Allogeneic Transplant with Reduced Intensity Conditioning Regimens may Overcome the Poor Prognosis of B-Cell Chronic Lymphocytic Leukemia with Unmutated Immunoglobulin Variable Heavy-Chain Gene and Chromosomal Abnormalities (11q− and 17p−)

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Abstract

Purpose: To evaluate the efficacy of reduced intensity conditioning (RIC) allogeneic transplant in 30 patients with poor-prognosis chronic lymphocytic leukemia (CLL) and/or high-risk molecular/cytogenetic characteristics.

Experimental Design: Eighty-three percent of patients had active disease at the moment of transplant. That is, 14 of the 23 patients analyzed (60%) had unmutated immunoglobulin variable heavy-chain gene (IgV_H) status; 8 of 25 patients (32%) had 11q−, with four of them also displaying unmutated IgV_H; and six (24%) had 17p− (five were also unmutated).

Results: After a median follow-up of 47.3 months, all 22 patients alive are disease free; overall survival and event-free survival (EFS) at 6 years were 70% and 72%, respectively. According to molecular/cytogenetic characteristics, overall survival and EFS for unmutated CLL and/or with 11q− aberration (n = 13) were 90% and 92%, respectively, not significantly different to those with normal *in situ* hybridization, 13q− and +12, or mutated CLL (n = 7). All six patients with 17p deletion were transplanted with active disease, including three with refractory disease; all except one reached complete remission after the transplant and two are alive and disease free. Nonrelapse mortality (NRM) was 20%; more than two lines before transplant is an independent prognostic factor for NRM (P = 0,02), EFS (P = 0.02), and overall survival (P = 0.01). Patients older than 55 years have a higher risk of NRM (hazard ratio, 12.8; 95% confidence interval, 1.5-111). Minimal residual disease was monitored by multiparametric flow cytometry in 21 patients. Clearance of CD79/CD5/CD19/CD23 cells in bone marrow was achieved in 68% and 94% of the patients at days 100 and 360, respectively.

Conclusion: According to these results, RIC allogeneic transplant could overcome the adverse prognosis of patients with unmutated CLL as well as those with 11q− or 17p−.

B-cell chronic lymphocytic leukemia (B-CLL) is a heterogeneous disease with some patients displaying an indolent clinical course with a similar survival to that of normal individuals, whereas others, frequently presenting with cytopenias, display a poor outcome with a median survival between 1 and 5 years (1, 2). Recently, it has been shown that the aggressive clinical course of the disease is associated with specific biological characteristics, such as an unmutated germ line configuration of the immunoglobulin variable heavy-chain gene (IgV_H), chromosomal aberrations (17p−, 11q−, or a complex karyotype) as well as overexpression of several antigens, such as CD38 or ZAP-70 (3–7).

To improve this dismal outcome in young B-CLL patients with poor prognosis, autologous stem cell transplantation (ASCT) has been increasingly used over recent years. Although some data suggests a survival benefit of ASCT over conventional therapy, its advantage for patients with unmutated CLL is controversial (8–12). Moreover, for patients with both unmutated IgV_H and chromosomal abnormalities (11q− and 17p), ASCT does not seem to offer any beneficial effect (12, 13). In addition, patients with advanced-stage or active B-CLL at the time of SCT, as well as those with an interval between diagnosis and transplant longer than 36 months, are associated with a poorer outcome (11). Finally, whereas there is no evidence that ASCT could cure CLL patients, long-term follow-up reports show that allogeneic transplant is able to cure some B-CLL patients, although the overall mortality of this strategy ranges between 30% and 60% (11, 14–18).

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Several groups of researchers have confirmed the feasibility of reduced intensity conditioning (RIC) in different hematological malignancies, but experience in B-CLL is scanty (19–22). Moreover, the efficacy of this approach in B-CLL patients with unfavorable biological features still needs to be verified (23).

We report here on the efficacy of RIC allogeneic related transplant in a group of 30 B-CLL patients, with adverse clinical and/or biological prognostic factors.

Patients and Methods

Patients. Between March 1999 and April 2004, 30 consecutive adult patients, with median age of 53 years (range, 35-67 years), underwent allogeneic RIC from an HLA identical sibling at eight transplant centers in Spain. Eligibility criteria for allogeneic RIC required one of the following characteristics: (a) progressive or relapsing disease after two or more lines of chemotherapy, including ASCT; (b) Ritcher syndrome; or (c) symptomatic CLL with one or more of these adverse molecular/cytogenetic factors: unmutated IgV_H, 17p−, 11q−, or complex karyotype. All 30 patients gave written informed consent for inclusion in the transplant program. Two of them have previously been reported elsewhere.

Patients' characteristics are shown in Tables 1 and 2: Seventy-seven percent of the patients were older than 50 years and 10 (33%) were older than 55 years. The median number of previous lines of therapy was 3 (1–8), and 87% had previously received fludarabine or 2-chlorodeoxyadenosine, with early relapse or progression after drugs in 44%. Two patients developed Ritcher syndrome. The interval between diagnosis and transplant was 44 months (range, 6-201). At transplant, 83% of patients had active disease and seven of them (23%) showed refractory progressive. Seven patients were transplanted after one line of chemotherapy due to the presence of both stage B or C and presence of poor biological factors, such as unmutated CLL ($n = 3$) or 11q− ($n = 4$).

Treatment. Twenty patients received the RIC regimen consisting of fludarabine (30 mg/m^2 i.v.) on days −8 to −4 and melphalan (70 mg/m^2 i.v.) on days −3 and −2 (22). In one patient, alemtuzumab was added. The remaining 10 patients received two different conditioning regimens: five patients received fludarabine + busulfan and rabbit antithymocyte globulin (20), and five patients received fludarabine (90 mg) + total body irradiation (200 cGy) + antithymocyte globulin. In all these latter patients, graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A alone. In the other 20 patients, GVHD prophylaxis included cyclosporine A plus a short course methotrexate; cyclosporine A tapering was started on day 90 if no GVHD or progression appeared.

Supportive care, grading, and treatment of acute and chronic GVHD were carried out using standard protocols (24, 25).

Biological characteristics. Fourteen of the 23 patients analyzed (60%) had an unmutated IgV_H status; 8 of 25 patients (32%) had 11q− with four of them also displaying unmutated IgV_H; six (24 %) had 17p− aberration (five were also unmutated); two patients had 13q−; one patient 13q− and one monosomy; and one patient with 13q− and +12 aberrations. In four patients, mutational status or fluorescence *in situ* hybridization (FISH) was not available.

Stem cells. All patients received peripheral blood stem cells from a related identical donor mobilized with 5 to 10 μg/kg of granulocyte colony-stimulating factor. The median number of CD34$^+$ cells infused was 4.9×10^6/kg (range, 1.9-8.8).

Molecular and minimal residual disease studies. *IgV_H* identification, sequencing, and mutational analysis as well as chimerism studies were done as previously described (26, 27). For FISH analysis, standard protocols were used (28).

Minimal residual disease (MRD) was studied by multiparametric flow cytometry assay using four-color multiparametric immunophenotyping analysis (CD79/CD5/CD19/CD23), yielding a sensitivity between 10^{-3} and 10^{-4} (one leukemic cell among 10,000 or 100,000 normal cells, as previously described; ref. 29). Analysis was done on bone marrow before transplant and at days 100, 180, 240, and 360 and later at least every 6 months until the last follow-up.

Assessment of clinical outcome. Data was analyzed as of October 30, 2004. Criteria for disease status at transplant were those proposed by Cheson et al. (30). Post-transplant evaluation was done at day 100 and then every 3 months during the first year and subsequently every 4 to 6 months. Complete remission (CR) after transplant was defined as disappearance of all CD79/CD5/CD19/CD23 clonal B cells from the bone marrow determined by multiparametric flow cytometric analysis (30) as well as regression of all tumor masses by image techniques. GVHD was graded according to published criteria (24, 25).

Statistical analysis. Events analyzed were calculated from the time of transplantation using Kaplan-Meier product limit estimates. Non-relapse mortality (NRM) was defined as death due to causes unrelated

Table 1. Patient characteristics and toxicity ($N = 30$)

Characteristics	*n* (%)
Median age (y), (range)	53 (35-67)
>50	23 (77)
>55	10 (33)
Sex	
Male	20 (67)
Binet stage at diagnosis	
Stage B	13 (43)
Stage C	10 (33)
Prior chemotherapy	
n lines, median (range)	3 (1-8)
Previous fludarabine	26 (87)
Refractory fludarabine	11 (37)
Previous autologous transplant	3 (10)
Status at transplant	
CR	5 (17)
PR	19 (63)
Refractory disease	6 (20)
Conditioning regimen	
Fludarabine (150 mg) + melphalan (140 mg)	19 (63)
Fludarabine (150 mg) + alemtuzumab (100 mg)	1 (3)
Busulfan (8 mg) + fludarabine (180 mg) + ATG (160 mg)	5 (17)
Fludarabine (90 mg) + TBI (200 cGy)	1 (3)
Fludarabine (90 mg) + TBI (200 cGy) + ATG (160 mg)	4 (13)
GVH prophylaxis	
CSA + MTX	28 (93)
CSA	2 (7)
Causes of death	
Sepsis	3 patients*
PTLPL	1 patient†
GVHD	2 patients

Abbreviations: PTLPL, posttransplant lymphoproliferative lymphoma; TBI, total body irradiation; PR, partial remission; ATG, antithymocyte globulin; MTX, methotrexate; CSA, cyclosporine A.

*One associated to GVH.

†The patient received alemtuzumab +ATG.

Table 2. Clinical course and patient characteristics ($n = 30$)

Patient no.	Age/sex	V_H homology	FISH/karyotype	Diagnosis to transplant interval (mo)	Prior chemotherapy (no. lines)	Status at transplant	Last follow-up from transplant (mo) and status
1	50/F	Unmutated	11q−	11	3	PGR	69, alive, CR
2	54/F	Mutated	11q−	50	3	PGR	61, alive, CR
3	48/F	Unmutated	17p−	14	2	PR	55, alive, CR
4	55/M	Mutated (ZAP-70+)	Normal	7	3	PR	31, alive, CR
5	35/M	Unmutated	+12	74	2	RC	36, alive, CR
6	45/M	Unmutated	11q−	26	3	PGR	31, alive, CR
7	55/F	Unmutated	11q−	62	3	PR	73, alive, CR
8	47/F	Unmutated	Normal	20	2	PR	30, dead, PGR
9	54/F	ND	Normal	13	2	PR	50, alive, CR
10	64/M	Mutated	Normal	74	4	PR	21, alive, CR
11*	62/M	Unmutated	Normal	94	4	PR	13, alive, CR
12	55/M	ND	ND	44	4	PGR	55, alive, CR
13	58/F	ND	17p−/Complex	35	2	PGR	37, alive, CR
14	47/M	ND	11q−	6	1	CR	19, alive, CR
15	55/M	Unmutated	11q−	10	1	CR	75, alive, CR
16	56/M	Mutated	11q−	37	2	PR	58, alive, CR
17	50/M	Unmutated	17p− and 12+	31	5	PGR	1.5, dead, PGR
18	53/M	Mutated	Normal	96	2	PR	51, alive, CR
19	37/M	ND	13q−/	81	1	CR	51, alive, CR
20	58/M	Unmutated	Normal	16	1	PR	50, alive, CR
21	51/M	Mutated	ND	201	8	PR	45, alive, CR
22	50/M	Mutated	13q−	91	1	PR	42, alive, CR
23	52/M	Mutated	11q− and 13q	49	1	PR	34, alive, CR
24	45/M	Unmutated	Normal	22	1	CR	12, alive
25	62/F	Unmutated	17p−	37	3	PR	8, dead by NRM (in CR)
26	61/M	Unmutated	17p−	111	4	PGR	4, dead by NRM (in CR)
27	67/M	ND	ND	140	3	PR	3, dead by NRM (in CR)
28	60/M	ND	ND	47	4	PR	22, dead by NRM (in CR)
29	51/F	ND	ND	56	4	PR	4,6, dead by NRM (in CR)
30	59/F	Unmutated	17p−	44	3	PR	7,5, dead by NRM (in CR)

Abbreviations: F, female; M, male; PR, partial remission; PGR, progression; ND, not determined.
*B-CLL+ refractory Hodgkin's lymphoma.

to the underlying disease. GVHD-related mortality was defined as death due to causes directly related to GVHD, and those deaths attributed to immunosuppression in patients requiring treatment for GVHD were also considered as GVHD-related mortality. Event-free survival (EFS) was calculated from transplant until disease progression or death, and those patients who did not reach disease response (complete or partial remission) any time after transplant were considered events on day 100 because that was the first date for complete disease evaluation. Overall survival was calculated from transplant until death from any cause, and surviving patients were censored at last follow-up.

Patients who showed evidence of engraftment were evaluable for acute GVHD, whereas patients who engrafted and survived >100 days were evaluable for chronic GVHD. The day of acute GVHD was calculated from transplant until diagnosis of acute GVHD among evaluable patients and the same for chronic GVHD. Variables included in the univariate and multivariate analysis for NRM, disease-free survival, EFS, overall survival, and GVHD were age (<55 or >55), status at transplant (chemorefractory or chemosensitive), type of conditioning (containing melphalan versus other), more or less than two lines of chemotherapy before the transplant, interval between diagnosis and transplant longer than 45 months, and development of acute and or chronic GVHD. Biological characteristics for mutational status and FISH aberrations, such as 11q− or 17p−, were also included in the analysis. For this purpose, the two-sided log-rank test was used to test the univariate association between variables and univariate analysis.

Univariate Cox regression was used to analyze the effect of time-dependent variables, such as chronic GVHD, on EFS and overall survival.

All factors that significantly or marginally ($P < 0.1$) influenced univariate analysis were included in a multivariate analysis using a forward-step Cox regression model.

For most of the statistical analyses, the SPSS software program (SPSS 10.0, Inc., Chicago, IL) was used. Computations and testing of cumulative incidences were carried out with the package cmprsk R 1.9.1. Differences were considered to be statistically significant when $P < 0.05$.

Results

Hematologic recovery and engraftment. All patients engrafted and they reached >500 granulocytes/mm^3 at a mean of 15 days (range, 8-23) and >20,000 platelets/mm^3 at a mean of 5 days after transplant (range, 0-29). Complete donor chimerism in

bone marrow was observed between days 21 and 28 in 67% of patients, and after day 180 in all except two patients who had previously relapsed.

Response to transplant and outcome. Of the 30 patients included in the study, at the time of transplant according to the Cheson criteria (30), 25 (83%) had active disease, including six with refractory progressive disease. At day 100, considering the 27 evaluable patients, 21 (78%) had achieved CR, five (18%) were on partial remission, and one had stable disease (3%). The three nonevaluable patients had died, two due to NRM (both in CR) and one due to early PGR on day 50. With a median follow-up of 47.3 months (range, 12-74.6), 22 patients are still alive and disease free with an actuarial disease-free survival, EFS, and overall survival at 5 years of 93%, 70%, and 72%, respectively (Fig. 1).

Overall, in 26 of the 30 patients, mutational IgH status and/or FISH were available; 14 of 23 patients in which IgV_H was analyzed (60%) had an unmutated germ line configuration, eight patients (30%) had 11q− (four were also unmutated), and six (23 %) had 17p− aberrations (four were unmutated and one mutated). Nine the 11 patients with 11q− and/or unmutated CLL were transplanted with active disease and three of them with progressive disease; of these, all except one reached CR after the transplant and were still alive and disease free between 4 and 62 months later. Only 1 of the 11 patients in this group, with unmutated CLL and normal FISH, transplanted at partial remission did not reach CR after the transplant and died due to progression 30 months later. Overall survival and EFS for this group of patients with unmutated CLL and or with 11q− aberration (n = 13) were 90% and 92%, respectively, not significantly different to those with normal FISH, 13q−, and +12 or mutated CLL (n = 7) who had an overall survival and EFS of 100% (P = 0.4; Fig. 2). Considering the six patients with 17p deletion (five also unmutated), all of whom were transplanted with active disease, including three with refractory disease, all except one reached CR after the transplant and two were still alive and disease free between 26 and 43 months after transplant. Three died in CR between 3.8 and 8 months after transplant (two due to GVH and one due to a post-transplant lymphoproliferative disorder). Only one patient died due to early progression at day 50.

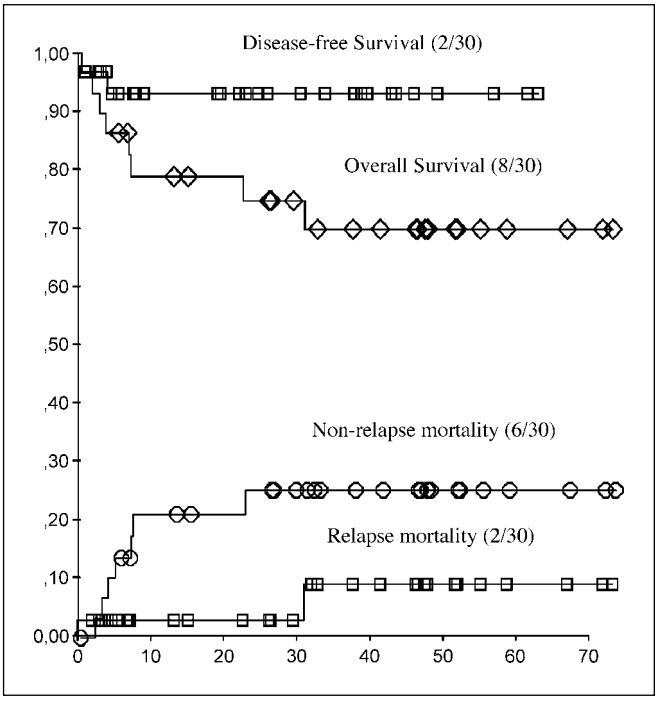

Fig. 1. Overall and disease-free survival was 70% and 93%, respectively. Nonrelapse and relapse mortality was 22% and 10%, respectively.

Toxicities, graft-versus-host disease, and prognostic factors. After a median follow-up of 47.3 months (range, 12-74.7), 22 patients (70%) are alive and disease free and eight patients have died, two of them (6%) due to disease progression and six (21%) due to NRM; none of them occurring within the first 30 days, with a probability of NRM at 68 months of 22%. Causes of death were sepsis (three cases, one with concomitant acute GVHD), acute GVHD (two cases), and a post-transplant lymphoproliferative disorder in one patient who had received alemtuzumab as conditioning. According to univariate analysis, in the current study, three variables had a significant influence on NRM: age, >55 years; acute GVHD; and more than two lines before transplant; whereas in multivariate analysis, only the latter variable remained an independent prognostic factor for NRM (P = 0.001). In the Cox regression analysis, patients older than 55 years have a significantly higher risk of NRM (hazard ratio, 12.8; 95% confidence interval, 1.5-111; P = 0.02).

In our series, 19 patients developed acute GVHD (12 of them, 40%, grades 2 to 4) at a median of 33 days (range, 17-150) after transplant. Seventeen of 26 evaluable patients developed chronic GVHD at a median of 185 days (range, 85-391), and eight of them developed extensive chronic GVHD for an incidence of 76%. Although GVH had no influence on outcome in the univariate and multivariate analysis, two of five patients who did not developed acute and/or chronic GVH died due to progressive disease, whereas no progressions were observed between those with GVH. Neither incidence of acute or chronic GVHD was significantly influenced by age, type of conditioning (melphalan versus other), number of lines of chemotherapy, or disease status at transplant.

Patients who received more than two lines had an EFS significantly worse than those who received two or less (53% versus 92%; P = 0.02). This variable also had a significant influence on the multivariate analysis in overall survival (54% versus 90% at 6 years; hazard ratio, 8.7; 95% confidence interval, 1.05-71; P = 0.01). Neither type of conditioning nor *in vivo* T-cell depletion with Campath, antithymocyte globulin, or GVH prophylaxis influenced EFS or overall survival in the univariate and multivariate analysis.

Minimal residual disease follow-up. In 21 of the 25 patients transplanted with active disease, kinetic of response was analyzed by clearance of CD79/$CD5^+$/$CD19^+$/CD23 cells from bone marrow by multiparametric flow cytometry. Sixty-five percent of the patients were in immunophenotypical remission at day 100; this percentage increases to 94% at day 360 (four patients reach CR on days 180, one patient on day 240, and one on day 360). In 90% of the patients, response was time related to the appearance of acute and or chronic GVHD. Regarding kinetic of response in the present study, although 35% of the patients still had CD79/CD5/CD19/CD23 leukemic cells in the bone marrow at day 100, none of them have relapsed. Interestingly, all of them developed chronic GVHD

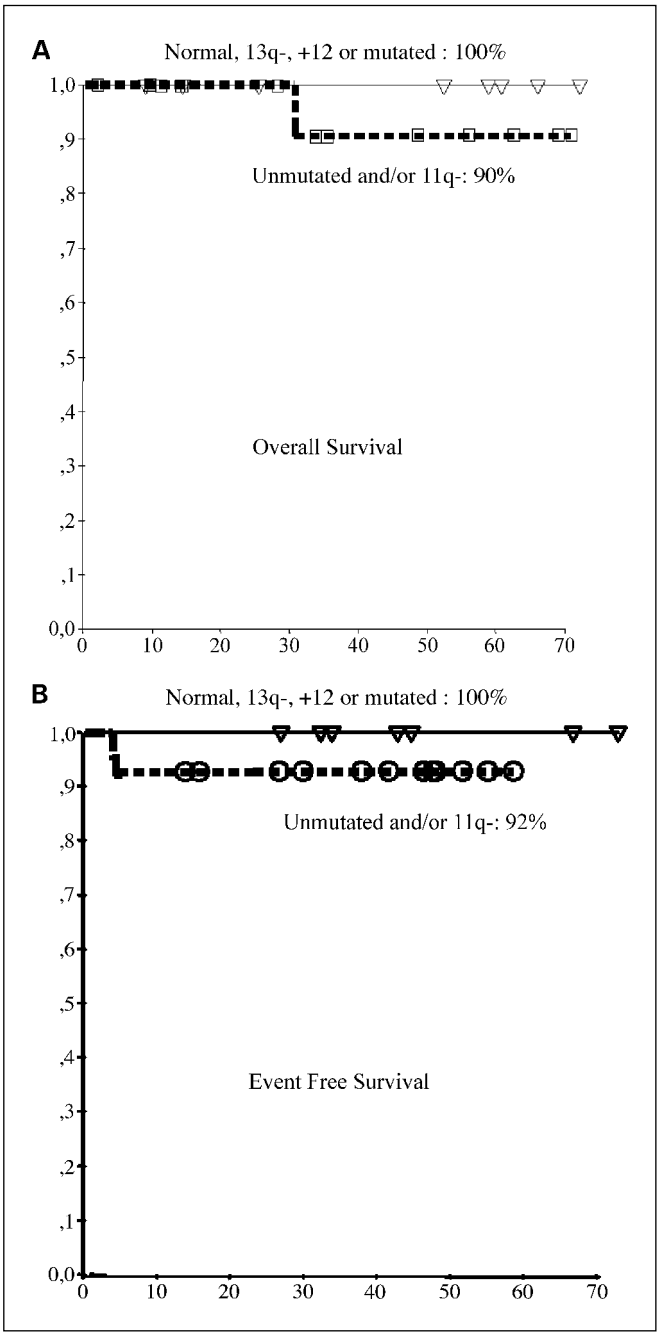

Fig. 2. Effect of mutational status and chromosomal abnormalities in overall survival (*A*) and EFS (*B*).

later on, and leukemic cells clearance occurred in a close time frame. The evolution of a 45-year-old male (patient 8, Table 2) with stage C unmutated and 11q− CLL refractory to fludarabine and transplanted with progressive disease (60×10^9 lymphocytes and huge hepatosplenomegaly), who received melphalan and fludarabine as conditioning, underlines the efficacy of this strategy and the graft-versus-tumor effect on eradication of MRD. At discharge at day 21, CD79/CD19/CD5/CD23 cells have decreased from 79% to 3%, but hepatosplenomegaly were almost similar. At day 42, he developed biopsy-proven skin grade 2 acute GVH, which was controlled with cyclosporine and topical steroids. At that moment, visceromegaly started to decrease, and at day 150, they had disappeared, as well as bone marrow infiltration (Fig. 3). Patient has not developed chronic GVH and he remained in CR with MRD negative from 20 months onwards.

Discussion

In this study, we report on the efficacy of RIC-related allogeneic transplant in patients with high-risk B-CLL and molecular poor-prognosis characteristics as unmutated CLL, 11q− and 17p− aberrations.

These results are at least similar to those recently reported (31) in a series of 30 patients with similar clinical characteristics but a shorter follow-up (24 months); in this series, at last follow-up 52% of the 23 patients still alive were in CR, whereas in our series, all 22 patients still alive were event free at the last follow-up, with a median follow-up of 47.3 (range, 12-74.6 months). Overall, the results from these two studies are superior to those reported for ASCT, thereby suggesting that, in the allogeneic transplantation setting, graft-versus-tumor effect plays a key role for disease control (11–13). Moreover, the lower NRM of RIC, compared with conventional allogeneic treatment, indicates that the former could be the treatment of choice for high-risk CLL patients (11, 14–18). Furthermore, in a recent Spanish comparative study (30 RIC versus 30 conventional allogeneic treatment), no differences were observed in terms of NRM, relapse rate, EFS, or overall survival between either group, although age was significantly higher in the RIC group (53 versus 45 years, respectively; ref. 32). In another retrospective comparative study, Dreger et al. (33) have recently reported a similar EFS and overall survival but with a higher relapse rate in the RIC group (28% versus 11%); in our series, with a longer follow-up (47 months), the relapse rate is inferior (7%), suggesting that myeloablative conditioning is not necessary in CLL.

Although unmutated CLL remains as a poor prognostic factor after high-dose therapy and ASCT (12, 13), recently, two articles have reported that allogeneic transplant may overcome this dismal prognosis (23, 34). The article from Ritgen et al. (23) also suggests that myeloablative conditioning is not necessary for unmutated CLL. Our results in a larger series of patients and with a longer follow-up confirm this hypothesis.. However, up to now, efficacy of RIC allogeneic transplant in patients with 11q− or with the poorest group with 17p− aberrations has not been tested. In our series, all six 17p− patients were transplanted with active disease. Apart from one patient, all achieved CR indicating the efficacy of this strategy. In the six patients, type of conditioning regimen seems to influence outcome. Thus, the five patients who reached CR after transplant had received melphalan plus fludarabine, one of them with Campath-1H, and this was the patient who developed a post-transplant lymphoproliferative disorder. The only patient who progressed had received the less intensive regimen (fludarabine plus low-dose total body irradiation), suggesting that in this high-risk group, "intermediate" chemotherapy could initially help to control disease while the immune system induces an adequate response. At present, two patients are alive and disease free (37 and 55 months after transplant), and three died in CR between 3.8 and 8 months after transplant. It is important to point out that the median age for 17p− patients

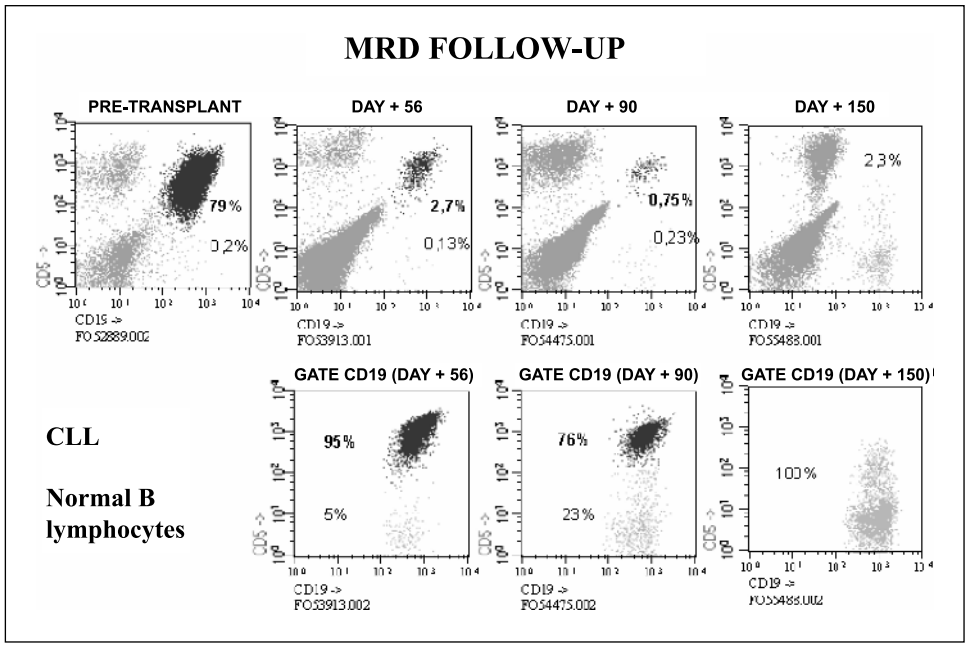

Fig. 3. Clearance of CD5/CD19 coexpression cells from peripheral blood in one patient with a well-defined cell population before transplant. Time intervals were measured from the day of transplant until the first negative result.

was 58 years and the number of previous lines of chemotherapy was 4, both characteristics associated with a significantly higher risk of NRM in our series, as shown below. Although numbers are very small, our data would suggest that 17p− patients could reach long-term disease-free survival after RIC allogeneic transplant. The recommendation in this particular poor-risk subgroup would be to do the transplant in an early phase of the disease, avoiding patient exposure to excessive lines of chemotherapy.

The mortality rate observed in this study is similar to the NRM reported by Dreger et al. in a retrospective European Bone Marrow Transplantation study (33). Efforts should be made to decrease the NRM while maintaining the efficacy. Two recent studies have reported lower NRM rates with RIC, including fludarabine, melphalan plus CAMPATH 1H (35), or cyclophosphamide plus fludarabine and rituximab (36).

In contrast with what we have observed in previous studies in patients with multiple myeloma and myeloid disorders (37–39), in the present study, we did not find a significant influence of chronic GVHD on outcome probably due to the small number of events. However, it is clear that the acquisition of CR was time related to the appearance of acute and or chronic GVH in most of the patients.

Regarding kinetics of response in the present study, although 35% of the patients still had CD79/CD5/CD19/CD23 leukemic cells in the bone marrow at day 100, none of them have relapsed. Interestingly, all of them developed chronic GVHD later on, and leukemic cell clearance occurred in a close time frame. This pattern is different from that observed after ASCT, where persistence of MRD determined by molecular biology or by cytometric assays are synonymous with relapse (24, 40). Previous data from Rawstron et al. have already suggested that eradication of B-CLL cells after autologous transplantation or Campath-1H treatment could have an effect on EFS and overall survival in CLL (41, 42). Regarding other MRD techniques, a recent comparative study among consensus IgH-PCR, quantitative PCR, and flow cytometry assay after autologous and allogeneic transplant in CLL shows that whereas the three techniques are equally suitable in allogeneic transplant, quantitative allele-specific oligonucleotide-PCR detects relapses after autologous transplant earlier (43).

In summary, our study, with a longer follow-up than previously reported, confirms the efficacy of RIC allogeneic transplant in CLL with adverse biological prognostic factors, such as unmutated status, and, for the first time, shows additional efficacy in patients with 11q− and 17p− aberrations.

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