME, Pracher E, Schmiegelow K, Verdirame JD, et al. Cure of X-linked lymphoproliferative disease (XLP) with allogeneic hematopoietic stem cell transplantation (HSCT): report from the XLP registry. Bone Marrow Transpl. 1996;17:741–4.
62. Zhu J, Zhang Y, Zhen ZJ, Chen Y, Wang J, Cai RQ, et al. Lymphoma and cerebral vasculitis in association with X-linked lymphoproliferative disease. Chin J Cancer. 2013;32:673.
63. Booth C, Gilmour KC, Veys P, Gennery AR, Slatter MA, Chapel H, Heath PT, Steward CG, Smith O, O'Meara A, Kerrigan H, Mahlaoui N, Cavazzana-Calvo M, Fischer A, Moshous D, Blanche S, Pachlopnik Schmid J, Latour S, de Saint-Basile G, Albert M, Notheis G, Rieber N, Strahm B, Ritterbusch H, Lankester A, Hartwig NG, Meyts I, Plebani A, Soresina A, Finocchi A, Pignata C, Cirillo E, Bonanomi S, Peters C, Kalwak K, Pasic S, Sedlacek P, Jazbec J, Kanegane H, Nichols KE, Hanson IC, Kapoor N, Haddad E, Cowan M, Choo S, Smart J, Arkwright PD, Gaspar HB. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease. Blood. 2011;117:53–62.