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ORIGINAL ARTICLE

Rituximab–cyclophosphamide–dexamethasone combination in the management of autoimmune cytopenias associated with chronic lymphocytic leukemia

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We report our experience on rituximab–cyclophosphamide–dexamethasone (RCD) combination therapy for the treatment of autoimmune disorders (AIDs) in 48 chronic lymphocytic leukemia (CLL) patients. Overall, 81% of patients were relapsing for AID after previous treatment with corticosteroids, splenectomy, rituximab or alemtuzumab. Diagnosis of AID was autoimmune hemolytic anemia (AIHA) in 26 (54%), autoimmune thrombocytopenia (AITP) in 9 (18.8%), Evan's syndrome in 8 (16.7%) and pure red cell aplasia (PRCA) in 5 patients (10.5%). Median time of autoimmune disorder (AID) onset from CLL diagnosis was 60 months (range: 0–240), and CLL was considered progressive in 40% of subjects upon AID diagnosis (complex AID). Median hemoglobin pre-treatment was 7.7 g/100 ml, and median platelet count 36.5×10^9/l, returning to a median of 12.5/100ml and 37.5×10^9/l, respectively. Overall, an 89.5% response rate was obtained with this combination, irrespective of the AID type. Relapse occurred in 19 patients (39.6%). Median duration of response for autoimmunity (DR-AI) was 24 months, but DR-AI was higher for patients presenting: (1) AID early during CLL course (<3 years), or (2) both PRCA and AIHA. Median time to CLL progression in 48 patients was 16 months, but this time was statistically shorter for Evan's syndrome and AITP patients as compared with AIHA and PRCA patients. This study emphasizes the relevance of CLL-directed immune chemotherapy in the management of CLL-associated AID.

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Introduction

Autoimmune complications occur frequently in chronic lymphocytic leukemia (CLL) patients and predominantly target red cells. Autoimmune hemolytic anemia or thrombocytopenia (AIHA or AITP), either alone or in combination (referred to as Evan's syndrome) and pure red cell aplasia (PRCA) may occur concomitantly to CLL diagnosis but more frequently complicate the evolution of the disease.[1] AIHA and AITP are the most common AIDs in CLL. There have been no systematic studies or controlled trials pertaining to AID treatment. The treatment choice is usually on the basis of small case reports. The most frequently used firstline therapy is prednisolone at a dose of 1 mg/kg per day given for 3–4 weeks, which is then tailored off over several months. If a rapid response is needed, immunoglobulin infusions may be administered (1 g/kg on days 1 and 2). The majority of patients respond, but in case of refractoriness or dependence on corticosteroids, the best treatment option is still unknown. Splenectomy is sometimes proposed in refractory cases, particularly in patients with uncontrolled hemolysis. Monoclonal antibodies may offer new therapeutic options. Rituximab has been used in the treatment of AID in CLL, and more recently, alemtuzumab has been reported in a few cases as possible alternative therapy in this indication.[2] CLL-targeted therapies may be proposed after failure of corticosteroids, according to the 2008 International CLL Workshop Group recommendations.[3] Indeed, clonal CD20+ B cells have a pivotal role in the tolerance breakdown that precedes the onset of AID, either acting as antigen presenting cells that stimulate autoantibodies secretion by polyclonal B cells, or through downmodulation of regulatory T-cells functions.[4,5] Recently, immunochemotherapy regimens, such as rituximab, cyclophosphamide, and dexamethasone (RCD) or rituximab, cyclophosphamide, vincristin and prednisone[6–8] were reported to provide efficient anti-leukemic and anti-autoimmune effects, without significant myelosuppression. It is still a matter of debate whether AID confers poor prognosis to CLL patients,[9] and whether CLL-targeted therapies provide long-lived protection against AID relapse after or during immunosuppressive therapy tapering.[10] It is also still unclear whether the occurrence of autoimmune complications is, in itself, an indicator for CLL therapy. We report here the experience of three French university hospitals regarding the management of CLL-associated AIDs using RCD therapy.

Patients and methods

Patients

Between 2003 and 2008, 48 patients with a diagnosis of CLL (Matutes score 4 or 5 out of 5) according to NCIWG (National Cancer Institute Working Group) presenting AIDs were treated with RCD (3–6 cycles). Median age at CLL diagnosis was 59 (range: 36–79) years, with 81% of patients being male; median age at AID diagnosis was 68 (range 41–85) years. Active CLL disease (progressive lymphadenopathy and/or rapid absolute lymphocyte count doubling time in the last 6 months, or general symptoms including weight loss, fever or night sweats) was present at the time of AID in 40% of patients (thus considered to have 'complex AID'.[11] In total, before RCD, 81% of patients had received a median of two therapy lines for their AID, consisting of prednisolone (81%), splenectomy (19%) and rituximab (23%). In all, 31 patients out of 48 had received previous treatments for CLL also, as indicated in Table 1.

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Table 1 Characteristics of 48 patients receiving RCD for CLL associated AID

AID type	
AIHA	26 (54%)
AITP	9 (18.75%)
Evan's syndrome	8 (16.75%)
PRCA	5 (10.5%)
Gender, F/M	19/81
Active CLL Y/N	20/28
FISH: del(11q)/del(17p)/normal	11/1/8
Onset AID after CLL diagnosis (months)	60 (0–240)
Median age (range)	68 (41–85)
AID therapies	
Median number of previous therapies	2 (0–6)
Prednisone	81%
Rituximab	23%
Splenectomy	19%
CLL therapies	64.6%
CLB or CHOP based	64.5%
F or FC	51.6%
FR or FCR	22.6%
Median pre-treatment counts (range)	
Haemoglobin (g/100 ml)	7.7 (3.8–10.1)
Platelets ($\times 1000/mm^3$)	36.5 (2–71)
Median number of RCD cycles (range)	4 (3–6)

Abbreviations: AID, autoimmune disorder; AIHA, autoimmune hemolytic anemia; AITP, autoimmune thrombocytopenic purpura; CLB, chlorambucil; F/FC, fludarabine/fludarabine cyclosposphamide; FR/FCR, fludarabine rituximab/fludarabine cyclosposphamide rituximab; PRCA, pure red cell aplasia; RCD, rituximab-cyclophosphamide-dexamethasone.

Diagnosis of AID

AIHA was diagnosed on the basis of hemoglobin (Hb) <10 g/100 ml, a positive direct antiglobulin test, low haptoglobin levels (<0.3 g/l) and hyper-reticulosis ($>100\times10^9$/l), in the absence of obvious bleeding. PRCA was diagnosed based on low hemoglobin levels (<10 g/100 ml), negative direct antiglobulin test, reticulocytopenia ($<10\times10^9$/l), absence of viral infection (CMV, EBV and parvovirus B19) and isolated absence of erythroid precursors in the bone marrow aspirate. AITP was diagnosed upon rapid decline of platelet levels ($<100\times10^9$/l), without splenomegaly or coagulation disorder (in some cases, presence of megakaryocytes in bone marrow smears was also confirmed) and with normal reticulocyte counts. Evan's syndrome was defined by the presence of both AITP and AIHA diagnostic criteria.

Therapy

Two RCD schedules were used. For the first RCD schedule ($n=27$ patients), which has been described elsewhere,[6,7] patients received rituximab 375 mg/m^2 intravenously on day 1, cyclophosphamide 750 mg/m^2 intravenously on day 1 and dexamethasone 12 mg daily and orally from day 1 to day 7, every 4 weeks (until best achievable response, 4–6 cycles were planned). The second ($n=21$ patients) consisted of a 15-day schedule, using the same doses of rituximab, whereas cyclophosphamide was given 1000 mg intravenously (flat dose) on day 1 and dexamethasone 40 mg was administered orally on day 1, every 2 weeks (until best achievable response, 4–6 cycles were planned). Pneumocystis carinii and varicella zoster virus /herpes simplex virus prophylaxes were mandatory. The total number of cycles was planned according to best response (median 4 cycles). Response criteria for AID were: (a) complete, if Hb >12 g/100 ml and/or platelets $>100\times10^9$/l, without transfusion requirements, and normalization of lactate dehydrogenase and reticulocyte counts (direct antiglobulin test was not always available at the end of therapy) or (b) partial, if Hb rise was at least 2 g/100 ml but with final Hb <12 g/100 ml and/or platelet counts within $50–100\times10^9$/l, along with biological parameter improvements and transfusion needs.

Response criteria for CLL were (2–3 months after day 1 of last RCD cycle): (a) complete, if there was no cytopenia (neutrophils >1500, Hb >11 g/100 ml and platelets $>100\times10^9$/l), no palpable lymph node >15 mm (and normal CT scan for patients with bulky disease before RCD), no constitutional symptoms and lymphocyte count $<4000/\mu$l), or (b) partial, if there was at least $>50\%$ reduction of preexisting lymph nodes/splenomegaly/hepatomegaly/lymphocytosis (more than two parameters out of four), and at least one marker of good hematologic recovery (neutrophil count >1500, Hb >11 g/100 ml, platelet count $>100\times10^9$/l, or at least $>50\%$ increase from baseline). Bone marrow biopsy was not done in patients meeting complete response rate (CR) criteria; therefore, according to 2008 NCIWG guidelines,[3] we only state clinical complete responders, partial responders or failures throughout the text.

Statistical analyses

Durations of response for AID (DR-AID) and CLL (DR-CLL), and overall survival were plotted according to Kaplan–Meier product-limit method (and compared using the log-rank test), and calculated from the end of RCD therapy to the occurrence of AID, CLL relapse or death, respectively. AID relapse diagnostic criteria were unchanged from those used at diagnosis; progression of CLL was assessed according to NCIWG criteria (lymphocytosis $>5\times10^9$/l and/or hepatosplenomegaly or palpable lymph nodes). All statistical analyses were performed using the Statistica software (StatSoft, Tulsa, OK, USA).

Results

Patient demographics

Characteristics of the 48 patients are listed in Table 1. As previously reported, male gender appeared to be associated with the development of AID. The median age was 68 years and the median time between RCD initiation and CLL diagnosis was 60 months (range: 1–240 months). Previous treatments for CLL included chlorambucil, fludarabine +/−cyclophosphamide +/− rituximab or CHOP-based regimen. The treatments for AID included corticosteroids (81% of cases), intravenous immunoglobulins, splenectomy or rituximab alone, patients receiving a median of two lines (range: 0–6). In this study, 19% of patients with AID were treated with first-line RCD. Of note, four patients with AIHA during fludarabine cyclosposphamide ($n=2$) and fludarabine cyclosposphamide rituximab (FCR) ($n=2$) therapy obtained a complete response after three (1 fludarabine cyclosposphamide, 1 FCR) or six (1 fludarabine cyclosposphamide, 1 FCR) courses of RCD. Median Hb and platelet counts before RCD were 7.7 g/100 ml (range: 3.8–10.1) and 36.5×10^9/l (range: 2–71), respectively. RCD was scheduled until the best hematologic response, a median of four cycles being given (range 3–6).

Responses and survivals after RCD regimen

Following RCD therapy, the overall response rates/CRs of AID were 89.5 and 83%, respectively, and were not correlated to the AID type (CR was 81% for AIHA, 89% for AITP, 75% for Evan's and 100% for PRCA). Median DR-AI was 24 months according to the Kaplan–Meier analysis (Figure 1a), and was correlated neither to the presence of active CLL at AID onset, gender, age, fluorescence in situ hybridization results and Binet stage, nor to the number of RCD cycles or the number and type of previous treatments for AID (splenectomy or rituximab) or CLL (alkylating agents, fludarabine and/or rituximab). The two RCD regimens (15-day or 28-day schedules) yielded very similar response durations, both in terms of AID and CLL (Figures 1b and c). The most relevant parameter linked to prolonged DR-AI after RCD was the achievement of CR (Figure 1d). Moreover, significantly shorter DR-AIs were observed in patients developing Evan's syndrome (log-rank $P=0.005$) (Figure 2a), and in patients developing AID at a late time point in the course of their CLL (>36 months, log-rank $P=0.035$) (Figure 2b). When comparing early versus late AID patients, only median age at CLL diagnosis (not age at AID) was significantly higher in the early AID cases (68.5 versus 57 years, $P=0.01$).

Overall response rate and clinical complete response (no bone marrow assessment) rates for CLL disease were 95 and 35%, respectively (one failure out of 20 patients), with a median DR-CLL of 16 months. Relapse of AID was strongly correlated with relapse of CLL following RCD therapy (Figure 2c, log-rank $P=0.0001$). Interestingly, patients developing Evan's syndrome or AITP presented significantly shorter DR-CLL than patients who suffered from AIHA or PRCA (log-rank $P=0.0001$ for the entire cohort, and $P=0.046$ when comparing AITP with AIHA), despite RCD therapy (Figure 3). Overall survival for the entire cohort was 52 months (Figure 4), irrespective of the AID type (log-rank $P=0.3$). Finally, median duration of response was longer for patients with AID without CLL evolution, provided that these patients received early RCD therapy, first line or after corticosteroid failure (Figure 5).

Tolerance

RCD has been reported to be remarkably safe.[6,7] In our cohort, chart review revealed no neutropenic fever episodes, re-hospitalization, dose reductions or treatment delays. G-CSF prophylaxis was not recommended. Of note is that in 18 patients aged over 70 years, the safety profile (especially lack of significant myelosuppression) was considered acceptable and therapy could be completed according to the planned schedule.

Management of post-RCD relapses

In all, 19 out of 48 patients experienced AID relapse after RCD (AIHA = 6 out of 26 (23%), AITP = 4 out of 9 (44.4%), Evan's syndrome = 8 out of 8 (100%) and PRCA = 1 out of 5 (20%)). As shown in Figure 2c, AID relapse was strictly correlated with CLL progression following RCD therapy (AIHA = 6 out of 26 (23%), AITP = 6 out of 9 (66%), Evan's syndrome = 8 out of 8 (100%) and PRCA = 1 out of 5 (20%)). Of these 19 patients, 1 died before re-treatment, 8 received a second course of RCD (RCD2), 2 were given another immune chemotherapy (R-miniCHOP or FCR), 5 benefited from splenectomy, while 3 were administered cyclosporin A alone. Among the eight patients receiving a second RCD course, seven obtained a second response (87.5%) and only one failed to respond. During the short median follow-up of 11 months, DR-AI from re-treatment with RCD2 was 11 months and 4 months with other regimens (log-rank $P=0.011$) (Figure 6a). In total, 3 out of 8 patients receiving RCD2 and 8 out of 10 alternatively treated patients presented AITP (or Evan's syndrome), but the AID type (thrombocytopenia versus anemia) did not correlate with the second remission duration (Figure 6b). Type of re-treatment (RCD2 versus others) was the only parameter that was linked to a significantly prolonged DR-AI from relapse following RCD therapy.

Discussion

Management of corticosteroid refractory or relapsing AID mostly relies on individual institution experiences, as there are no

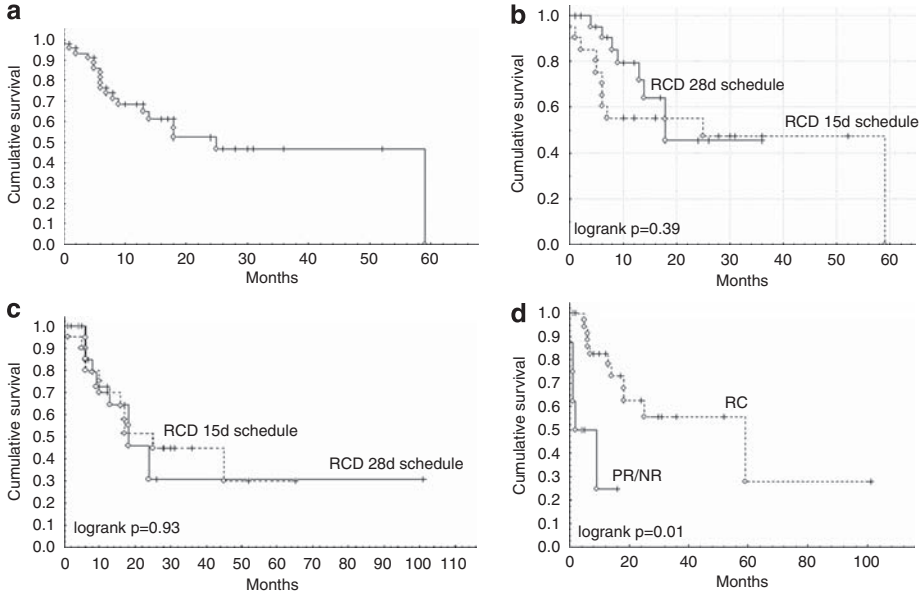

Figure 1 Duration of response of autoimmunity (DR-AI) and of CLL (DR-CLL) after RCD treatment. (**a**) Median DR-AI in 48 patients receiving RCD is 24 months. (**b**) DR-AI and (**c**) DR-CLL according to the schedule of RCD given to patients (every 15-days 4–6 cycles, or 28-days 3–6 cycles). There was no difference observed between these two RCD schedules. (**d**) Complete response after RCD has a strong impact on prolonged DR-AI post-RCD. CR, complete response; NR, no response; PR, partial response.

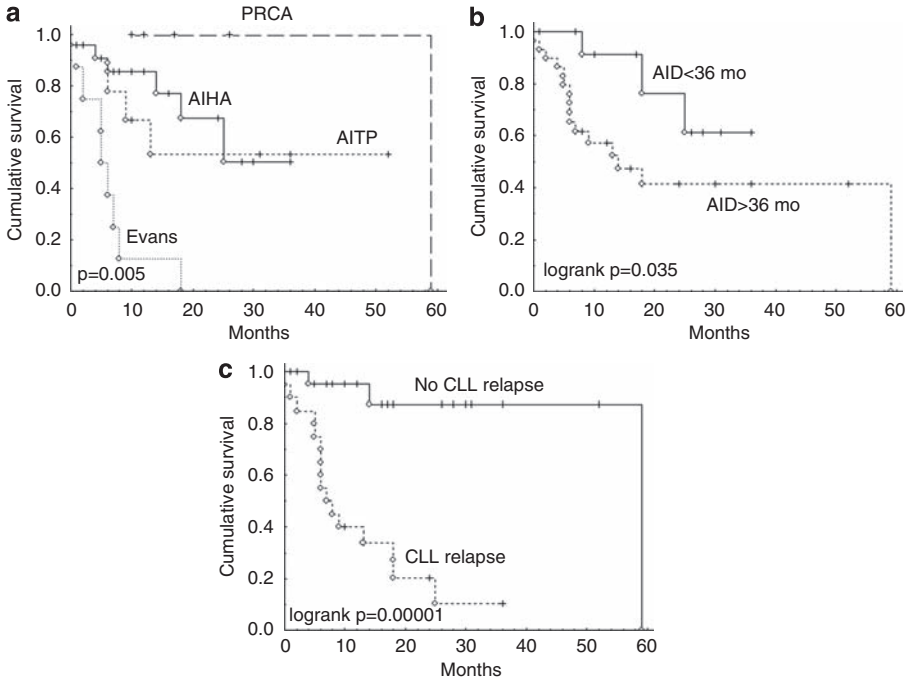

Figure 2 Parameters impacting duration of response of autoimmunity (DR-AI) after RCD therapy. (**a**) DR-AI of Evan's syndrome patients is significantly shorter than for all other AID types. (**b**) DR-AI is significantly prolonged after RCD therapy, if AID occurs early in the course of CLL (within 3 years from CLL diagnosis). (**c**) DR-AI is significantly shorter in those patients presenting CLL relapse after RCD therapy. AIHA, autoimmune hemolytic anemia; AITP, autoimmune thrombocytopenic purpura; PRCA, pure red cell aplasia.

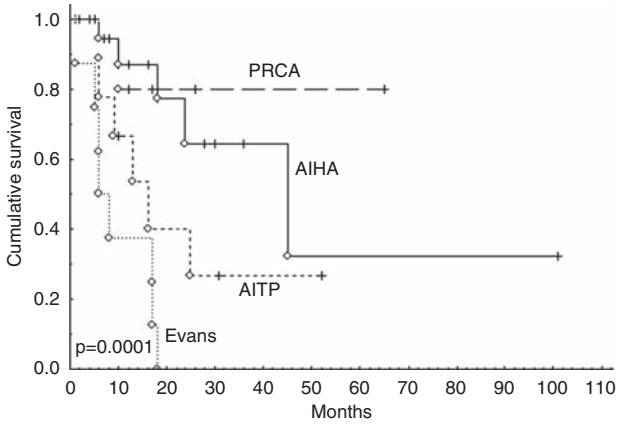

Figure 3 Duration of response of chronic lymphocytic leukemia (DR-CLL) according to the type of AID. Patients with immune anemia exhibit superior CLL disease-free survival than those with AITP or Evan's syndrome ($P=0.0001$). A significant difference was observed between AITP and AIHA patients ($P=0.046$). AID, autoimmune disorder; AIHA, autoimmune hemolytic anemia; AITP, autoimmune thrombocytopenic purpura; PRCA, pure red cell aplasia.

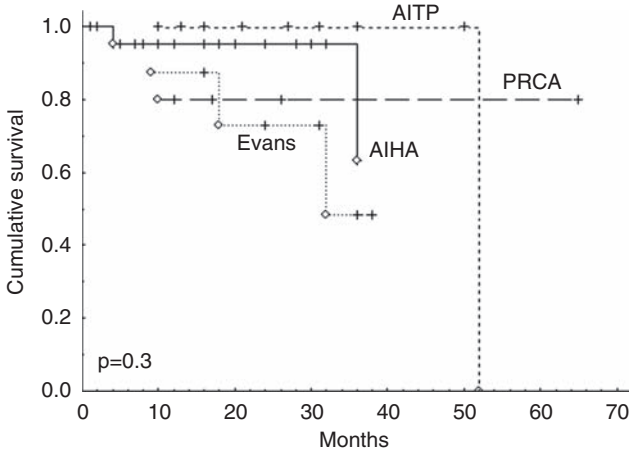

Figure 4 Overall survival is not statistically linked to the AID type. AIHA, autoimmune hemolytic anemia; AITP, autoimmune thrombocytopenic purpura; PRCA, pure red cell aplasia.

randomized controlled studies for therapy guidance. Based on case-reports or small patient series, splenectomy and monoclonal antibodies (rituximab and alemtuzumab) have been proposed with relative success, though with disappointing disease-free survival. Recently, immunochemotherapy combinations of RCD have been shown to be effective in controlling AIDs complicating CLL disease.

We report here on a retrospective study evaluating RCD efficacy in the treatment of CLL associated AID. In this series, the overall response rate to RCD therapy was very similar to previously published results,[7,8] while involving the largest patient cohort reported to date (48 versus 20 or 21) with different AID types (AIHA, AITP, Evans's syndrome and PRCA). Considering the two others studies, the first[7] reviewed 21 CLL patients treated for AIHA alone ($n=18$), AITP ($n=1$) or a combination of both ($n=2$), with no PRCA or Evan's syndrome cases reported. In this study, only very few patients were corticosteroid refractory versus 81% in our study. The second publication involved patients treated using the combination of rituximab, cyclophosphamide, prednisone and vincristine for AIHA complicating progressive CLL (complex AID[11]), also with some PRCA ($n=2$) and AITP ($n=8$) cases. In contrast with

this latter report, active CLL disease was present upon AID diagnosis in only 40% of our patients. With 24 months, the median duration of response was similar in our study, as compared with 22 months observed in the two others.[7,8] Out of our 20 patients with complex AID, 60% were found to have del11q23 by fluorescence in situ hybridization. This occurrence is rarely reported in literature, but AID patients frequently present with CLL-specific adverse prognostic factors (IgVH unmutated, ZAP70/CD38+ and rapid lymphocyte doubling time[11]). Among the 48 patients, detection of del11q23 by fluorescence in situ hybridization had no detrimental impact on DR-AI or DR-CLL (data not shown). Finally, in line with previously reported studies, RCD proved to be safe, as no hospitalizations or infections were directly related to this association. In our study, given the inclusion of AIDs other than immune anemia, the DR-AI appeared to be dependent on the AID type. Indeed, DR-AI was shown to be significantly shorter for patients with Evan's syndrome and to a much lesser extent, for those with AITP. Furthermore, during follow-up, patients with Evan's syndrome or AITP presented more rapid CLL progression despite receiving RCD at the time of AID onset. This detrimental impact of low platelet counts may appear confusing, as AITP diagnosis is at times less evident than AIHA or PRCA (though our patients fulfilled common diagnosis criteria: no concurrent infection, no or small spleen enlargement, fast drop in platelet counts and (although not obtained in all cases) normal megakaryocyte counts in bone marrow). Recently, an Italian study has highlighted the negative prognostic impact of ITP during CLL.[12] Moreover, subjects with low platelet counts because of marrow infiltration or AITP presented similar poor outcomes as compared with all the other CLL patients. According to the treatment response criteria used in this study, our nine patients receiving RCD therapy would have been classified as complete responders ($>150\times10^9$/l) in 6 out of 9 (66.7%) patients with AITP and 6 out of 8 (75%) patients with Evan's syndrome. The short response durations (both DRAI and DR-CLL) despite good clinical and biological responses in immune thrombocytopenias in our study and other reports suggest that we should prospectively evaluate highly active anti-CLL regimen. For those patients relapsing with complex AID after RCD, FCR could be considered for more effective treatment of the underlying CLL once the autoimmune cytopenia has been controlled. On the other hand in our study and others, high response rates and response durations were observed for immune anemia. These results are in line with the good prognosis previously reported for patients with CLL-associated AID.[9,10] We confirm excellent results in five patients with PRCA using RCD. This event, rarely occurring in CLL, is usually controlled by either corticosteroids or cyclosporin A. Yet, some case reports indicated a beneficial role of rituximab in patients refractory to first-line therapy,[13,14] although the duration of follow-up was short. Among our five patients, four have not yet relapsed following RCD (ongoing responses), and the remaining patient relapsed 5 years after the first RCD course. Currently, this patient is in second complete remission of PRCA after a second RCD course.

It is still a matter of debate whether the occurrence of autoimmune complication is to be considered in itself an indicator for CLL therapy, and if CLL targeted therapies provide long-lived protection against AID relapse. We demonstrated that the most relevant parameter linked to prolonged response duration for autoimmune disease was the achievement of CR. Relapse of AID was strongly correlated with relapse of CLL following RCD. Furthermore, median duration of response was higher for patients with AID without CLL evolution, if these patients had received early RCD therapy. The necessity of controlling leukemic cells should be prospectively assessed in a controlled trial, on the basis of all these considerations. Our data also suggests that CLL directed therapy such as RCD is

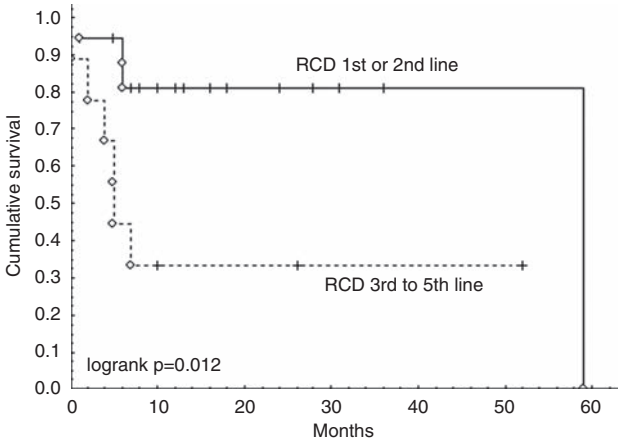

Figure 5 Duration of response of autoimmunity (DR-AI) in 28 patients without CLL active disease at the time of AID onset, according to early ($n=20$) or late ($n=8$) introduction of RCD in the AID treatment lines.

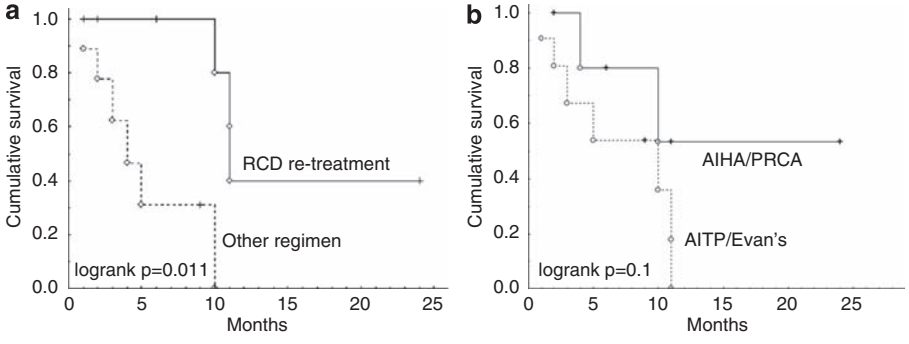

Figure 6 Duration of response of autoimmunity (DR-AI) according to management of relapse after a first course of RCD. (**a**) 19 patients relapsed, 18 received either a second course of RCD (RCD2) or another treatment (R-chemo, splenectomy, alemtuzumab or cyclosporin A). Patients who benefited from RCD2 still present good responses, and better DFS-AI from relapse than those who were given any other therapy (median 11 versus 4 months, log-rank $P=0.011$). (**b**) AID types do not influence DFS-AI. AID, autoimmune disorder; AIHA, autoimmune hemolytic anemia; AITP, autoimmune thrombocytopenic purpura; PRCA, pure red cell aplasia.

highly efficient when given early in the course of AID (first or second line), even in the absence of CLL disease progression.

A second course of RCD was given to 8 out of 18 (44%) patients who experienced AID relapse. Despite this small sample size, our results indicate that RCD2 was again effective, with a significantly prolonged DR-AI, as compared with splenectomy (5 out of 18 patients) or any other treatment (alemtuzumab, R-chemotherapy or immunosuppressive drugs such as cyclosporin A. In our patients, splenectomy only offered transient improvement of blood cell counts, with responses lasting 4 months. This is in accordance with previously published works,[7] further strengthening the message that RCD is particularly effective in multirelapsing AID patients.

We believe that compared with other therapies, RCD constitutes a corticosteroid-sparing, CLL-directed and anti-AID strategy with an improved safety profile, especially in elderly patients. Rituximab is well tolerated when used either alone[15] or in combination with CD for the treatment of AIHA.[6–7] Given the close relationship between AID and CLL activities, the French CLL intergroup intends to promote a comparative trial to assess the impact of immunosuppressants versus RCD as frontline treatment to manage these patients.

Conflict of interest

The authors declare no conflict of interest.

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