Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study – a prospective clinical trial by the *Grupo Español de Linfomas/ Trasplante de Médula Osea* (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation

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ABSTRACT

Background
Although Hodgkin's lymphoma is a highly curable disease with modern chemotherapy protocols, some patients are primary refractory or relapse after first-line chemotherapy or even after high-dose therapy and autologous stem cell transplantation. We investigated the potential role of allogeneic stem cell transplantation in this setting.

Design and Methods
In this phase II study 92 patients with relapsed Hodgkin's lymphoma and an HLA-identical sibling, a matched unrelated donor or a one antigen mismatched, unrelated donor were treated with salvage chemotherapy followed by reduced intensity allogeneic transplantation. Fourteen patients showed refractory disease and died from progressive lymphoma with a median overall survival after trial entry of 10 months (range, 6-17). Seventy-eight patients proceeded to allograft (unrelated donors, n=23). Fifty were allografted in complete or partial remission and 28 in stable disease. Fludarabine (150 mg/m^2 iv) and melphalan (140 mg/m^2 iv) were used as the conditioning regimen. Anti-thymocyte globulin was additionally used as graft-*versus*-host-disease prophylaxis for recipients of grafts from unrelated donors.

Results
The non-relapse mortality rate was 8% at 100 days and 15% at 1 year. Relapse was the major cause of failure. The progression-free survival rate was 47% at 1 year and 18% at 4 years from trial entry. For the allografted population, the progression-free survival rate was 48% at 1 year and 24% at 4 years. Chronic graft-*versus*-host disease was associated with a lower incidence of relapse. Patients allografted in complete remission had a significantly better outcome. The overall survival rate was 71% at 1 year and 43% at 4 years.

Conclusions
Allogeneic stem cell transplantation can result in long-term progression-free survival in heavily pre-treated patients with Hodgkin's lymphoma. The reduced intensity conditioning approach significantly reduced non-relapse mortality; the high relapse rate represents the major remaining challenge in this setting. The HDR-Allo trial was registered in the European Clinical Trials Database (EUDRACT, *https://eudract.ema.europa.eu/*) with number 02-0036

Key words: allogeneic stem cell transplantation, reduced intensity conditioning, Hodgkin's lymphoma relapsed, refractory.

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Introduction

Hodgkin's lymphoma (HL) is highly responsive to conventional chemotherapy.[1,2] Autologous stem cell transplantation (ASCT) is the standard of care for patients with relapsed HL.[3,4] The results of ASCT vary significantly depending on a number of prognostic factors.[5-7] Only 20–35% of patients with HL refractory to first-line therapy currently go on to achieve long-term survival after ASCT.[8-10] For patients relapsing after ASCT the outcome is generally dismal.

Registry data[11,12] showed that allogeneic stem cell transplantation (SCT) after myeloablative conditioning resulted in lower relapse rates but significantly higher toxicity than ASCT.[13-14] Although the poor results after myeloablative conditioning could be explained by the very poor-risk features of many individuals included in these early trials, the high non-relapse mortality (NRM) prevented the widespread use of allogeneic SCT.

Reduced-intensity conditioning (RIC) regimens would appear particularly attractive for patients in need of allogeneic SCT. The literature contains several reports detailing the outcomes of RIC transplants for patients with relapsed HL.[15-20] Compared to myeloablative conditioning regimens, RIC has reduced NRM and improved overall survival.[21]

In spite of the increasing evidence of a clinical benefit of RIC-allogeneic SCT in patients with relapsed HL, many questions remain. The Lymphoma Working Party (LWP) of the European Group for Blood and Marrow Transplantation (EBMT) together with the *Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea* (GEL/TAMO) undertook the largest multicenter phase 2 prospective clinical trial presented so far with the objective to analyze NRM and other major outcome parameters after allogeneic SCT in relapsed HL.

Design and Methods

The HDR-Allo study protocol was approved by the LWP of the EBMT, the GEL/TAMO steering group, by the ethics committees of participating centers and registered in the European Clinical Trials Database (EUDRACT, *https://eudract.ema.europa.eu/*) with the number 02-0036. This was a prospective, multicenter phase 2 study in which ten European centers participated (Appendix 1). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Eligibility and exclusion criteria

Eligibility criteria included patients with biopsy proven classical HL with primary refractory disease after two lines of chemotherapy, relapses after first-line therapy with a short complete remission (<12 months), multiply relapsed patients and patients who relapsed after an ASCT, aged between 18 and 65 years, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 unless impaired performance status was progressive disease-related at the time of entry into the trial, adequate renal function (serum creatinine <2 x upper limit of normal), hepatic function (serum bilirubin <2 x upper limit of normal or alanine aminotransaminase, aspartate aminotransaminase, alkaline phosphatase <2 x upper limit of normal), cardiac function (left ventricle ejection fraction >40%), and pulmonary function (DL_{CO} >40%) and an HLA identical sibling or a fully matched or one antigen mismatched (9 out of 10 antigens), unrelated donor. All patients were required to provide written informed consent.

Exclusion criteria included known positivity for human immunodeficiency virus, other serious, uncontrolled medical conditions, concurrent or previous malignancy, or pregnancy.

Registration and end-points

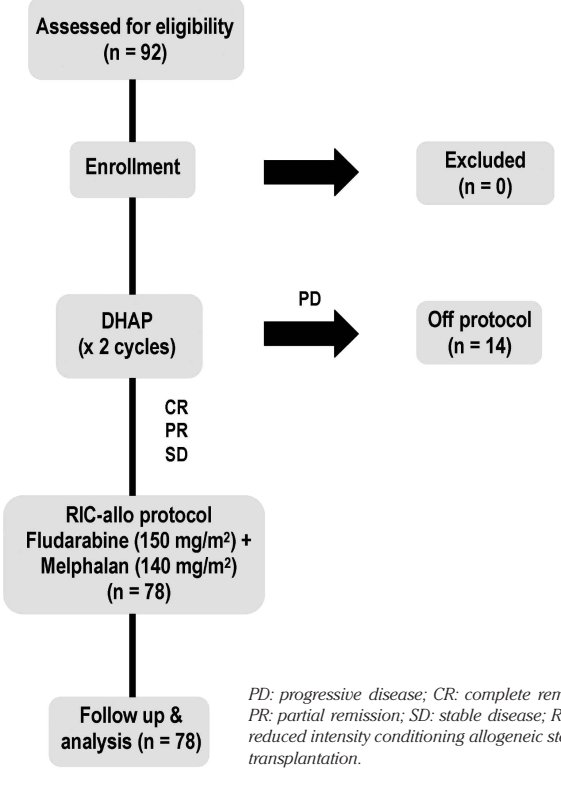
Patients were centrally registered (Figure 1). Although patients were registered before receiving salvage chemotherapy, the study focused on patients able to proceed to allogeneic transplantation. The primary end-point was NRM at 1 year post-transplant. Secondary end-points were: NRM at day +100 post-transplantation, relapse rate, progression-free survival, overall survival, hematologic and extra-hematologic toxicities, incidences of acute and chronic graft-*versus*-host disease (GVHD), and evaluation of chimerism after fludarabine-melphalan conditioning. On an intention-to-treat basis, progression-free and overall survival were also calculated from trial entry in the whole population of patients.

Salvage therapy

After trial registration, patients were treated with two courses of salvage DHAP (dexamethasone 40 mg iv days 1-4; cytarabine 2 x 2000 mg/m^2 iv over 3 h, day 2, bid; cisplatinum 100 mg/m^2 iv over 24 h, day 1) although other salvage protocols were allowed by choice of the investigator depending on the salvage therapy that the patient had received before. Only patients in complete remission or with a partial response or stable disease after salvage chemotherapy were allowed to continue on trial.

Stem cell collection and conditioning regimen

Both bone marrow and peripheral blood were allowed as sources of stem cells. Conditioning consisted of fludarabine 150



PD: progressive disease; CR: complete remission; PR: partial remission; SD: stable disease; RIC-allo: reduced intensity conditioning allogeneic stem cell transplantation.

Figure 1. Study design.

mg/m^2 iv (from day -8 to day -4) and melphalan 140 mg/m^2 iv (from day -3 to day -2). Recipients of stem cells from matched unrelated donors also received anti-thymocyte globulin 45 mg/kg iv (from day -4 to day – 2).

Graft-versus-host disease prophylaxis

GVHD prophylaxis consisted of cyclosporine A at an initial dose of 1.5 mg/kg bid iv from day -2 and a short course of methotrexate at a dose of 10 mg/m^2 iv on days +1, +3, +6 and +11. In the absence of acute GVHD of grade 2 or more, cyclosporine A was tapered down by 10% weekly starting on day +90 after the RIC-allogeneic SCT and was discontinued by day +180 post-transplantation.

Assessment of graft-versus-host disease and donor chimerism

The diagnosis of acute GVHD was based on the classical clinical presentation with confirmatory pathological findings. Acute and chronic GVHD were assessed and graded according to published criteria.[22,23] Chimerism was evaluated at day 21-28 after transplantation and every 15 days thereafter until complete donor chimerism of T cells was achieved. Complete donor chimerism was defined as the presence of at least 95% donor DNA in the sample analyzed.

Donor lymphocyte infusions

Patients who relapsed or progressed after allogeneic SCT were eligible for donor lymphocyte infusions (DLI) in the absence of GVHD grade 2 or more. Escalating doses of CD3-positive donor lymphocytes (from 1×10^7 to 5×10^8 CD3$^+$/kg body weight) were given every 2 months if there was no evidence of GVHD and disease response. Patients with persistent mixed donor chimerism were also eligible for DLI.

Definitions and response criteria

Patients were staged according to the Ann Arbor system[24] and evaluated by means of computed tomographic scans and gallium[67] gammagraphy. Patients were clinically staged at protocol entry, after salvage chemotherapy, on day +90 after transplantation, every 6 months for the first 2 years, and then yearly or as clinically indicated. Patients who received DLI for disease relapse or progression were also evaluated 1 month after the infusions. Patients who survived more than 90 days after RIC-allogeneic SCT without evidence of tumor were classified as having a complete response. Relapse after RIC-allogeneic SCT was histologically confirmed when possible. Disease response was evaluated according to Cheson's criteria.[25] For the purposes of this study, those patients allografted in complete or partial remission were considered as chemosensitive patients while those allografted in stable disease were considered chemorefractory.

Sample size calculation and statistical analysis

To determine the main end-point, NRM at 1 year after transplantation, to a precision of ± 10% (95% confidence interval), 80 transplanted patients were necessary (expected NRM at 1 year of 40%). Taking into account the expected percentage of patients who would not be transplanted because of no response to salvage chemotherapy, 132 patients needed to be included. The first patient was included in April 2000 and 92 patients had been recruited by August 2007. At that time the trial was prematurely closed by the steering committee because of the low patient recruitment. The database was closed and the final statistical analysis performed as of August 2009.

Data were analyzed according to previously published guidelines.[26,27] Time-to-event outcomes with competing risks (NRM, relapse incidence and GVHD) were estimated as cumulative incidence curves. NRM was calculated from the date of transplantation until death from causes other than relapse whenever it occurred. Actuarial curves were estimated for progression-free and overall survival (measured from transplantation until progression or death from any cause) according to the Kaplan-Meier method. Overall and progression-free survival were also calculated from trial entry in the whole population of patients. The log-rank test was used to compare survival curves in univariate analyses. Any *P* values less than or equal to 0.05 were defined as statistically significant. Potential prognostic factors for overall survival, progression-free survival, relapse incidence and NRM were evaluated in multivariate analyses by using Cox proportional hazards regression. Cumulative incidences were calculated using NCSS97 software (NCSS, Kaysville, UT, USA). All other computations were

Table 1. Clinical characteristics of the patients at diagnosis and before entering the HDR-Allo protocol (n=92).

	Measurement
Sex	
Males	51 (55%)
Females	41 (45%)
Age [median (range)] in years at diagnosis	28 (13-54)
Histology subtype at diagnosis	
Nodular sclerosis	50 (54%)
Mixed cellularity	20 (22%)
Lymphocyte rich	17 (18%)
Lymphocyte depletion	5 (6%)
Clinical characteristics at diagnosis	
Ann Arbor stage III-IV	59 (64%)
B symptoms	39 (42%)
Bone marrow involvement	8 (9%)
Bulky disease	31 (34%)
Clinical characteristics at entry into the trial	
Ann Arbor stage III-IV	70 (79%)
B symptoms	47 (53%)
Bone marrow involvement	18 (20%)
Bulky disease	35 (40%)
Diagnosis – entry in the trial [median (range)], months	41 (6-295)
> 2 lines of therapy	83 (90%)
Prior radiotherapy	80 (87%)
Prior ASCT	79 (86%)
Time to progression from allogeneic SCT [median (range)] in months	8 (12-144)
< 12 months	55 (70%)
Salvage therapy before RIC-allogeneic SCT	
GEMOX	45 (58%)
ESHAP/DHAP	23 (30%)
ICE	6 (8%)
Others	4 (4%)
Reason for entering the HDR-Allo trial	
Primary refractory disease	2 (2%)
Relapse after a short 1st complete remission	3 (4%)
Multiple relapses	7 (8%)
Failure of a prior ASCT	76 (86%)

ASCT: autologous stem cell transplantation; RIC: reduced intensity conditioning; SCT: stem cell transplantation; DHAP: dexamethasone, cisplatin, cytarabine; ESHAP: etoposide, cisplatin, cytarabine, prednisone; GEMOX: gemcitabine, oxaliplatin; ICE: ifosfamide, carboplatin, etoposide.

performed using the SPSS 15.0 statistical package (SPSS, Chicago, IL, USA). All *P* values were two-sided.

Results

The patients' characteristics are presented in Table 1. Fifty-one males and 41 females with a median age at diagnosis of 28 (13 – 54) years were included. Most patients had received more than two lines of therapy (90%), prior radiotherapy (87%) and a previous ASCT had failed (86%). The median number of cycles of salvage chemotherapy before undergoing RIC-allogeneic SCT was two (range, 2 to 3). Fourteen patients (15%) progressed under salvage therapy and were excluded from further study treatment. None of these patients received an allograft and were only considered candidates for palliative treatment. The median overall survival of these patients was 10 (6–17) months; all of them died from disease progression.

Seventy-eight patients (85%) went on to RIC-allogeneic SCT (Table 2). Fifty patients (67%) were allografted with chemosensitive disease (i.e. they were in complete or partial remission) and 28 (33%) with chemoresistant disease (i.e. the patients had stable disease). Ten patients (13%) had an ECOG score of 2 or more. A matched sibling donor was used in 55 procedures (70%). The median follow up of the surviving patients was 48 months (range, 24–84).

Non-relapse morbidity and mortality and engraftment

Ten patients died before day +100 from transplant-related causes: two from interstitial pneumonitis, four from infectious episodes, three from multi-organ failure and one from a pulmonary hemorrhage. Eight additional patients died from transplant-related causes without evidence of disease: two from bacterial infections, two from invasive aspergillosis, three from chronic GVHD and one patient from an Epstein-Barr virus-positive post-transplant lymphoproliferative disorder. The cumulative incidence of NRM was 8% (95%CI, 6–11) at 100 days, 15% (95%CI, 13–17) at 1 year, and 17% (95%CI, 15–19) at 2 years (Figure 2A). Age over 45 years at the time of RIC-allogeneic SCT, poor performance status and refractory disease were significantly associated with a higher NRM (*P*=0.05, *P*=0.05 and *P*=0.01, respectively) (Table 3).

All patients experienced complete hematologic recovery after RIC-allogeneic SCT. The median time to achieve more than 0.5×10^9/L neutrophils in the peripheral blood was 13 days (range, 10–18) days after transplantation; a sustained platelet count greater than 20×10^9/L was achieved at 14 days (range, 10–35, 3 patients did not reach this count by the time of death) after transplantation. Of note and as opposed to what has been seen with Campath-containing strategies, all patients were full

Table 2. Characteristics of the patients at RIC-allogeneic SCT.

	Measurement
Dx – RIC-Allo [median (range)] in months	46 (9-300)
Disease status at RIC-allo	
Sensitive disease (CR, PR)	50 (67%)
CR	20 (40%)
PR	30 (60%)
Refractory disease (SD)	28 (33%)
ECOG ≥ 2 at RIC-allo (%)	10 (13%)
Donor age [median (range)] in years	36 (18-63)
Donor sex	
Male	37 (47%)
Female	41 (53%)
Donor-recipient sex matching	
Donor (M) – Receptor (F)	21 (27%)
Donor (M) – Receptor (M)	16 (20%)
Donor (F) – Receptor (F)	25 (32%)
Donor (F) – Receptor (M)	16 (21%)
CMV status (donor and receptor)	
Both negative	8 (10%)
Other combinations	70 (90%)
Type of donor	
Matched sibling donor	55 (70%)
Matched unrelated donor	23 (30%)
Stem cell source	
Bone marrow	3 (4%)
Peripheral blood	75 (96%)

Dx: diagnosis; RIC-allo. reduced intensity conditioning allogeneic stem cell transplantation; CR: complete remission; PR: partial remission; SD: stable disease; M: male; F: female; CMV: cytomegalovirus.

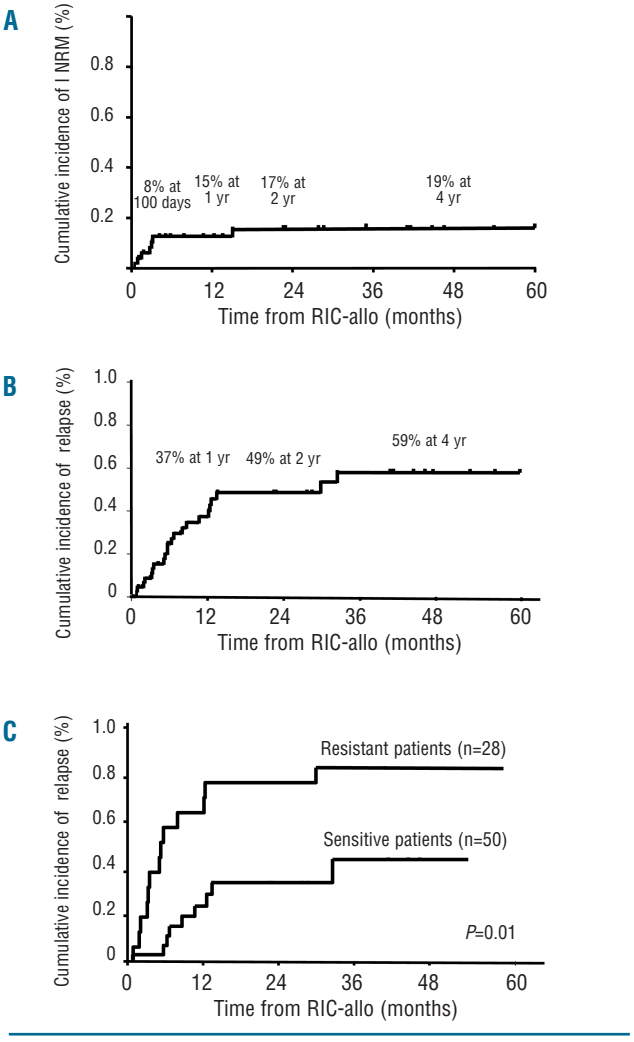


Figure 2. (A) Non-relapse mortality of the allografted patients. (B) Relapse incidence. (C) Impact of disease chemosensitivity on relapse incidence.

donor chimeras at day +28 after RIC-allogeneic SCT. The most important extra-hematologic toxicity seen in the early post-transplant period was oral mucositis, with 40% of our series having grade 3 or more oral mucositis.

Incidence of acute and chronic graft-versus-host disease

Among 73 patients at risk, 35 patients (48%) developed acute GVHD. It was grade 2 or more in 11 patients (15%). The median time to develop acute GVHD was 36 days (range, 21–63). The cumulative incidence of acute GVHD at day +100 was 32% (94%CI 28–36). The development of acute GVHD was not associated with a decreased relapse incidence after transplantation, but a non-significant increase in NRM was observed.

Among 68 patients at risk, 32 patients (47%) developed chronic GVHD, which was extensive in 15 patients (46%). The median time to develop chronic GVHD was 187 days (range, 100–424) after RIC-allogeneic SCT. Six-month, 1-year and 2-year cumulative incidences of chronic GVHD were 30% (95%CI, 24–34), 40% (95%CI 37–44) and 44% (95% 41–47), respectively. Chronic GVHD was analyzed as a time-dependent variable and was associated with a significantly lower relapse incidence after RIC-allogeneic transplantation (P=0.04) (Figure 3). A significant improvement in progression-free survival was also found in patients developing chronic GVHD (P=0.05).

Relapse incidence

Forty (51%) patients have relapsed at a median of 6 months after RIC-allogeneic SCT (range, 3-35 months). The cumulative incidence of relapse was 37% (95%CI, 34–40) at 1 year and 59% (95%CI, 55–63) at 4 years (Figure 2B). The strongest predictor of relapse was refractory disease [HR 2.0 (1.6–3.0), P=0.01] (Figure 2C, Table 3).

Donor lymphocyte infusions

Twenty patients (50% of the relapsed patients) received DLI for relapse or progressive disease after RIC-allogeneic SCT; nine patients had cytoreductive therapy before DLI. The median number of DLI received per patient was three (range, 2–4) and the median time from the allogeneic procedure to the first DLI was 6 months (range, 4–12). The median number of $CD3^+$ lymphocytes infused was 0.5×10^8 $CD3^+$ cells/kg (range, 1×10^7 – 1×10^8). The response rate (complete and partial responses) was 40% in those patients receiving DLI alone (3 complete responses and 3 partial responses in 11 patients) and 53% (3 complete responses and 2 partial responses) for those patients receiving additional chemotherapy. None of the five patients achieving a partial remission after DLI showed a continuous remission; the median time to progression was 7 months (range, 3–12). None of the complete remissions achieved after DLI with or without chemotherapy was long-lasting. All patients suffered from a disease relapse at a median time of 13 months (range, 12–15) after the last infusion.

Progression-free survival

The estimated progression-free survival rate from trial entry for the 92 patients was 48% (95%CI, 43–52) at 1 year and 18% (95%CI, 15–21) at 4 years (Figure 4A). For the allografted population, 22 patients remain alive and progression-free since RIC-allogeneic SCT after a median follow up of 32 months (range, 12–71). The estimated progression-free survival rate for the allografted population was 48% (95%CI, 44–52) at 1 year and 24% (95%CI, 22–27) at 4 years (Figure 4B). Chemosensitivity was the most important prognostic factor (HR = 2.3; 95%CI, 1.3–3.1; P=0.001) (Figure 4C) (Table 3). Patients allografted in complete remission had the best outcome, with progression-free survival rates at 1 and 4 years of 70% (95%CI 67–73) and 50% (95%CI 47–53), respectively (*data not shown*). The type of donor did not have any influence on progression-free survival after RIC-allogeneic SCT.

Overall survival

The estimated overall survival rate from trial entry was 64% (95%CI, 60–69) at 1 year and 41% (95%CI, 37–45) at 4 years (Figure 4D). In the allografted population and after a median follow-up for the surviving patients of 48 months (range, 24–82), 33 patients were alive (43%) and 45 had died (57%). The estimated overall survival rate was 71% (95%CI, 67–76) and 43% (95%CI, 39–46) at 1 and 4 years, respectively (Figure 4E). Refractory disease (Figure 4F) and a poor performance status were associated with a significantly worse overall survival (HR 1.9, 95%CI 1.0–2.7, P=0.001 and HR 2.5, 95%CI 1.3–4.2, P=0.01, respectively) (Table 3). The fact of having a matched unrelated donor rather than a related donor did not have a significant impact on overall survival either.

Table 3. Multivariate analysis of the four major outcomes.

	HR	95%CI	*P* value
Non-relapse mortality			
Age > 45 years	2.1	1.0-4.5	0.05
ECOG score ≥ 2	3.4	1.6-7.6	0.05
Refractory disease	2.8	1.8-4.6	0.01
Relapse incidence			
Refractory disease	2.0	1.6-3.0	0.01
Progression-free survival			
ECOG score ≥ 2	1.8	1.5-3.2	0.01
Refractory disease	2.3	1.3-3.1	0.001
Overall survival			
ECOG score ≥ 2	2.5	1.3-4.2	0.01
Refractory disease	1.9	1.0-2.7	0.001

HR: hazard ratio; CI. confidence interval.

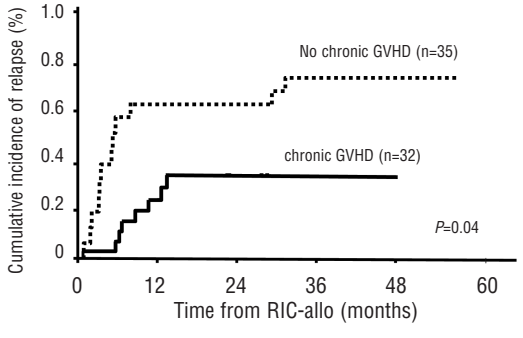


Figure 3. Impact of the development of chronic GVHD on relapse incidence after transplantation.

Discussion

In spite of early data showing promisingly low relapse rates after allogeneic transplantation, the transplantation community was not very enthusiastic about considering allogeneic SCT for HL patients because of the exceedingly high NRM.[11,12] The advent of RIC regimens was most welcome to overcome the problem by reducing NRM while, it was hoped, preserving the beneficial effect of the donor's alloreactive T cells infused with the graft. In addition, it has been demonstrated that better supportive care has significantly improved the results of allogeneic SCT over time.[28]

Retrospective analyses of the EBMT LWP demonstrated that a reduction in NRM had been achieved.[21] Nevertheless and in spite of the increasing number of HL patients allografted over the last 15 years, published studies do have important limitations, such as the small numbers of patients included, the use of different conditioning regimens and GVHD prophylaxis, and the relatively short follow up. In addition, all studies were retrospective in nature with selection biases and other confounding factors.

Of note, this is the largest prospective clinical trial looking at the outcome of patients with relapsed HL treated with a RIC allograft both in terms of numbers of patient included and follow up. Unfortunately, despite the fact that the trial was actively recruiting for several years, it finally had to be closed because of poor accrual of patients. This fact as well as the year when the trial was opened justifies some of its potential pitfalls: Positron emission tomography scanning was not included as a method to assess disease response to therapy and potential co-morbidities of the patients were more strictly considered. Although this prospective trial was to have included four different subgroups of patients, the vast majority (86%) were enrolled because a prior autograft had failed. Keeping this in mind, a NRM of 15% at 1 year looks very promising. NRM was adversely influenced by older age, poor performance score and, most importantly,

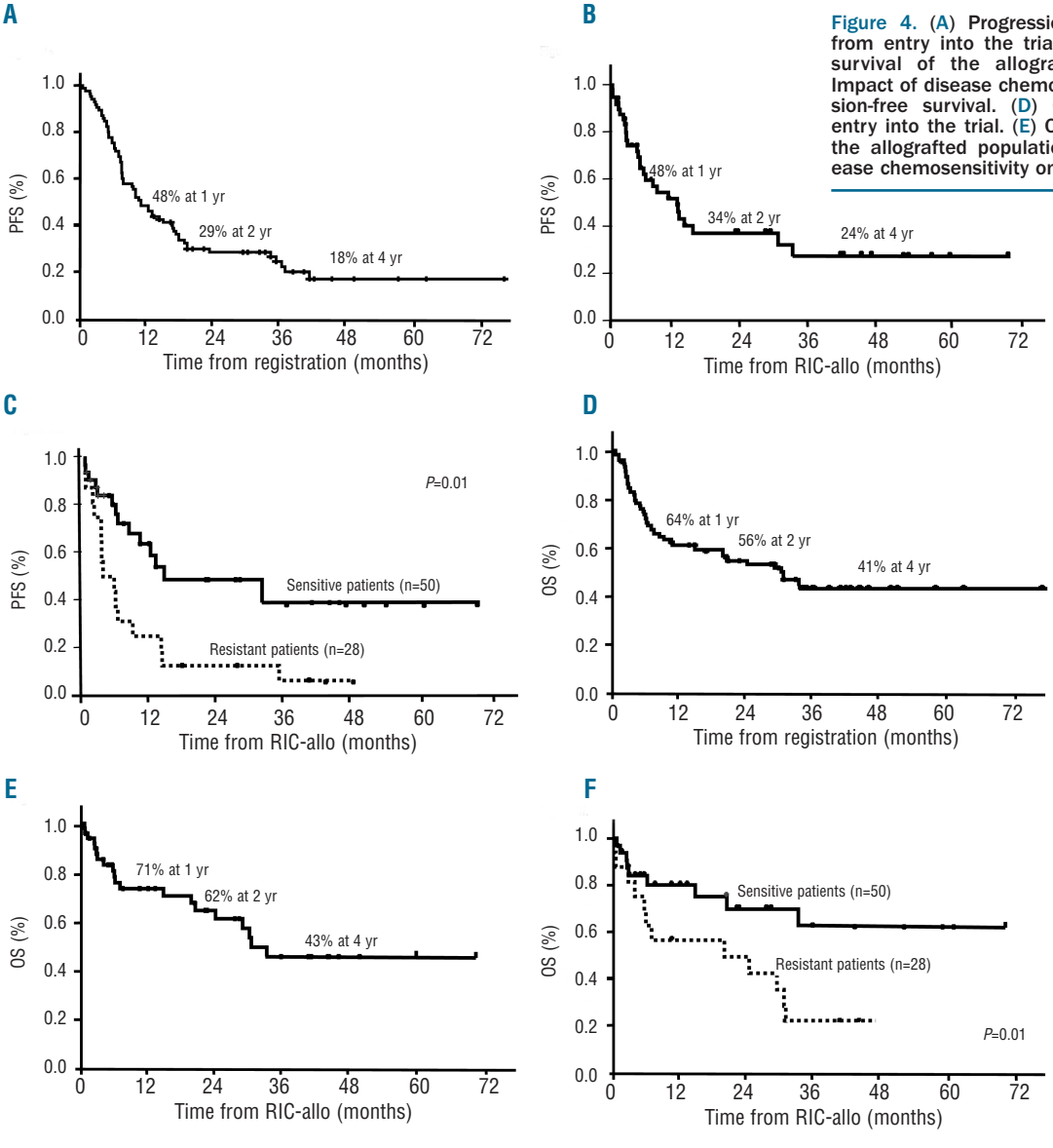


Figure 4. (A) Progression-free survival (PFS) from entry into the trial. (B) Progression-free survival of the allografted population. (C) Impact of disease chemosensitivity on progression-free survival. (D) Overall survival from entry into the trial. (E) Overall survival (OS) of the allografted population. (F) Impact of disease chemosensitivity on overall survival.

by the presence of refractory disease, an observation in line with registry data published by the EBMT.[19]

Disease relapse or progression represents the major cause of failure. The cumulative incidence of relapse was 59% at 3 years; it was significantly higher in patients with resistant disease. These figures are in agreement with those published by other groups.[15,17,18,20] Chemoresistant patients with HL should not offered allogeneic SCT – at least with the protocol we used. These patients might benefit from more aggressive conditioning and/or changing the GVHD prophylaxis.[29]

The progression-free survival rate was 48% (95%CI, 44–52) at 1 year and 24% (95%CI, 22–27) at 4 years for the allografted population. The figures are significantly better for patients allografted with chemosensitive disease and particularly for patients allografted in complete remission. Accordingly, more emphasis should be laid on achievement of complete remission prior to transplantation.

There is no evidence that the use of a matched unrelated donor impaired the outcome of the procedure as has been extensively indicated by others.[30] If a patient is considered a candidate for an allogeneic procedure and does not have a matched sibling donor, a search for a matched unrelated donor should be started immediately.

The lower NRM associated with the use of RIC protocols allows the detection of a clinically meaningful graft-*versus*-HL effect. Chronic GVHD was associated with a significantly lower relapse incidence after transplantation. This has also been shown by the two registry analyses of the LWP of the EBMT[19,21] and also by the Spanish series.[18] The low incidence of relapse translated into a significant improvement of progression-free survival after the procedure. Indirect evidence of a graft-*versus*-HL effect may be the plateau seen in both the progression-free and overall survival curves after 3 years. Finally, we and others observed significant responses to DLI although we, in contrast to the UK Cooperative Group,[17] were unable to find durable remissions after DLI.

In spite of the increasing number of HL patients being allografted there is no agreement among investigators about who should be offered an allogeneic SCT. Two retrospective analyses including HL patients who relapsed after an ASCT[31,32] seem to indicate that for those patients with a HLA compatible donor and who are able to reach the transplant procedure, consolidation with a RIC-allogeneic SCT offers a better long-term outcome than the use of conventional strategies. In our trial, none of the 14 patients not transplanted because of insufficient response to salvage chemotherapy was alive at the time of this analysis. Taking into account the results of this study, one might think that better salvage strategies should be investigated in order to try increase the percentage of patients demonstrating chemosensitivity. The introduction of so-called 'new drugs' (e.g. brentuximab vedotin) in the relapse setting could eventually help to improve this percentage.

Even with the results of this prospective study many questions remain to be answered. The best conditioning protocol is unknown, although information from registry analyses indicates that the intensity of the conditioning regimen matters. In children and adolescents, the use of myeloablative protocols was not associated with higher NRM but significantly reduced the relapse incidence as compared to RIC protocols[29] The use of low dose total body irradiation (2 Gy) seems to be associated with a higher incidence of relapse and a lower progression-free survival.[16,19] Accordingly, enforcing the debulking of the tumor by adding further drugs or otherwise strengthening the anti-tumor effect may help to reduce the relapse rates after allogeneic SCT. In this sense, a tandem ASCT – RIC-allogeneic SCT approach has been tested by several authors[31] in those patients with highly refractory HL. ASCT would be used as "debulking therapy" in order to render to the patient chemosensitive to the last line of treatment and take advantage of the allogeneic effect in a second step. A better selection of patients may be another aspect. Positron emission tomography may help to determine the most suitable group.[32] The emerging concept of maintenance with new drugs after ASCT could eventually be transported to the allogeneic field and, finally, the allogeneic procedure might be moved forwards in the therapeutic strategy of HL and tested in those relapsed patients in whom a poor outcome after ASCT is anticipated.

In summary, the results of this prospective clinical trial emphasize the role of RIC-allogeneic SCT in patients with relapsed HL after ASCT. The plateau phase in the survival curve of those patients allografted in complete remission supports the existence of a clinically beneficial graft-*versus*-HL effect. Major efforts should be made to bring patients to an allogeneic procedure, as the results of other therapies seem to be significantly worse, and to reduce the still too high relapse incidence after it.

Appendix 1

SPAIN: A. Sureda, Hospital de la Santa Creu I Sant Pau, Barcelona; Reyes Arranz, Hospital de la Princesa, Madrid; Dolores Caballero, Hospital Clínico Universitario, Salamanca; Josep Maria Ribera, Hospital Germans Trias I Pujol, Badalona; Joan Besalduch, Hospital Son Dureta, Palma de Malorca; Rafael Duarte, Institut Català d'Oncologia, L'Hospitalet de Llobregat; Angel León, Hospital de Jerez de la Frontera, Cádiz; Maria Jesús Pascual, Hospital Universitario Carlos Haya, Málaga; SWITZERLAND: Jacob Passweg; SWEDEN: Mats Brune, Sahlgrenska University Hospital, Göteborg.

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