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Lenalidomide in combination with R-ESHAP in patients with relapsed or refractory diffuse large B-cell lymphoma: a phase 1b study from GELTAMO group

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Summary

Diffuse large B-cell lymphoma (DLBCL) patients failing rituximab-containing therapy have a poor outcome with the current salvage regimens. We conducted a phase 1b trial to determine the maximum tolerated dose (MTD) of lenalidomide in combination with R-ESHAP (rituximab, etoposide, cisplatin, cytarabine, methylprednisolone) (LR-ESHAP) in patients with relapsed or refractory DLBCL. Efficacy data were collected as a secondary objective. Subjects received 3 cycles of lenalidomide at escalating doses (5, 10 or 15 mg) given on days 1–14 of every 21-day cycle, in combination with R-ESHAP. Responding patients received BEAM (carmustine, etoposide, cytarabine, melphalan) followed by autologous stem-cell transplantation. Lenalidomide 10 mg/d was identified as the MTD because, in the 15 mg cohort, one patient experienced dose-limiting toxicity (grade 3 angioedema) and two patients had mobilization failure. A total of 19 patients (3, 12 and 4 in the 5, 10 and 15 mg cohorts, respectively) were evaluable. All toxicities occurring during LR-ESHAP cycles resolved appropriately and no grade 4–5 non-haematological toxicities were observed. The complete remission and overall response rates were 47·4% and 78·9%, respectively. With a median follow-up of 24·6 (17·4–38·2) months, the 2-year progression-free survival and overall survival were 44% and 63%, respectively. In conclusion, the LR-ESHAP regimen is feasible and yields encouraging outcomes.

Keywords: diffuse large B-cell lymphoma, lenalidomide, salvage, R-ESHAP, rituximab.

Diffuse large B-cell lymphoma (DLBCL) treatment results have significantly improved since the introduction of rituximab into CHOP (cyclophosphamide, daunorubicin, vincristine, prednisone)-like schedules (Coiffier *et al*, 2002; Pfreundschuh *et al*, 2011), and it is now the standard of care. Nevertheless, even with R-CHOP-like treatments, up to 40% of patients will ultimately relapse or progress (Sehn *et al*, 2007). To date, high-dose therapy followed by autologous stem-cell transplantation (ASCT) is the reference treatment for patients with relapsed or refractory DLBCL, provided the disease is sensitive to salvage therapy (Philip *et al*, 1995; Oliansky *et al*, 2011).

Several studies indicate that the use of highly effective rituximab-containing primary therapy makes it more difficult to salvage patients who are refractory or who relapse**.** A retrospective study performed by our group analysed 163 patients with relapsed or refractory DLBCL treated with R-ESHAP (rituximab, etoposide, cisplatin, cytarabine, methylprednisolone). Patients without prior exposure to rituximab had significantly better overall response rates (81% vs. 67%,

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$P = 0{\cdot}045$) and 3-year progression-free survival (PFS) (57% vs. 17%) than patients previously exposed to rituximab (Martin *et al*, 2008). The results of the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study that compared R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatin) and R-ICE (ituximab, ifosfamide, etoposide, and carboplatin) in 396 patients with relapsed or refractory DLBCL confirmed these results (Gisselbrecht *et al*, 2010). This study showed that patients with primary refractory disease or early relapse after rituximab-containing first-line therapy had a very poor prognosis; thus, their 3-year PFS was only 23%, with no difference between R-ICE and R-DHAP (Gisselbrecht *et al*, 2010). Accordingly, prospective studies incorporating new agents are needed for these patients.

Lenalidomide, an analogue of thalidomide, showed significant activity in relapsed DLBCL as both a single agent (Wiernik *et al*, 2008; Witzig *et al*, 2011) and in combination with rituximab (Zinzani *et al*, 2011; Wang *et al*, 2013). The mechanism of action of lenalidomide is complex, including an immunomodulatory effect by inhibiting the interactions between tumour cells and stromal cells. Furthermore, lenalidomide can inhibit neoangiogenesis, induce apoptosis and activate T cells and natural killer cells (List, 2007). The novel and distinct mechanisms of action of lenalidomide, from both traditional chemotherapy and rituximab, combined with the *in vitro* synergy of lenalidomide with rituximab (Zhang *et al*, 2009), provide a rationale for introducing lenalidomide to salvage therapy in DLBCL, which could increase the response rate and quality of response, allowing more patients to proceed to ASCT.

With this background, the GELTAMO (Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea) group, after evaluating the preclinical evidence of synergy of the combination, designed the current phase 1–2 trial to evaluate the safety and efficacy of lenalidomide in combination with R-ESHAP (LR-ESHAP) in patients with relapsed or refractory DLBCL. Here we report the results from the phase 1 part of the study.

Methods

Patients

Eligible patients were aged 18–70 years, diagnosed with histologically confirmed DLBCL (Swerdlow *et al*, 2008) with refractory or relapsed disease following first-line treatment with rituximab in combination with an anthracycline-containing regimen, and measurable disease, with baseline positron emission tomography (PET) scans demonstrating positive lesions compatible with anatomical tumour sites identified by computerized tomography (CT). Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2, and be deemed eligible for ASCT. Exclusion criteria were: pregnant or nursing women; human immunodeficiency virus infection; active hepatitis B or C infection; presence of central nervous involvement; history of myocardial infarction within the past 6 months; any significant concurrent, uncontrolled medical condition; absolute neutrophil count $<1{\cdot}5 \times 10^9$/l; platelet count of $<50 \times 10^9$/l; total bilirubin $>2\times$ upper limit of normal (ULN), and/or alkaline phosphatase or aspartate aminotransferase $>2{\cdot}5\times$ ULN unless there was evidence of direct liver involvement by lymphoma, and creatinine $>1{\cdot}5\times$ ULN.

Study design and treatment

This open-label, multicentre phase I/II study was performed in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. It was approved by the national authorities and the institutional ethics committee of each participating centre. The trial was registered at ClinicalTrials.gov (identifier: NCT02340936). Informed consent was obtained from all subjects.

Phase 1 was designed as a dose-escalation study to determine the maximum tolerated dose (MTD) of lenalidomide given on days 1–14 of every 21-d cycle, in combination with R-ESHAP salvage chemotherapy at standard doses (rituximab 375 mg/m^2 day 1, etoposide 40 mg/m^2 days 1–4, cisplatine 25 mg/m^2 days 1–4; cytarabine 2000 mg/m^2 day 5, and methylprednisolone 500 mg days 1–5) (Martin *et al*, 2008). Lenalidomide dose-escalation levels were 5, 10, 15 and 20 mg/d. A 3×3 dose-escalation design was used to determine the MTD. Patients were assigned in consecutive order starting at the lowest dose (5 mg). For dose escalation, three patients had to have completed the first cycle without dose-limiting toxicities (DLT). Upon occurrence of a DLT during cycle 1 of a given patient, an additional three patients had to receive 1 cycle without a DLT being observed. Under such circumstances, further dose escalation was permitted. If two of the initial three patients or two of six patients experienced a DLT during the first cycle, then the MTD was established as the dose from the next lower dose. Once the MTD was determined, additional patients were enrolled at this dose to assess the toxicities more fully, for a total of 12 patients treated at the MTD.

All patients received pegfilgrastim (6 mg on day +6) or filgrastim ($\geq$5 μg/kg/d from day +6 until neutrophil recovery). Antithrombotic prophylaxis and supportive care were provided at the discretion of the treating physician. During the second cycle of salvage therapy, stem cells were mobilized with granulocyte colony-stimulating factor (G-CSF) and harvested. A second mobilization procedure was performed after the third cycle if necessary. Patients in complete remission (CR) or partial response (PR) after 3 cycles of LR-ESHAP received BEAM (carmustine, etoposide, cytarabine, and melphalan) followed by ASCT, while those subjects with stable or progressive disease were removed from the study. Involved-field radiation of residual masses was allowed after ASCT recovery.

Assessments, study endpoints and statistical considerations

DLT was defined as an adverse event during the first cycle at least possibly related to LR-ESHAP that fulfilled one of the following criteria: (i) any grade 3–4 non-haematological toxicity according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), with the exception of grade 3 nausea, vomiting, mucositis, or electrolyte abnormalities, which were only considered DLT if they lasted more than 7 d; (ii) febrile neutropenia lasting ≥7 d; (iii) delayed recovery (to NCI ≤grade 1 or baseline) from a toxicity that delayed the second cycle by >2 weeks. Additionally, any related adverse event that did not meet the above criteria for a DLT, could be considered DLT at the monitoring committee's discretion. The primary endpoint of phase 1 was to determine the MTD and DLTs of the study protocol.

Secondary endpoints included assessment of peripheral-blood stem-cell (PBSC) mobilization, and evaluation of antitumour activity measured by CR and overall response rates (ORR), PFS and overall survival (OS). Response was assessed after 3 cycles of LR-ESHAP and 3 months after ASCT by PET, CT and bone marrow biopsy if previously involved, using the 2007 revised response criteria for malignant lymphoma (Cheson *et al*, 2007). PFS was calculated from the date of first LR-ESHAP cycle until the date of relapse, progression, or death from any cause. OS was calculated from the date of the first cycle to the date of death or of last follow-up. Survival endpoints were assessed on the date of the last patient contact; the most recent follow-up was in October 2014. Survival analyses were performed according to the Kaplan–Meier method.

In vitro *studies*

The potential synergistic effect of lenalidomide with the drugs included in the ESHAP schema was also evaluated *in vitro*. The SUDHL6 cell line, obtained from a DLBCL patient carrying the t(14;18) was selected and kindly provided by Dr. Martínez Climent (Centro de Investigación de Medicina Aplicada, Universidad de Navarra, Spain). Etoposide, methylprednisolone, cytarabine, cisplatin and lenalidomide were obtained from Sigma-Aldrich Inc. (St. Louis, MO, USA). Cells were cultured in RPMI 1640 medium containing 10% fetal bovine serum, 2×10^{-3} mol/l glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin at 37°C in a humidified 5% CO_2/95% atmosphere. To evaluate the activity of the combination, cells were cultured for 48 h with increasing doses of lenalidomide, the separate agents included in the ESHAP regimen and the combination of the two treatments. Cell viability was analysed using the colorimetric MTT assay as previously described (Ocio *et al*, 2010). The results are expressed as the percentage of cells surviving compared with the untreated control. The potency of the combination was quantified with the Calcusyn software (Biosoft, Ferguson, MO, USA). This employs the Chou Talalay method, which calculates a combination index (CI) whose values signify the following effects: CI > 1, antagonistic effect; CI = 1, additive effect; and CI < 1, synergistic effect (Chou & Talalay, 1984).

Results

Patient characteristics

Between March 2011 and May 2013, 20 patients from five GELTAMO centres were enrolled into the phase 1 part of this study. One patient was excluded due to a screening failure (hepatic disease unrelated to lymphoma), so 19 patients were

Table I. Patient characteristics.

Characteristic	*N*	%
Total number of evaluable patients	19	
Male sex	12	63·2
Age, years: median (range)	58 (23–70)	
Older than 60 years (*n*)	8	42·1
Histological diagnosis		
DLBCL	17	89·5
Intermediate DLBCL/BL	1	5·3
Grade 3B follicular lymphoma	1	5·3
First-line treatment		
R-CHOP-like	17	89·5
BL protocols	2	10·5
IPI at study entry		
0–1	9	47·4
2	4	21·0
3	3	15·8
4–5	3	15·8
Bulky disease at study entry	7	36·8
Increased β_2-microglobulin at study entry	6	31·6
Disease status at study entry		
Early relapse (<1 year from diagnosis)	3	15·8
Late relapse (≥1 year from diagnosis)	3	15·8
PR after first-line treatment	7	36·8
Less than PR after first-line	6	31·6
Lenalidomide dose in LR-ESHAP		
5 mg	3	15·8
10 mg	12	63·2
15 mg	4	21·0
Antithrombotic prophylaxis during LR-ESHAP		
None	10	52·6
Acetyl salicylic acid	8	42·1
Low molecular-weight heparin	1	5·3

DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; IPI, International Prognostic Index; PR, partial response; LR-ESHAP, lenalidomide, rituximab, etoposide, cisplatin, cytarabine, methylprednisolone.

evaluable. Patient characteristics are summarized in Table I. The median age was 58 (range, 23–70) years. 17 patients had DLBCL, one had grade 3B follicular lymphoma and one had unclassifiable B-cell lymphoma with features intermediate between DLBCL and Burkitt lymphoma, confirmed by central pathology review. The majority of patients (84%) had primary refractory disease or early relapse.

Dose escalation and MTD determination

In the 5 and 10 mg cohorts, there were no events fulfilling DLT criteria during cycle 1. One patient had a DLT in the 15 mg cohort (grade 3 facial angioedema). In addition, 2 out of 4 patients treated in this cohort had a mobilization failure after the second LR-ESHAP cycle. The monitoring committee judged that 15 mg was too toxic and recruitment in this cohort was stopped after 4 patients included. Therefore, the MTD was established as being 10 mg of lenalidomide and this cohort was expanded to explore further the safety of LR-ESHAP. Overall, three, twelve and four patients received 5, 10 and 15 mg of lenalidomide, respectively.

Feasibility

Eighteen patients (95%) completed the planned three cycles of treatment and 1 patient received only two cycles due to persistent neutropenia and thrombocytopenia after the second cycle. Lenalidomide was permanently interrupted in four patients (21%): 1 patient at day +10 of the first cycle due to grade 3 angioedema, and 3 patients after completion of the second cycle due to grade 3 thrombosis ($n = 2$) and mobilization failure ($n = 1$). Lenalidomide was temporary interrupted in four cycles in 3 patients due to toxicity. The median interval between the LR-ESHAP courses was 23 (range, 19–39) days. 14 out of 19 patients were successfully mobilized with G-CSF after the first ($n = 1$) or second ($n = 13$) cycle. Five patients required a second mobilization with G-CSF ($n = 1$) or G-CSF + plerixafor ($n = 4$) after the second ($n = 1$) or third ($n = 4$) cycle. Finally, all patients were successfully mobilized (median of 4×10^6/kg $CD34^+$ cells harvested, range 2–17·04) and 14 patients (74% of the overall series) underwent ASCT according to protocol. Three patients received involved-field radiation of residual masses after the ASCT. Five patients were withdrawn from the trial due to stable disease ($n = 1$) or progressive disease ($n = 4$) after the third cycle.

Toxicity

Haematological and non-haematological toxicities are summarized in Tables II and III, respectively. The incidence of grade 3–4 haematological toxicity was very high, especially after the third cycle. The percentages of patients requiring red blood cell and platelet transfusions were, respectively: 16% and 16% during cycle 1; 47% and 5% during cycle 2; and 67% and 50% during cycle 3. Febrile neutropenia occurred in 12·5% of the 56 treatment cycles administered. No grade 4 non-haematological toxicities were observed. The most frequently occurring grade 3 non-haematological toxicity were infections (6 episodes) and metabolism disorders (3 episodes). Two patients had a jugular and/or subclavial thrombosis after the second cycle, possibly related to the regimen, but a central venous catheter was present in both cases. One of the patients was receiving antithrombotic prophylaxis with low molecular weight heparin and the other was not receiving antithrombotic prophylaxis. All toxicities resolved appropriately, and no patients died during treatment.

Concerning toxicity after ASCT, 14 out of 15 patients engrafted, after a median of 11 (range, 10–19) and 12 (range, 7–26) days to achieve more than $0{\cdot}5 \times 10^9$/l neutrophils and 20×10^9/l platelets, respectively. One patient had a graft failure and underwent allogeneic stem-cell transplantation 9 months after the ASCT, and finally died due to toxicity (hepatic veno-occlusive disease). This patient had received involved-field radiotherapy of a residual abdominal mass after the ASCT. The remaining adverse events reported after the ASCT were expected and reversible.

Antitumour activity

In an analysis of the 19 evaluable patients, the CR and ORR to LR-ESHAP were 47·4% (9 patients) and 78·9% (15 patients), respectively. At the time of this analysis, the disease had progressed in nine patients and seven of them had died from lymphoma. With a median follow-up of 24·6 (range 17·4–38·2) months, the estimated 2-year PFS and OS were 44% and 63%, respectively (Fig 1).

In vitro *studies*

The *in vitro* activity of the combination of lenalidomide and ESHAP is illustrated in Fig 2. Despite the low activity of lenalidomide as a single agent, the addition of this drug to the

Table II. Documented grade 3–4 haematological toxicity.

	Cycle 1 ($n = 19$)		Cycle 2 ($n = 19$)		Cycle 3 ($n = 18$)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Anaemia	15·8	0	47·4	0	66·7	0
Neutropenia	15·8	63·2	36·8	15·8	38·9	44·4
Thrombocytopenia	31·6	31·6	10·5	26·3	22·2	61·1

Results are expressed as percentages of patients.

Table III. Non-haematological toxicity during LR-ESHAP cycles.

Toxicity, *n* (% of cycles)	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac disorders	2 (4)			
Gastrointestinal disorders	13 (23)	12 (21)		
General disorders	7 (12·5)	4 (7)		
Immune system disorders				
Anaphylaxis (angioedema)			1 (2)	
Infections/febrile neutropenia				
Febrile neutropenia			7 (12·5)	
Lung infection		1 (2)	2 (4)	
Skin infection			1 (2)	
Catheter-related infection			3 (5)	
Upper respiratory infection	1 (2)	2 (4)		
Lip infection		1 (2)		
Metabolism disorders				
Hyperglycaemia	2 (4)		1 (2)	
Hypocalcaemia	1 (2)	1 (2)		
Hypokalaemia		2 (4)		
Mixed	1 (2)	1 (2)	2 (4)	
Nervous system disorders	2 (4)			
Renal disorders	1 (2)	1 (2)		
Vascular disorders				
Thrombosis			2 (4)	
Hypertension		1 (2)		

Values in parenthesis are expressed as percentage.

ESHAP combination was able to potentiate its activity by decreasing the viability of the cultured cells, with combination indexes up to the synergistic range (around 0·3) for the lower and intermediate doses.

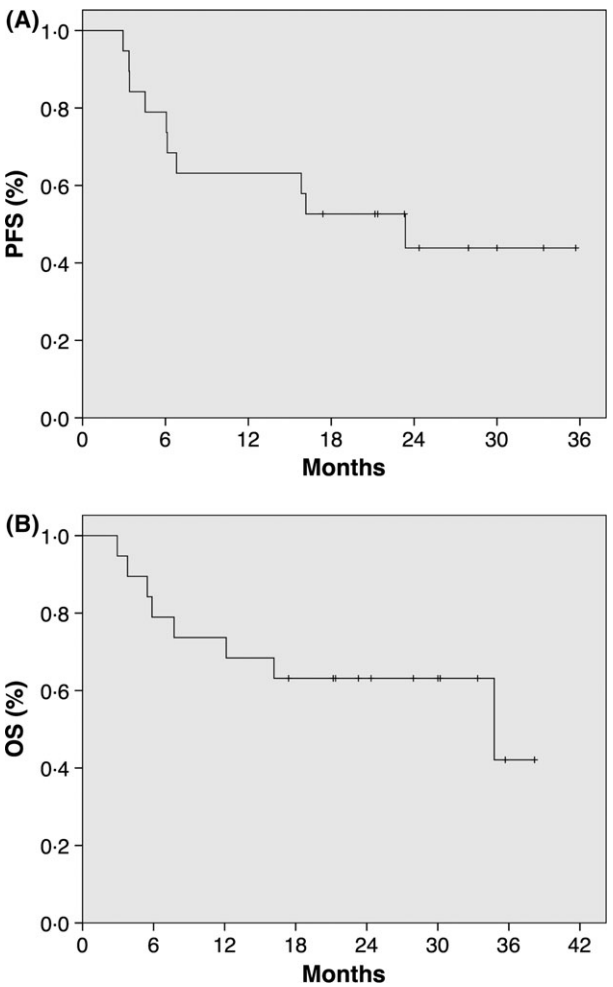

Fig 1. Kaplan–Meier estimation of (A) progression-free survival (PFS) and (B) overall survival (OS) of the 19 evaluable patients.

Discussion

For this phase 1–2 clinical trial, we hypothesized that lenalidomide could be safely combined with the salvage regimen R-ESHAP to increase its effectiveness. This study is the first, to our knowledge, to examine the combination of lenalidomide with R-ESHAP. Our preclinical experiments indicate that the addition of lenalidomide to the ESHAP regimen potentiates its activity with combination indexes up to the synergistic range. The results of our *in vitro* studies should be interpreted with caution, as they were only based on a single cell line. However, these studies provided a preclinical rationale for setting up the clinical trial. The results of phase 1b of the trial reported here indicate that the combination of lenalidomide with R-ESHAP is feasible, resulting in a high response rate in patients with relapsed or refractory DLBCL.

In our trial, lenalidomide 10 mg/d was identified as the MTD because, in the 15 mg cohort, one patient experienced DLT (grade 3 angioedema) and two out of four patients had a mobilization failure. In the 5 and 10 mg cohorts, there were no events that fulfilled the criteria listed in the DLT definition. In another phase 1 study, Feldman *et al* (2014) showed that the combination of R-ICE with lenalidomide (RICER) at doses of 25 mg on days 1–7 of each cycle is also safe and effective. In addition, two recent phase I-II trials have shown that lenalidomide can be safely combined with R-CHOP21 in patients with untreated aggressive B-cell NHL (Nowakowski *et al*, 2011; Chiappella *et al*, 2013). The results of these studies, like ours, demonstrate that the combination of lenalidomide with immunochemotherapy is feasible and safe.

The main toxicity of the LR-ESHAP regimen was haematological, as expected. Despite this, 18 patients (95%) completed the planned three cycles of treatment and, although lenalidomide was permanently interrupted in five patients, this was due to haematological toxicity in only one of them. The incidence of febrile neutropenia and grade 3 infections was 12·5% and 11% of cycles, respectively, similar to that reported with R-DHAP or R-ICE (16% and 17% of patients, respectively, had infections with neutropenia grade 3–4 in the CORAL study) (Gisselbrecht *et al*, 2010). The incidence

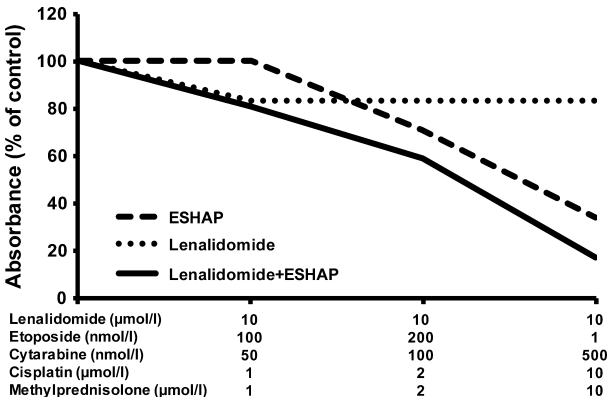

Fig 2. *In vitro* activity of the combination of lenalidomide and ESHAP in a B-cell line obtained from a diffuse large B cell lymphoma patient carrying the t(14;18) (SUDHL6). ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin.

of other grade 3 non-haematological toxicities was very low and no grade 4 non-haematological toxicities were observed. There were no cases of severe renal toxicity described with other cisplatin-containing regimens like R-DHAP (Gisselbrecht *et al*, 2010). It is important to note that all toxicities resolved appropriately, with no treatment-related deaths.

Several prospective studies have shown a significant increase in the incidence of deep vein thrombosis (DVT) in patients with multiple myeloma (MM) receiving lenalidomide in combination with chemotherapy and/or dexamethasone, especially in patients not receiving thromboprophylaxis (Weber *et al*, 2007; Dimopoulos *et al*, 2009). In our study, only half of the patients received thromboprophylaxis, and 2 patients (4%) had grade 3 jugular and/or subclavial thrombosis during the second cycle of LR-ESHAP that led to suspension of lenalidomide. However, it is notable that the two patients had a central venous catheter in the area of the thrombosis, which could have been its main cause. In other lymphoma trials, the incidence of DVT in patients treated with lenalidomide is very low (0–4%), when used alone (Wiernik *et al*, 2008; Witzig *et al*, 2011) or in combination with rituximab (Zinzani *et al*, 2011; Wang *et al*, 2013) and chemotherapy (Feldman *et al*, 2014; Vitolo *et al*, 2014; Nowakowski *et al*, 2015).

We also evaluated the ability to mobilize PBSC following LR-ESHAP. Unlike the reported ≥90% collection rate after R-DHAP (Gisselbrecht *et al*, 2010; Crump *et al*, 2014) or R-ICE (Gisselbrecht *et al*, 2010) schemes, 14 out of 19 patients (74%) successfully mobilized with G-CSF and collected PBSC during the first ($n = 1$) or second ($n = 13$) cycle of LR-ESHAP. This observation may suggest a negative effect of lenalidomide on mobilization. However, the five patients who failed the first mobilization collected PBSC successfully after a second attempt using plerixafor. In patients with MM, two large studies found that one of the most significant factors influencing the ability to collect adequate numbers of PBSC appeared to be initial therapy with lenalidomide, in addition to patient age and duration of lenalidomide therapy (Kumar *et al*, 2009). The exact mechanism by which lenalidomide inhibits stem cell mobilization is not clear. In accordance with our results, other studies have shown that plerixafor overcomes mobilization failures after lenalidomide treatment (Costa *et al*, 2012). The fact that plerixafor antagonizes the binding of the chemokine stromal-cell-derived factor-1α (SDF-1α, also termed CXCL12) to its receptor CXC chemokine receptor 4 (CXCR4) suggests a potential role of the CXCR4/SDF-1α axis in mediating mobilization failure after lenalidomide treatment. Following this hypothesis, a recent study found a lenalidomide-induced up-regulation of CXCR4 in $CD34^+$ haematopoietic cells (Li *et al*, 2013). In the phase 2 part of our study, the use of plerixafor is recommended if the PBSC count is not adequate after G-CSF treatment.

We also preliminarily analysed the effectiveness of the LR-ESHAP regimen. We observed 47% CR and 79% overall response, which allowed 74% of patients to undergo the ASCT, resulting in a 2-year PFS of 44%. Although the number of patients is small, these results are promising, considering the poor prognosis of the study population,

Table IV. Prospective studies of salvage regimens in DLBCL patients pre-treated with rituximab.

Regimen	Reference	Design	*n*	CR (%)	ORR (%)	ASCT (%)	PFS/EFS
R-DHAP/R-ICE	Gisselbrecht *et al* (2010)	Phase 3	244	NA	51	52*	21% at 3 years
R-DHAP/R-GDP	Baetz *et al* (2014)	Phase 3	318	15·7	45·6	51·9	22% at 4 years
R-DHAP	van Imhoff *et al* (2014)	Phase 3	223	22	42	33	26% at 2 years
O-DHAP	van Imhoff *et al* (2014)	Phase 3	222	15	38	36	21% at 2 years
O-DHAP/O-ICE	Matasar *et al* (2013)	Phase 2	61	37	61	55	31% at 1 year
RICER	Feldman *et al* (2014)	Phase 1	15	60	73	67	NA
LR-ESHAP	Present study	Phase 1	19	47	79	74	44% at 2 years

CR, complete remission; ORR, overall response rate; ASCT (%), percentage of patients proceeding to autologous stem-cell transplantation; PFS, progression-free survival; EFS, event-free survival; R, rituximab; DHAP, dexamethasone, cytarabine, cisplatin; ICE, ifosfamide, carboplatin, etoposide; GDP, gemcitabine, dexamethasone, cisplatin; O, ofatumumab; RICER, R-ICE plus lenalidomide; LR-ESHAP, lenalidomide, rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; NA, not available.
*Overall series, including rituximab-naïve patients ($n = 398$).

which consists of patients with primary refractory disease or early relapse (only three patients had late relapse), all pre-treated with rituximab. Our results are similar to those achieved with the combination of lenalidomide and R-ICE (RICER regimen) in another phase 1 study (Feldman *et al*, 2014), and appear to be superior to those obtained with standard salvage regimens combined with rituximab or ofatumumab (Table IV). Therefore, the results obtained with the combination of lenalidomide with R-ESHAP ($n = 19$, present study) or R-ICE ($n = 15$) (Feldman *et al*, 2014) are very encouraging and merit further investigation in larger phase 2 studies.

Previously published data suggest that the clinical activity of lenalidomide is higher in patients with non-germinal centre B-cell-like (GCB) DLBCL than in GCB patients (Hernandez-Ilizaliturri *et al*, 2011; Nowakowski *et al*, 2015). We plan to analyse biopsy samples from patients who are being enrolled in the on-going phase 2 to determine if cell of origin (using gene expression profile in addition to immunohistochemistry) and other molecular biomarkers are correlated with response and long-term outcomes.

In conclusion, the results of our study indicate that the addition of lenalidomide to the R-ESHAP salvage regimen is safe, feasible and associated with promising response rates and survival outcomes in patients with relapsed or refractory DLBCL. A phase 2 study is on-going.

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Author contributions

A.M. and D.C. were responsible for the conduct of the study; A.M. and A.-M.R. performed the data analysis and interpretation; A.M. drafted the report that all co-authors critically revised for significant scientific content; I.D., A.S., E.G.-B., M.C. and A.L.-G. contributed research data to the study; E.-M.O. was responsible for the *in vitro* analysis; S.M.-M. was responsible for the centralized histopathological review; all co-authors contributed to data analysis and interpretation; all co-authors approved the submitted version.

Conflict of interests

A.S., A.L.-G. and D.C have been paid for consulting or advisory role by Celgene. E.-M.O. has conducted research projects funded in part by Celgene. A.M, A.-M.R., I.D., E.G.-B., M.C. and S.M.-M. declare no competing financial interests related to this study.

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