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Treatment of autoimmune cytopenia complicating progressive chronic lymphocytic leukemia/small lymphocytic lymphoma with rituximab, cyclophosphamide, vincristine, and prednisone

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Abstract

Treatment of autoimmune cytopenia complicating progressive chronic lymphocytic leukemia (CLL) is constrained by intolerance of myelosuppression and the risk of exacerbation of autoimmune cytopenia by purine analogs particularly when used as single agents. We report on 20 such patients treated with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). Autoimmune cytopenia responded in 19 patients (14 complete remissions (CR), five partial remissions (PR)) with a median time to next treatment (TTT) for autoimmune cytopenia of 21.7 months. Progressive CLL responded in 17 patients (nine CR/complete clinical response, eight PR) with a median TTT of 27.7 months. Five patients have not required any re-treatment at 15–30 months. Grade 3–4 toxicities were infections ($n = 3$) and drug-induced pneumonitis ($n = 1$). No patient required blood cell transfusions after cycle 1 of therapy. We conclude that R-CVP is effective and tolerable therapy for autoimmune cytopenia complicating progressive CLL, but the duration of response is suboptimal.

Keywords

Chronic lymphocytic leukemia; autoimmune hemolytic anemia; immune thrombocytopenia; pure red blood cell aplasia; therapy

Introduction

Cytopenia caused by autoimmune disease (autoimmune cytopenia) is a potentially serious complication that occurs in approximately 5–10% of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) [1,2]. Many of these patients have ‘simple’ autoimmune cytopenia without concurrent progressive CLL and can be managed with immunosuppressive therapy [3]. In contrast, those patients with concomitant progressive CLL requiring treatment or autoimmune cytopenia that does not respond to immunosuppressive therapy have ‘complex’ autoimmune cytopenia that is more difficult to manage [3].

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Treatment outcomes for progressive CLL have been greatly improved by the use of highly effective chemoimmunotherapy regimens combining purine analogs, cyclophosphamide, and rituximab [4,5]. However, use of these therapies can be problematic in patients with CLL with autoimmune cytopenia. Patients with autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) usually have increasing blood cell production, which can be an important mechanism for mitigating cytopenias. In these patients, the myelosuppressive effects of purine analog-based chemoimmunotherapy can cause severe and prolonged exacerbation of their cytopenia. In addition, use of purine analog therapy particularly as a single agent can lead to life-threatening exacerbation of autoimmune cytopenias [6,7]. There are limited data on the safety of the use of combination therapy containing purine analogs in patients with autoimmune cytopenia and progressive CLL. Two of the randomized controlled trials comparing fludarabine monotherapy to fludarabine and cyclophosphamide (FC) specifically excluded patients with autoimmune cytopenia [8,9], and a third trial required successful treatment of AIHA before allowing entry into the study [10]. In these studies, the FC combination was associated with the development of *de novo* AIHA in 2.8–5% of patients treated with FC. This rate was not significantly lower than in the fludarabine-treated cohort in the US Intergroup [9] and German CLL Study Group [8] trials, but was significantly lower than the rates for patients treated with either chlorambucil or fludarabine in the Lymphoma Research Foundation (LRF) CLL4 study [10]. There are even fewer data on the safety of treatment of ‘complex’ autoimmune cytopenia in patients with CLL with chemoimmunotherapy. The M.D. Anderson group reported that 6.5% of patients with progressive CLL but no evidence of autoimmune cytopenia developed autoimmune anemia (AIHA or pure red blood cell aplasia [PRBCA]) after treatment with fludarabine, cyclophosphamide, and rituximab (FCR) [11]. Among nine CLL patients with ‘complex’ autoimmune cytopenia treated with FCR only two responded [11]. These data suggest that purine analog-based chemoimmunotherapy regimens are not appropriate initial therapy for patients with uncontrolled ‘complex’ autoimmune cytopenia.

Optimal therapy for ‘complex’ autoimmune cytopenia complicating CLL would selectively suppress the autoimmune cytopenia, be cytotoxic to CLL cells without causing excessive myelosuppression, and have a low risk of exacerbating the autoimmune process. Although such a therapy has not yet been developed, we propose that the combination of rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) [12] does provide effective therapy for many CLL patients with ‘complex’ autoimmune cytopenia. As proof, we describe the treatment of 20 such patients with R-CVP at Mayo Clinic Rochester (MCR) over a period of 7 years.

Patients and methods

This retrospective study was conducted at MCR with the approval of the Institutional Review Board. Patients treated for both autoimmune cytopenia and progressive CLL from the beginning of 2002 to the end of 2008 were identified using the MCR CLL Database. The diagnosis of CLL was made using standard immunophenotypic criteria as previously described [13,14]. Autoimmune cytopenias including AIHA, ITP, and PRBCA were diagnosed as previously described [1,15]. In brief, AIHA was diagnosed in patients with a hemoglobin level <10.0 g/dL, with at least one marker of hemolysis (increased indirect bilirubin in the absence of liver disease, increased lactate dehydrogenase without another etiology, increased reticulocyte count, or increased bone marrow [BM] erythropoiesis without bleeding), and evidence of an autoimmune mechanism for hemolysis (positive direct antiglobulin test [DAT] for either immunoglobulin G [IgG] or C3d, or cold agglutinins, or at least two markers of hemolysis without evidence of bleeding or hypersplenism). PRBCA was diagnosed in patients with a hemoglobin level <10.0 g/dL who had an absolute reticulocytopenia and a specific absence or marked decrease in erythroid precursors in the

BM with relatively preserved granulocyte and platelet production. ITP was diagnosed in patients with a platelet count $<100 \times 10^9/L$ with evidence of normal or increased platelet production on BM biopsy examination and no evidence of hypersplenism. Progressive CLL requiring treatment was defined according to the National Cancer Institute Working Group Criteria of 1996 (NCI-WG 1996) [16]. Patients with concomitant autoimmune cytopenia and progressive CLL requiring treatment were included in this study if they received therapy based on the R-CVP regimen [12]. Treatment was cyclophosphamide 750 mg/m^2 , vincristine 1.4 mg/m^2 (maximum 2 mg), and rituximab 375 mg/m^2 intravenously on day 1 and oral prednisone 40 mg/m^2 days 1–5 of each 21-day cycle with the intent to treat with six cycles of therapy.

The electronic medical records of the 20 patients meeting the criteria for inclusion in this study were abstracted for data on demographics, prognostic factors, clinical presentation, treatment, and response. Molecular prognostic factors, including immunoglobulin heavy chain variable region (IGHV) mutation status, chromosomal defects detected by fluorescent *in situ* hybridization (FISH) analysis, and expression of ZAP-70 and CD38, were assayed as previously described [5]. The response to treatment of CLL was defined using the NCI-WG 1996 criteria [16]. Response to treatment of autoimmune cytopenia was classified as either complete (normal blood counts with or without maintenance therapy) or partial (hemoglobin $>10 \text{ g/dL}$, platelets $>30 \times 10^9/L$ with or without maintenance therapy) as previously described [17]. Time to next treatment (TTT) was defined as the time from initiation of treatment with R-CVP to the time of start of the next treatment required for either progressive autoimmune cytopenia or CLL. Toxicity was evaluated using NCI Common Toxicity Criteria Version 3.0.

Statistical analysis

Characteristics of the patients with CLL treated for ‘complex’ autoimmune cytopenia are reported and compared to those of patients without autoimmune cytopenia who required treatment for progressive CLL (comparison group 1) and the subgroup of that population that was also treated with R-CVP (comparison group 2). Demographic (age, sex, residency) and prognostic factors (IGHV mutation status, FISH, CD38 and ZAP-70) were compared between the 20 patients treated for ‘complex’ autoimmune cytopenia and the two comparison CLL groups. Either χ^2 or Fisher’s exact test statistics are reported for qualitative variables, and *t*-test or Kruskal–Wallis statistics are reported for quantitative variables. TTT and overall survival (OS) from R-CVP administration date are displayed using Kaplan–Meier curves.

Results

Patient population

Demographic, CLL prognostic factor, and autoimmune cytopenia data are reported in Table I. We compared the available prognostic factors in the study patients with those in patients treated for progressive CLL who did not have autoimmune cytopenia ($n = 553$). Although there were no overall statistically significant differences in FISH-detected chromosomal abnormalities between groups, the patients with autoimmune cytopenia did have a significantly higher frequency of 11q22– (39% vs. 14%, $p = 0.03$). More patients with autoimmune cytopenia had unmutated IGHV compared to the comparison group, but this difference was not statistically significant (80% vs. 64%, $p = 0.86$).

Eighteen patients had received prior treatment for autoimmune cytopenia, with a median interval from their first treatment for autoimmune cytopenia to their first treatment with R-CVP of 20 months (range 1–40 months). Previous treatments for autoimmune cytopenia

included corticosteroid monotherapy ($n = 8$), rituximab monotherapy ($n = 1$), rituximab and corticosteroids ($n = 5$), and intravenous immunoglobulin (IVIG) ($n = 4$). Fifteen patients had been previously treated for progressive CLL; 10 had one prior regimen, three had two prior regimens, and two patients had more than four prior regimens. Prior therapies of progressive CLL included purine analog monotherapy ($n = 4$), alkylating agent monotherapy ($n = 4$), purine analog, alkylating agent, and rituximab combination therapy ($n = 5$), and alemtuzumab and rituximab ($n = 1$). Three of the patients who had previously been treated for their CLL had also received the experimental synthetic oligonucleotide CpG7909 [19]. Four patients developed autoimmune cytopenia within 6 months of their last treatment for progressive CLL. Of these four, two had received alkylator monotherapy (interval 1–2 months), one received CpG7909 (interval 4 months), and one pentostatin, cyclophosphamide, and rituximab (interval 10 days). Eleven patients developed autoimmune cytopenia more than 6 months after completing their most recent treatment for progressive CLL with a median interval of 21 months (8–33 months).

All patients enrolled in this study had progressive CLL based on the NCI-WG 1996 criteria [16]. Twelve patients had a bone marrow examination immediately prior to treatment with R-CVP, and the biopsy specimens showed a median bone marrow involvement by CLL cells of 68% (range 30–90%). The five patients having greater than 80% bone marrow involvement with CLL were considered to have bone marrow failure, and were thus categorized as advanced stage CLL (Rai stage III/IV, Binet stage C) [1]. The seven patients with ‘adequate’ BM function (e.g. <80% involvement and adequate trilineage hematopoiesis) were considered to have intermediate stage (Rai stage I/II) CLL with cytopenia due to autoimmune disease, and in the eight patients without a BM study prior to initiation of therapy, the clinical stage of disease could not be determined.

Therapy with R-CVP

Patients received a median of 4.9 cycles of R-CVP (range 2–6) at a planned interval of every 21 days in 18 patients and a planned interval of 28 days in two patients who had significant additional comorbidities. Therapy was delayed for three patients because of treatment-related complications (treatment cycle range 28–35 days). In one patient, treatment was stopped after cycle 2 due to pneumonitis (grade 3) considered to be drug-induced (either rituximab or cyclophosphamide). Four patients did not receive vincristine as part of their treatment because of advanced age ($n = 3$) and pre-existing diabetic neuropathy ($n = 1$). Twelve patients received all cycles of therapy, with a vincristine dose of 1–2 mg per cycle. Vincristine therapy was discontinued in two patients who developed grade 1 peripheral neuropathy between cycles 2 and 5. There were no data on the vincristine dose in one patient. Treatment-induced neutropenia was reported in only one patient (grade 1). Three patients did have significant infections (pneumonia, grade 3, $n = 2$ and *Clostridium difficile* diarrhea, grade 2, $n = 1$); however, all had full recoveries with appropriate treatments. No patients required blood product transfusions after completion of the first cycle of R-CVP therapy.

Response

Autoimmune cytopenia—Autoimmune cytopenia responded to treatment in 19 patients: 14 achieved a complete response (CR) and five a partial response (PR). Changes in the blood counts after treatment are summarized in Table II. The median increase in hemoglobin in the 17 patients with autoimmune anemia was 4.2 g/dL (range 1.4–7.4), and the median increase in platelet count in the six patients with ITP was $106 \times 10^9/L$ (range 31–216). The median TTT was 21.7 months (Figure 1). The patient who did not respond to R-CVP subsequently had a sustained CR of his ITP after splenectomy. Among the four patients who did not receive vincristine, two had a CR of autoimmune cytopenia, one PR, and one

progressive disease. The two patients with discontinuation of vincristine during therapy had a CR of their autoimmune cytopenia. Three patients had progression of their CLL despite achieving a PR of their autoimmune cytopenia on R-CVP. Six responding patients required maintenance corticosteroid therapy because of evidence of early recurrence of autoimmune cytopenia after completing R-CVP. Of these, three were able to stop corticosteroid therapy within 2–4 months of completing R-CVP, two remained on long-term corticosteroid therapy, and one patient required splenectomy and then maintenance cyclosporine therapy for long-term control of ITP. Five patients remain in sustained remission without maintenance therapy at last follow-up (range 15–30 months).

Progressive CLL—Treatment of progressive CLL resulted in CR/complete clinical response (CCR) in nine patients, eight PR, and progressive disease in three patients. The median TTT for responding patients was 27.7 months (Figure 2). Among the patients with omission ($n = 4$) or discontinuation ($n = 2$) of vincristine, all had a CR/CCR of CLL. One patient went directly to reduced-intensity allogeneic hematopoietic stem cell transplant after R-CVP and remains in sustained remission for both CLL and autoimmune cytopenia 34 months after transplant. Four patients have died, two of progressive CLL and two of complications from subsequent reduced-intensity allogeneic hematopoietic stem cell transplant. The five patients with a sustained response to treatment of their autoimmune cytopenia described above have not required additional treatment for their CLL (Figure 3). Median OS from the start of R-CVP therapy for the 20 patients is 61.2 months (Figure 4).

Discussion

Autoimmune cytopenia complicating CLL can cause considerable morbidity and even death. In patients who have ‘complex’ autoimmune cytopenia, treatment of the progressive CLL with myelosuppressive drugs can worsen the cytopenia, and purine analogs can exacerbate the autoimmune process. This clinical challenge is well recognized, but patients with CLL with complex autoimmune cytopenia are relatively rare, and there is limited published experience on management of this condition. This retrospective analysis of a single institution’s experience shows that treatment based on the R-CVP regimen is an effective and tolerable therapy for CLL patients with ‘complex’ autoimmune cytopenia. However, the duration of response is suboptimal, and better treatment options need to be developed.

Purine analog-based chemoimmunotherapy is highly effective for the initial management of progressive CLL and purine analog-sensitive relapsed CLL [4,5,20]. However, purine analog and chlorambucil monotherapy are well-established risk factors for autoimmune cytopenia [6,7,21]. There is now evidence suggesting that purine analog combination therapy using cyclophosphamide and fludarabine [11] and fludarabine, cyclophosphamide, and rituximab [22] do not increase the risk of autoimmune cytopenia in patients who do not have pre-existing autoimmune cytopenia, compared to other therapies. However, the safety of treatment of patients with active ‘complex’ autoimmune cytopenia with purine analog combination therapy is not established because most of these trials have limited inclusion of patients with active autoimmune cytopenia. In addition, purine analog-based chemoimmunotherapy, and especially combinations including fludarabine and cyclophosphamide, are myelosuppressive, and thus can severely exacerbate the cytopenia in patients with autoimmune cytopenia by suppressing the compensatory BM response to increased blood cell loss. We thus propose that chemoimmunotherapy regimens including purine analogs should only be used to treat CLL patients with ‘complex’ autoimmune cytopenia within the context of clinical trials designed to ensure the safety of this approach. Based on these considerations, it has been our practice to use the R-CVP regimen for initial treatment of patients with ‘complex’ autoimmune cytopenia. This approach is similar to that of Kaufman *et al.*, who used a combination of rituximab, cyclophosphamide, and

dexamethasone (RCD) to treat CLL patients with ‘complex’ autoimmune cytopenia [22,23]. The results of our study support their conclusion that combination therapy with cyclophosphamide, corticosteroids, and rituximab is an effective and well-tolerated therapy for ‘complex’ autoimmune cytopenia. However, both reports suggest that the duration of response for both autoimmune cytopenia and CLL are suboptimal. Consequently, many patients will need re-treatment or maintenance immunosuppression.

The challenge is to develop a more efficacious and safe therapy for ‘complex’ autoimmune cytopenia. Future treatment regimens could include initial use of R-CVP or RCD to control the autoimmune cytopenia, followed by a purine analog-containing chemoimmunotherapy in patients with complete resolution of autoimmune cytopenia. An additional option is the use of maintenance therapy (e.g. rituximab) in patients without a complete response to treatment of their autoimmune cytopenia. Alternatively, therapies such as high dose methylprednisolone and rituximab could also be used for initial therapy in patients with ‘complex’ autoimmune cytopenia, especially patients with purine analog-refractory disease [24,25]. Because of the rarity of this condition, any clinical trials to test these and other regimens would need to be multi-institutional.

The most important toxicity of R-CVP in this study was infection. Patients with CLL and ‘complex’ autoimmune cytopenia have a high risk of infection because of both the immunosuppressive effects of their CLL and the use of immunosuppressive therapies to control their autoimmune cytopenia. Thus, patients treated with R-CVP need to be observed carefully and treated aggressively for fevers. An additional concern is the potential neurotoxicity of vincristine, especially in older patients. The advantage of the use of vincristine is that it is not immunosuppressive, has activity in CLL, and is a useful agent in patients with autoimmune cytopenia [26]. In our experience, neurotoxicity was mild and infrequent, but this result was likely only achieved by omitting vincristine in four patients at high risk of neuropathy, and careful monitoring for autonomic and peripheral neuropathy with appropriate dose reductions and cessation of therapy in patients who developed symptoms of neuropathy. These precautions ensured that no patients had significant persistent neurotoxicity, and allowed safe use of this drug with non-additive toxicity, which is likely to contribute to treatment efficacy.

In conclusion, this study shows that treatment with R-CVP can benefit patients with progressive CLL complicated by autoimmune cytopenia. However, the duration of response to this treatment remains suboptimal, and additional interventions should be developed to improve management of this problem.

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Figure 1. Time to next treatment for autoimmune cytopenia. The median time to next treatment for autoimmune cytopenia was 21.7 months from the start of R-CVP therapy.

Figure 2. Time to next treatment for progressive CLL. The median time to next treatment for progressive CLL was 27.7 months from the start of R-CVP therapy.

Figure 3. Time to next treatment for either autoimmune cytopenia or progressive CLL. The median time to next treatment for either autoimmune cytopenia or progressive CLL was 19.3 months from the start of R-CVP therapy.

Figure 4. Overall survival. The median survival of patients from the start of R-CVP therapy for autoimmune cytopenia complicating progressive CLL was 61.2 months.

Patient demographics and clinical characteristics.

Table 1

	Treatment for 'complex' autoimmune cytopenia with R-CVP (n = 20)	Treatment for progressive CLL (n = 553)	p-Value	Treatment for progressive CLL with R-CVP (n = 59)	p-Value
Age at CLL diagnosis (years)			0.93		0.42
Mean (SD)	61.9 (10.9)	62 (10.6)		64.2 (9.3)	
Median (range)	61 (40–80)	63 (22–87)		66 (44–82)	
Sex			0.27		0.27
Male	17 (85%)	405 (74%)		43 (73%)	
Female	3 (15%)	142 (26%)		16 (27%)	
Residency★			0.001		0.01
Local	13 (65%)	169 (31%)		20 (34%)	
Referral	7 (35%)	384 (69%)		39 (66%)	
Immunoglobulin heavy chain gene (IGH) mutation			0.21		0.86
Unmutated	12 (80%)	166 (64%)		14 (82%)	
Mutated (>2%)	3 (20%)	93 (36%)		3 (18%)	
Not available	5	294		42	
FISH analysis †			0.16		0.51
17p13–	1 (8%)	14 (6%)		0 (0%)	
11q22–	5 (39%)	33 (14%)		5 (23%)	
12+	4 (31%)	62 (26%)		8 (36%)	
No abnormality	2 (15%)	49 (21%)		5 (23%)	
13q14–	1 (8%)	75 (31%)		4 (18%)	
Other	0 (0%)	6 (3%)		0 (0%)	
Not done	7	314		37	
CD38 expression			0.51		0.28
Positive (>30%)	8 (40%)	220 (47%)		25 (54%)	
Negative (30%)	12 (60%)	243 (53%)		21 (46%)	
Not done	0	90		13	
ZAP-70 expression			0.10		0.30
Positive (>20%)	13 (72%)	160 (52%)		19 (58%)	
Negative (20%)	5 (28%)	147 (48%)		14 (42%)	

	Treatment for 'complex' autoimmune cytopenia with R-CVP (n = 20)	Treatment for progressive CLL (n = 553)	Treatment for progressive CLL with R-CVP (n = 59)	p-Value
Not done	2	246	26	
Vital status				
Deceased	4 (20%)	162 (30%)	12 (20%)	
Alive	16 (80%)	385 (70%)	47 (80%)	
Autoimmune cytopenia [‡]				
AIHA	17 (85%)			
ITP	8 (40%)			
PRBCA	2 (10%)			
Age (years) at diagnosis of autoimmune cytopenia				
Mean (SD)	67 (10.5)			
Median (range)	66 (47–83)			
Autoimmune cytopenia				
Diagnosed before CLL	1 (5%)			
Diagnosed w/CLL (1 month)	1 (5%)			
Diagnosed after CLL	18 (90%)			
Treatments prior to R-CVP				
Any prior treatment	17 (85%)		30 (51%)	0.007
Purine analog therapy	10 (50%)		14 (24%)	0.03
Alkylator combination	4 (20%)		3 (5%)	0.07
Alkylator w/rituximab	4 (20%)		2 (3%)	0.03

★Patients were considered local if they lived within 120 miles (200 km) of Mayo Clinic Rochester excluding the Minneapolis/St. Paul metropolitan area.

[‡]Fluorescent *in situ* hybridization (FISH) analysis was done using probes to detect 17p13–, 11q22–, 12+, 6q–, 13q14–, and abnormalities of IGHV (immunoglobulin heavy variable). The results are reported using the hierarchical method of Dohner *et al.* [18].

[‡]Six patients had more than one manifestation of autoimmune cytopenia. Four patients had autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) (Evans syndrome), one patient had AIHA and pure red blood cell aplasia (PRBCA), and one patient had AIHA, PRBCA, and ITP.

CLL, chronic lymphocytic leukemia; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.

Table II

Response to R-CVP therapy.

Parameter	Pretreatment★	Post-treatment★
WBC ($\times 10^9/L$) (normal 3.5–10.5)	80.0 (5.4–300.7)	7.0 (2.5–59.7)
Absolute lymphocyte count ($\times 10^9/L$) (normal 0.9–2.9)	75.0 (2.1–275.0)	2.5 (0.22–50.0)
Hemoglobin (g/dL) (normal males 13.5–17.5, females 12.0–15.5)	8.7 (4.2–15.7)	12.6 (11.1–14.7)
Platelets ($\times 10^9/L$) (normal 150–450)	130 (1–362)	185 (32–316)
Absolute reticulocytes ($\times 10^9/L$) (normal 29.5–87.3)	148.8 (3.7–355.6)	58.5 (16–118)
LDH (U/L) (normal 122–222)	312 (59–847)	207 (170–469)
Lymphadenopathy (palpable >1 cm in diameter)	17 (85%)	9 (45%)
Lymphadenopathy (palpable >3 cm in diameter)	9 (45%)	0 (0%)
Organomegaly (palpable liver or spleen)	8 (40%)	2 (10%)

★ Blood count and lactate dehydrogenase (LDH) values are reported as median (range); lymphadenopathy and organomegaly as number of patients (% of total) ($n = 20$).

WBC, white blood cells.