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Use of Rituximab for Refractory Cytopenias Associated with Autoimmune Lymphoproliferative Syndrome (ALPS)

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Abstract

Background—ALPS is a disorder of apoptosis resulting in accumulation of autoreactive lymphocytes, leading to marked lymphadenopathy, hepatosplenomegaly and multilineage cytopenias due to splenic sequestration and/or autoimmune destruction often presenting in childhood. We summarize our experience of rituximab use during the last 8 years in twelve patients, 9 children and 3 adults, out of 259 individuals with ALPS, belonging to 166 families currently enrolled in studies at the National Institutes of Health.

Methods—Refractory immune thrombocytopenia (platelet count <20,000) in 9 patients and autoimmune hemolytic anemia (AIHA) in 3 patients led to treatment with rituximab. Among them, 7 patients had undergone prior surgical splenectomy; 3 had significant splenomegaly; and 2 had no palpable spleen.

Results—In 7 out of 9 patients with ALPS and thrombocytopenia, rituximab therapy led to median response duration of 21 months (range 14–36 months). In contrast, none of the 3 children treated with rituximab for AIHA responded. Noted toxicities included profound and prolonged hypogammaglobulinemia in 3 patients requiring replacement IVIG, total absence of antibody response to polysaccharide vaccines lasting up to 4 years after rituximab infusions in 1 patient and prolonged neutropenia in 1 patient.

Conclusion—Toxicities including hypogammaglobulinemia and neutropenia constitute an additional infection risk burden, especially in asplenic individuals, and may warrant avoidance of rituximab until other immunosuppressive medication options are exhausted. Long term follow up

of ALPS patients with cytopenias after any treatment is necessary to determine relative risks and benefits.

Keywords

ALPS; cytopenias; lymphadenopathy; splenomegaly; Rituximab

Introduction

ALPS is a disorder of apoptosis resulting in accumulation of autoreactive lymphocytes, leading to childhood onset of marked lymphadenopathy, hepatosplenomegaly and multilineage cytopenias due to splenic sequestration and/or autoimmunity^{1–8}. Affected individuals have characteristic increases (>1%) in circulating (TCR $\alpha\beta$ + CD3+CD4–CD8–) double negative T (DNT) lymphocytes in their peripheral blood. ALPS Type Ia, Ib, II and IV are associated with germline genetic mutations in apoptosis pathway genes like Fas, FasL, Caspases and NRAS respectively, while patients without identified mutations are classified as Type III or ALPS phenotype^{9–13}. Defective in vitro lymphocyte apoptosis is noted in patients with germline mutations in apoptosis pathway genes and those classified as ALPS Type III; whereas patients with ALPS phenotype and Fas mutation limited to the circulating DNT cell population (ALPS Somatic Ia) have no demonstrable in vitro apoptosis defect¹⁴. Patients with ALPS Type Ia associated with heterozygous mutation of the Fas gene comprise 65% of the cases and have an increased risk of developing B-cell neoplasms like Hodgkin and non-Hodgkin lymphoma¹⁵. Some of these patients also have supporting evidence of autoimmune hematological disease with or without autoantibodies and family history of similar disease including lymphadenopathy, hypersplenism, ITP, AIHA and lymphoma. Nearly 50% of them have undergone splenectomy as a treatment for refractory cytopenias associated with hypersplenism leading to associated long term risk of pneumococcal sepsis with significant morbidity and mortality^{16–17}. Currently published reports include two single case reports of rituximab being used for refractory ITP and AIHA in patients classified as ALPS^{18–19}.

Patients and Methods

Of the estimated 400 ALPS patients reported worldwide, 259 individuals with ALPS, belonging to 166 families, have been enrolled with informed consent in IRB approved studies at the National Institutes of Health (NIH) Clinical Center over the last 15 years. All NIH patients meet the required diagnostic criteria, i.e. chronic, non-malignant and non-infectious lymphadenopathy and/or splenomegaly associated with increased (>1% or >17) circulating DNT cells in the peripheral blood⁷. In this retrospective study, we summarize our experience of rituximab use during the last eight years in 12 ALPS patients with refractory cytopenias. Nine of them had ALPS Type Ia with a germline Fas mutation along with in vitro Fas mediated apoptosis defect and 3 patients were categorized as ALPS phenotype as they did not have evidence of in vitro apoptosis defect or genetic mutations. Among them, 7 patients had undergone prior surgical splenectomy; 3 had significant splenomegaly; and 2 had no palpable spleen.

Failure to respond to steroids and other treatments for grade 4 thrombocytopenia (platelet count <20,000) in 9 patients and DAT positive severe AIHA (hemoglobin <7.5gm) in 3 patients led to treatment with rituximab at a dose of 375 mg/m² weekly for 4 weeks. Therapies prior to rituximab included, prednisone and IVIG (N=9), splenectomy (N=7), mycophenolate mofetil (MMF) (N=3), vincristine (N=1), cyclophosphamide (N=1) and red cell transfusions (N=3). The mean age of 9 children at the time of therapy with rituximab was 10 years (Range: 1–15 years). Three adults were aged 18, 45 and 47 years (Table I).

Response was defined by the maintenance of an adequate hemoglobin, white blood cells and platelet counts, free from the need for other medications including corticosteroids, IVIG, MMF or splenectomy within 6 months of rituximab therapy.

Results

Seven out of 12 patients responded with stabilization of cytopenia for greater than 6 months. With greater than 12 months follow up, their median response duration was 21.5 months (range 14–36 months). None of the three children treated with rituximab for DAT positive AIHA responded. In this group, two had splenomegaly and one was asplenic. Two patients, #38 and #223, relapsed with thrombocytopenia at 15 and 18 months following initial rituximab therapy and received 4 further weekly doses of rituximab more than 1 year apart. Patient #223 responded to the second course, while patient #38 was retreated with MMF to control relapse of thrombocytopenia that was refractory to the second course of rituximab.

Five non-responding patients' cytopenias progressed. One required splenectomy (Patient #159) and the other four, including the 2 asplenics, responded to high dose prednisone pulses (5–30 mg/kg) followed by a slow tapering schedule over 8–12 weeks along with MMF (1200 mg/m² divided twice daily) used as a steroid sparing measure. Patient #128 had successful resolution of AIHA after receiving vincristine (2 mg/m²) weekly for 6 weeks, corticosteroids and MMF following failure to respond to rituximab. Patient #159 relapsed with cytopenias 2 years after splenectomy, and at that time responded to reinstitution of therapy with MMF. One of the non-responders (Patient #50) has failed multiple non-steroidal therapies post rituximab and is currently receiving hydroxychloroquine off label for her corticosteroid responsive thrombocytopenia. Adverse events following rituximab therapy included prolonged neutropenia in 1 patient as well as both qualitative and quantitative hypogammaglobulinemia requiring IVIG supplementation for more than 6 months in 3 patients. One of them (Patient #130) continues to have normal serum immunoglobulin levels with total absence of specific antibody response to polysaccharide vaccines 4 years after rituximab monotherapy (Tables II and III). Two patients (#45 and #1) died due to squamous cell carcinoma of head and neck and opportunistic infection associated with asplenia, respectively.

Discussion

Earlier published reports are single cases of rituximab use for refractory ITP and AIHA in patients classified as ALPS^{18,19}. Notwithstanding the initially promising reports related to use of rituximab in adults and children with autoimmune cytopenias^{20,21}, recent reports have been less salutary, especially among children with chronic ITP^{22,23}. While treatment results of ALPS associated lymphadenopathy and splenomegaly have been variable^{24,25}, chronic use of immunosuppressive medications like mycophenolate mofetil (MMF) has shown promise in controlling autoimmune cytopenias in these patients^{17,26}. In this retrospective study, rituximab relieved thrombocytopenia for 14–36 months in 7 out of 12 ALPS patients. None of the three children treated with rituximab for DAT positive AIHA responded, suggesting that in the setting of ALPS, role of rituximab may be limited compared to its reported safety and utility in patients with sporadic AIHA and post transplant lymphoproliferative disorders (PTLD)^{27,28}. Patients #151 and #159, both younger than 2 years of age at study entry had splenomegaly extending below the umbilicus during the time their cytopenias failed to respond to rituximab. Most of the younger patients with ALPS have significant lymphoproliferative burden with massive splenomegaly and lymphadenopathy. Use of rituximab in these patients did not produce clinically significant shrinkage of lymph nodes or spleen. Hence empirical administration of rituximab as a single agent in the standard schedule of 4 weekly treatments may not be the optimal method of B

cell lymphodepletion to ameliorate the autoimmune hematological process in ALPS patients. Patients with ALPS, despite their presentation with hypergammaglobulinemia, have a notably significant reduction in CD27 + memory B cells (<16% of total B lymphocytes) in their peripheral blood similar to patients with CVID (Common Variable Immunodeficiency)^{29–31}. Associated toxicities of rituximab, including quantitative and qualitative IgG deficiencies as noted in our cohort pose additional infection risk, especially in asplenic individuals with ALPS that are potentially vulnerable to lag of memory B cell recovery and differentiation to plasma cells following exposure to rituximab. There have been other reports of prolonged hypogammaglobulinemia associated with selectively delayed memory B cell recovery in peripheral blood and lymphoid tissue after B cell depletion therapy with rituximab in patients with SLE (Systemic Lupus Erythematosus) and NHL (non-Hodgkin Lymphoma)^{32,33}. Nishio et al reported that following rituximab therapy in NHL patients, B cells showed significantly impaired IgG and IgA production upon engagement of surface immunoglobulin receptors in the presence of interleukin (IL)-2, IL-10 and CD40 ligand in comparison with samples from healthy controls. Delayed recovery of memory B cells in their cohort demonstrates that their naive B cells failed to differentiate into plasma cells, resulting in hypogammaglobulinaemia³³. These toxicities constitute an additional infection risk burden, especially in asplenic individuals, and may warrant avoidance of empirical use of rituximab until other immunosuppressive medication options are exhausted in children with ALPS associated cytopenias. Moreover, only 1/12 ALPS patients (#160) included in this case series is currently without further need of other immunosuppressive medications including MMF and IVIG (Table III). It is never the less, critical to assess the role of rituximab towards relief of refractory thrombocytopenia in some ALPS patients, including its optimal dose, schedule as well as its long term impact on memory B cell dysfunction.

As ALPS associated chronic cytopenias are often refractory we have included a treatment algorithm broadly outlining our current approaches to using chronic immunosuppressive medications in these patients as a steroid sparing measure while avoiding surgical splenectomy (Figure I). This issue warrants further investigation including long term follow up of ALPS patients with cytopenias through tailored prospective clinical trials with conventional as well as novel agents^{17,34–37}.

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Management Suggestions for ALPS Associated Chronic Refractory Cytopenia

Figure 1.

This schematic diagram is included only as a suggested guideline for managing children with ALPS associated autoimmune multilineage cytopenias. Use of G-CSF may be warranted for severe neutropenia associated with systemic infections. Similarly use of other chemotherapeutic and immunosuppressive agents* (e.g. vincristine, methotrexate, mercaptopurine, azathioprine, cyclosporine, hydroxychloroquine, tacrolimus, sirolimus) besides mycophenolate mofetil (MMF) should be considered as a steroid sparing measure; or while avoiding or postponing surgical splenectomy at the discretion of the treating clinicians based on the circumstances of a specific patient.

Clinical Characteristics

Table 1

Patient ID	ALPS Dx	Mutation	DNT % (#) §	Age at onset of cytopenias requiring Rituximab	Condition	Prior Splenectomy	Treatment immediately prior to Rituximab
1	Type Ia	429delG; D62fs	19.1% (1989)	12.9 years	Thrombocytopenia	yes	Cyclophosphamide, prednisone, vincristine weekly $\times$ 4 doses
2	Phenotype	No mutation identified	1.9% (65)	13.4 years	Thrombocytopenia	yes	Dexamethasone, MMF
38			1.5% (37)	15.3 years	Thrombocytopenia	yes	Dexamethasone, IVIG, prednisone
3 45*	Type Ia	779del11; V179fs	1.4% (80)	47 years	Thrombocytopenia	yes	Prednisone, IVIG
4 50	Type Ia	383T->A; C47X	1.7% (21)	18 years	Thrombocytopenia	no	Prednisone, MMF, IVIG
5 102	Type Ia	972G->T; D224Y in ex 9	32% (653)	9.2 years	Thrombocytopenia	yes	Prednisone, IVIG $\times$ 2, methylprednisolone
6 128	Type Ia	952G->T; G237V in ex 9	18.5% (511)	9 years	Anemia, DAT (+)	yes	Prednisone, MMF, IVIG
7 130	Type Ia	526A->G; H95R ex 3	9.6% (939)	10.8 years	Thrombocytopenia	yes	Prednisone, IVIG
8 151	Type Ia	774G->A, E178K	21.6% (1814)	1.9 years	Anemia, DAT (+)	no	Methylprednisolone, RBC transfusions, IVIG
9 159	Type Ia	942C->T; R234 stop in ex 9	4.8% (229)	1 year	Anemia, DAT (+)	no	Prednisone, MMF
10 160**	Type Ia	214T->C; L (-10)P	1.1% (22)	45.4 years	Thrombocytopenia	no	Prednisone, IVIG
11 223	Phenotype	No mutation identified	3.6% (70)	12.7 years	Thrombocytopenia	no	Dexamethasone, WinRho, IVIG, prednisone
223			1.3% (23)	15 years	Thrombocytopenia	no	IVIG, prednisone
12 226	Phenotype	No mutation identified	0.3% (22)	12.6 years	Thrombocytopenia	yes	Prednisone, IVIG

* Father of proband

** Mother of proband

§ Double negative T cell/TCR $\alpha\beta$ + % normal range at the NIH Clinical Center = 0.1-0.9% (95% CI) Double negative T cell/TCR $\alpha\beta$ + # absolute number normal range at the NIH Clinical Center = 2-17 cells/microliter (95% CI) based on the absolute lymphocyte count derived from CBC (Complete Blood Count) done concurrently with flowcytometry.

Changes in laboratory profile of patients treated with Rituximab

Table II

Pre CBC					Post CBC					3–9 months post IgG [£] (mg/dL)			
Patient ID	WBC [§] (K/uL)	ANC [¶] (K/uL)	Hb [~] (g/dL)	Plt [⊖] (K/uL)	WBC (K/uL)	ANC (K/uL)	Hb (g/dL)	Plt (K/uL)	Pre CD20 ± # (uL)	3–9 months post CD20 # (uL)	Pre IgG [£] (mg/dL)	3–9 months post IgG (mg/dL)	
1	1	7.9	4.8	11.9	16	7.8	3.6	624	2520	4	1710	340	
2	38	7.50	4.0	14.3	8	11.1	8.5	220	475	0	1096	795	
38	38	8.80	5.8	15.5	8	11.1	5.9	15.6	7	NA	820	529	
3	45*	22	15.0	14	7	22	19	8	222	565	1140	NA	
4	50	11.6	10	13.5	74	7.3	4	12.2	15	327	0	777	
5	102	9.5	3.1	10.5	9	5.2	2.8	12.1	594	328	2840	2430	
6	128	7.20	0.1	5.0	418	13.2	0.78	6.6	<10	1665	602	566	
7	130	21.60	11.0	15.2	16	12.8	3.8	14.7	161	1251	2310	1560	
8	151	4.00	1.6	4.6	266	4.5	0.8	6.3	263	1746	5	1950	435
9	159	3.7	1.2	7.4	162	2.0	0.10	6.3	160	893	0	1960	346
10	160**	8.6	5.5	11.6	3	6.5	4.4	11.3	249	261	7	832	534
11	223	3.8	1.5	14.6	15	5.8	2.8	13.4	230	@254	NA	241	
	223	2.1	0.7	9.4	3	14.7	11.6	13.6	321	131	NA	188	82
12	226	13.9	10.0	12.8	2	6.2	2.1	13.1	487	2516	<50	1220	
										@CD 19 (B cells)	NA: not available		

* Father of proband

** Mother of proband

[§] White blood cell count normal range at the NIH Clinical Center = 11.5–15.5 g/dL

[¶] Absolute neutrophil count normal range at the NIH Clinical Center = 1.290–7.500 K/uL < Hemoglobin normal range at the NIH Clinical Center = 11.5–15.5 g/dL

[~] Platelet count normal range at the NIH Clinical Center = 162–380 K/uL ± CD20 normal range at the NIH Clinical Center = 49–424/uL

[£] Quantitative IgG immunoglobulin normal range at the NIH Clinical Center = 642–1730 mg/dL

Follow-up

Table III

Patient ID	Currently receiving IVIG	Response Duration	Current Follow up Status
1	no	23 months	Deceased due to asplenic sepsis
2	no	15 months	Rituxan administration repeated 6 months after relapse
38	no	no response	Currently on MMF
45*	no	14 months	Deceased due to progressive malignancy
4	no	no response	Currently on hydroxychloroquine for recurrent thrombocytopenia
5	no	36 months	Cytopenias in remission, Currently on MMF for autoimmune uveitis
6	no	no response	Currently on MMF
7	yes	5 months	Currently on MMF, persistent hypogammaglobulinemia
8	no	no response	Currently on MMF
9	no	no response	Currently on MMF
10	no	32 months	Cytopenias in remission
11	yes	18 months	Rituxan administration repeated 9 months after relapse, hypogammaglobulinemia
223	yes	24 months	Cytopenias in remission, persistent hypogammaglobulinemia
226	yes	20 months	Cytopenias in remission, persistent hypogammaglobulinemia

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