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A phase II study to evaluate lenalidomide in combination with metronomic-dose cyclophosphamide in patients with heavely pretreated classical Hodgkin lymphoma.

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ABSTRACT

Background: Relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) after autologous stem cell transplantation (ASCT) remains a challenge. For these patients treatments with different mechanisms of action rather than classical chemotherapy are needed.

Patients and methods: Patients with R/R cHL after ASCT were recruited in a phase II trial (EUDRA CT: 2009-016588-12). Lenalidomide was administered at 20 mg/day for 21 days and cyclophosphamide at 50 mg/day for 28 days (cycles every 28 days). Dose escalation for lenalidomide was permitted. In 2009 we considered that this treatment would be promising if response rate were over 60% and a Simon 2-stage binomial design was used to calculate the sample size. A total of 46 patients were planned but the trial would be stopped if less than 7 responses after 4 cycles were obtained in the first 16 patients.

Results: The trial was closed early because only 5 responses were observed after 4 cycles in the first 16 patients included. Median age was 34 years (18-77). The median number of previous lines was 5 (2-6). At inclusion, 10 pts were primary refractory and 11 refractory to the last therapy. A total of 110 cycles were administered, with grade ≥3 toxicity in 43 cycles (39%). A toxic death was observed after a septic shock in a non neutropenic patient.

An ORR of 38% (1 CR and 5 PR) was observed and a total of 10 pts (62%) achieved clinical benefit. Median progression free survival and overall survival were 7 and 19 months, respectively. With a median follow-up of 19 months (3-38+), 3 year PFS and OS were 6% and 31%, respectively.

Conclusion: The optimistic assumptions of this trial led to an early closure. However, the clinical benefit rate of lenalidomide associated with metronomic cyclophosphamide looks promising as an outpatient palliative treatment.

KEYWORDS:

Lenalidomide, metronomic cyclophophamide, relapsed/refractory Hodgkin lymphoma.

INTRODUCTION

The standard treatment for patients with classical Hodgkin's lymphoma (cHL) who relapse or progress after primary treatment consists of salvage chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT). This treatment strategy results in cure in 50% to 60% of patients [1]. Unfortunately, patients who are refractory to salvage chemotherapy or relapse after ASCT have a median survival of 2 years, and only exceptionally achieve durable complete remissions [2]. Recently new active drugs have been approved, but most of these patients benefit only marginally from them [3,4]. Therefore, there is still a need to search for new therapies that are both active and tolerable for this heavily pretreated patient population.

The importance of cellular immunity in the regulation of cHL suggests that immunomodulatory agents might be active against this disease. Lenalidomide is an immunomodulatory drug with antiangiogenic properties. Its mechanism of action has recently been described [5,6]. Lenalidomide binds to cereblon and the resulting complex activates proteasomal degradation of two B-cell-specific transcription factors, the Ikaros proteins IKZF3 and IKZF1, which play a central role in the biology of B cells and T cells. The lack of the proteins that are produced as a result of the activity of these transcription factors account for the effects of lenalidomide in lymphoid cells. These effects include, most prominently, reversal of resistance to conventional chemotherapy in several B-cell-derived malignant cell lines [7], and increased activity of cytotoxic T cells and NK cells by stimulating IL2 and gamma interferon production and inhibiting IL10 production [8]. In addition, lenalidomide inhibits the migration and invasiveness of human endothelial cells via inhibition of VEGF production and Tie2/VEGF1 receptor activity [9].

There is scientific evidence of the antiangiogenic and antitumor effects of continuous oral low-dose cyclophosphamide (metronomic doses) [10,11]. The antiangiogenic activity of cyclophosphamide may be increased by combining it with other drugs that act by inhibiting VEGF or its receptors. Specifically, the combination of metronomic-dose cyclophosphamide with high-dose celecoxib has proven active in relapsed or refractory aggressive non-Hodgkin's lymphoma [12]. Unfortunately, only limited data are available on the efficacy of metronomic-dose cyclophosphamide —combined or not with other antiangiogenic agents— in cHL. A phase-II study evaluated the efficacy of the combination of metronomic-dose cyclophosphamide and vinblastine with rofecoxib in 50 patients with advanced malignancies (45 solid tumors and 5 lymphomas) [13]. Three patients with cHL were enrolled and all three achieved a response (two complete and one partial responses), with a time to progression of 748, 418, and 749 days respectively.

Combining lenalidomide with metronomic-dose cyclophosphamide in cHL might have the advantage that, in addition to the antiangiogenic and antitumor activity of both drugs, the

immunomodulatory effect of lenalidomide might enhance the efficacy of a metronomic dosing schedule. In a preclinical study by Blansfield et al. [14], the combination of lenalidomide with metronomic-dose cyclophosphamide increased their respective antiangiogenic and antitumor activities.

On this basis, a phase-II clinical trial was designed to evaluate the efficacy and safety of lenalidomide in combination with metronomic-dose cyclophosphamide in patients with cHL refractory or relapsed after ASCT.

PATIENTS AND METHODS

Eligible patients

Patients aged 18 years or older previously diagnosed with classical Hodgkin's lymphoma according to the World Health Organization (WHO) classification [15], who had progressed after autologous stem cell transplantation (ASCT) or had shown disease progression or refractoriness to at least 2 prior lines of chemotherapy and were not considered eligible for ASCT were included. Patients who had previously undergone allogeneic transplantation were also eligible. Refractoriness was defined as the lack of complete response (CR) or partial response (PR) to the last prior therapy. Additional inclusion criteria included: Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, measurable disease ≥ 2 cm, adequate renal function (serum creatinine clearance > 30 mL/min), hepatic function (bilirubin < 2 mg/dL and aspartate aminotransferase/alanine aminotransferase < 5 times the upper limit of normal), and hematopoietic function (absolute neutrophil count > 1000/μL and platelet count > 50,000/μL). Pregnant or breastfeeding women were excluded from enrollment. The study (EUDRA CT no. 2009-016588-12) was conducted in compliance with the recommendations of the Declaration of Helsinki. It was approved by the Research Ethics Committees of all participating institutions and all patients signed informed consent.

Study design and treatment

A phase-II, open-label, multicenter, prospective, single-treatment-arm study was carried out. Study patients were treated in 28-day cycles. Cycle 1 (level 0) consisted of lenalidomide 20 mg/day for 21 days plus cyclophosphamide 50 mg/day on all 28 days of the cycle. Escalation of the lenalidomide dose to level 1 (table 1) was allowed in patients who did not experience any grade ≥3 hematologic toxicity or grade ≥2 non-hematologic toxicity during treatment cycle 1, and to level 2 in patients who received cycle 2 at dose level 1 and did not experience these toxicities. Patients who experienced grade 3-4 toxicity at any dose level received the next cycle at the next lower dose level. In patients who received lenalidomide at dose level -1 or lower and experienced grade ≥3 hematologic toxicity, the cyclophosphamide dose was reduced to 50 mg q48h. If grade ≥3 hematologic toxicity recurred, cyclophosphamide was discontinued and lenalidomide was continued as monotherapy if clinical benefit was achieved. The requirements for starting a new treatment cycle were an absolute neutrophil count > 1000/μL, a platelet count > 50,000/μL, and any previous toxicity returned to grade ≤2. If these criteria were not met, treatment was delayed for one week and resumed at a lower dose level. Treatment was continued until disease progression or unacceptable adverse effects, for a maximum of 24 cycles.

Use of G-CSF was not allowed except for febrile neutropenia or serious infection-related neutropenia. Patients at risk of thromboembolic events received aspirin (100 or 325 mg/day) or prophylactic doses of low-molecular-weight heparin. All adverse events (AEs) were assessed and coded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Assessment of response and statistical analysis

The primary endpoint was the overall objective response rate (ORR) as defined by the 1999 International Working Committee (IWC) criteria. Responses were assessed according to the 1999 IWC criteria [16]. Restaging computerized tomography scans were performed after cycles 2, 4, and 7, and every 3 cycles thereafter. Responses were evaluated by the principal investigator and the radiologist at each study site. Clinical benefit was defined as complete remission (CR), partial remission (PR), or stable disease (SD) lasting longer than 6 months. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety assessment of the drug combination.

The sample size was calculated according to a Simon's two-stage design, with an alpha error of 0.025 and a beta error of 0.8. The activity of the drug combination would be considered clinically no significant if the ORR was lower than 40% (H0) and treatment would be considered promising if the ORR was higher than 60% (H1). Under these assumptions, 16 patients would be recruited for the first stage and, if at least 7 objective responses were achieved (in the assessment after cycle 4), the study would proceed to the second stage. Failure to achieve 7 responses would constitute a reason to halt the study because the efficacy would be below the expected range. In the second stage, recruitment would continue up to 46 patients.

Study results were analyzed by intention-to-treat, and all patients who initiated study treatment were considered evaluable for efficacy and toxicity. The correlation between two quantitative variables that did not conform to a Gaussian distribution was examined using non-parametric correlation analysis, by calculating the Spearman correlation coefficient. The Chi-square test was used to measure the association between categorical variables in both groups; but if the expected frequency in any cell was less than 5, the Fisher's exact test was used instead. The non-parametric Wilcoxon's signed-rank median test was used to compare between-group differences for quantitative variables that did not conform to a Gaussian distribution. Time to progression or death was analyzed using the Kaplan-Meier method. The groups (according to categorical variables) were compared using the log-rank test. The proportional hazards regression model was used to examine the association between a quantitative variable and time to onset of the event. A 5% two-sided significance level was used for all tests.

RESULTS

Patient characteristics

The study was stopped after 16 patients were enrolled because only 5 objective responses had been achieved (ORR 31%, 95%CI 11%-58%) after treatment cycle 4. The patient characteristics are summarized in Table 2.

The median number of prior therapies was 5 (range 2-6), 11 (71%) patients were refractory to the last prior therapy and 10 (68%) were primarily refractory. Four (25%) patients had not previously undergone autologous hematopoietic stem cell transplantation (ASCT): 3 because they were refractory to all previous therapies, and 1 patient aged 77 who was also refractory to second-line therapy (the last before enrollment). The 12 (75%) patients who underwent ASCT had progressed within a median of 5 months (range 3-23) after ASCT, and had received a median of 2 therapies after ASCT. Five (31%) patients had undergone allogeneic hematopoietic stem cell transplantation before study enrollment.

General condition was good in most patients, and only 1 patient was enrolled with a Eastern Cooperative Oncology Group (ECOG) performance status of 2. Twelve (75%) patients had stage IV disease, all because of extranodal disease. Five (31%) patients had B symptoms and 6 (38%) had bulky disease. Blood test data indicated that 8 (50%) patients had hemoglobin below 10.5 g/dL, 6 (38%) had albumin below 40 g/l, 4 (25%) had more than 15,000 WBC per microliter, and 5 (31%) had less than 600 lymphocytes per microliter.

Treatment administration

A total of 110 cycles were administered to the 16 study patients. The median duration of treatment was 7 cycles (range 1-24). The lenalidomide dose was escalated to level 1 (20 mg/day for 28 days) in 9 (56%) patients at treatment cycle 2, and to level 2 (25 mg/day for 28 days) in 7 (44%) patients at cycle 3. Subsequently, 5 patients required a reduction of the maximum dose reached. At the time of treatment completion, 6 patients were being treated at dose level 2, 1 patient at level 1, 5 patients at level 0, 2 patients at level 1, and two patients at level -2 (table 1). The cyclophosphamide dose was reduced to level -1 (50 mg every other day for 28 days) in two patients and was discontinued in 2 other patients.

The reasons for discontinuing treatment were as follows: disease progression in 12 (75%) patients, investigator's decision in 1, patient's decision in 1, and 1 toxic death. Only 1 (6%) patient completed the 24 protocol-planned treatment cycles.

Toxicity

Some type of toxicity was recorded in 76% (84 out of 110) of the lenalidomide-cyclophosphamide cycles. The recorded toxicity was severe (grade ≥3) in 43 (39%)

cycles. The most common severe toxicities per cycle were as follows: neutropenia (14%), thrombocytopenia (7%), anemia (6%), lymphocytopenia (5%), and infections (4%).

The analysis of maximal toxicity per patient is shown in Table 3. Three patients (19%) experienced no grade >2 toxicities. Fifty-six percent of patients experienced severe neutropenia in at least one treatment cycle. Severe thrombocytopenia, anemia, and lymphocytopenia occurred in 32%, 25%, and 19% of patients, respectively.

Special mention should be made to infections and liver toxicity. A total of 11 infectious events were noted in 7 patients, of which 5 were severe (grade ≥3). Of these, three patients with grade 3 pneumonia and one patient with grade 3 bacteremia recovered fully. However, a non-neutropenic patient developed pneumonia that rapidly progressed to septic shock and respiratory failure that led to the patient's death. This event occurred after treatment cycle 5; the patient was in partial remission and had not experienced any other toxicity in the previous 4 cycles.

As regards to liver toxicity, one patient developed grade 3 cholestatic hepatitis and responded favorably to low-dose corticosteroids (<10 mg/day), so that treatment could be continued. Another patient had two episodes of elevated transaminases (grade 3 and grade 4) and recovered after the lenalidomide dose was delayed and reduced. Finally, one patient developed grade 2 transaminitis that resolved spontaneously.

Efficacy and outcome

The response rate after cycles 2 and 4 and the best response achieved during the study period are shown in Table 6. Overall, 6 patients (38%, 95%CI 15%-64%) achieved objective response; 5 of them achieved partial response and one achieved complete response (and has maintained it to date). Five patients achieved stable disease lasting at least 6 months and 5 patients developed disease progression (one patient who was in CR after cycle 2 progressed before cycle 4). Ten patients (62%) achieved clinical benefit. Of the 11 patients who did not progress during the first 4 cycles, one died from toxicity in treatment month 5 and was considered not to have achieved clinical benefit despite being in PR.

The correlation of clinical and prognostic factors listed in Table 2 with response to treatment was examined. Patients refractory to the last prior therapy were less likely to respond (2 out of 11, 18%) than non-refractory patients (4 out of 5, 80%) ($p = 0.036$). The other variables examined showed no correlation with response or clinical benefit (data not shown).

At the time of data analysis, 15 patients had progressed (one due to toxic death) and 11 had died (9 from disease progression, 1 from treatment toxicity, and 1 from toxicity of a subsequent therapy). Of the 5 living patients, 2 are free of disease (one without any additional treatment). The median time to progression was 7 months (range 1-38+) and

the median survival was 19 months (range 3-38+). With a median follow-up of 19 months (37 months for living patients), the 3-year PFS and OS was 6% and 31%, respectively (Figures 1 and 2).

Another interesting issue is patient management after disease progression on study treatment. Of the 14 patients eligible for subsequent therapies, 4 developed rapidly progressive disease with poor general condition and received no further therapy. Nine patients received brentuximab vedotin and three received everolimus (2 after brentuximab). Two of them achieved complete response with brentuximab vedotin and underwent allogeneic transplantation (one is still alive with no progression and one died from allogeneic transplantation toxicity), 1 is still alive and in partial response after brentuximab, and 2 are in partial response and receiving everolimus. The remaining patients died of lymphoma progression.

DISCUSSION

When this study was being designed, the German Hodgkin Study Group (GHSG) reported the results of treatment with lenalidomide for 10 patients with cHL and 2 patients with lymphocyte-predominant HL, all heavily pretreated (median of 4 prior chemotherapies), within a compassionate-use (named-patient) program [17]. The GHSG reported an ORR of 50% and no grade >2 toxicity in this small group of patients. These striking results were used to define our study hypothesis, since the addition of cyclophosphamide might enhance not only the activity but also the toxicity. Therefore, an ORR lower than 60% would add nothing to lenalidomide monotherapy.

Two years later, Fehniger et al. [18] reported the results of a phase-II multicenter study conducted in North America, which enrolled 38 heavily pretreated patients with cHL relapsed or refractory after ASCT, whose prognostic features were very similar to those of our study patients. Lenalidomide was administered at 25 mg/day for 21 days in 28-day cycles (the standard dosage used for multiple myeloma and in the GHSG Hodgkin lymphoma study). The intention-to-treat analysis yielded an ORR of 18% and a clinical benefit rate of 31%, with a median PFS of 4 months and a median OS of 20 months. The toxicity observed per patient, including serious infections, was very similar to that observed in the 16 patients reported in the present study.

Despite the small number of patients enrolled, the results achieved by our study appear to be better than those reported by the North American study. The combination of lenalidomide with metronomic-dose cyclophosphamide achieved an ORR of 38% and a clinical benefit rate of 62%, with a median time to progression of 7 months. As in the North American study, a patient who was in PR after treatment cycle 4 achieved CR subsequently, completed the planned 24 cycles, and remains free of disease progression 38 months after study enrollment. We do not know whether this increase in activity is due to the addition of cyclophosphamide, to lenalidomide dose escalation (as allowed in our study), or to chance (due to the small number of patients enrolled).

Until a few years ago, the most active treatment for patients with cHL refractory or relapsed after ASCT was dose-adjusted chemotherapy with the GVD regimen (gemcitabine, vinorelbine, and liposomal Adriamycin), which achieved an ORR of 75% and a CR rate of 17%, with a median survival of 3.5 years [19]. However, it should be kept in mind that their study population had a better prognosis, 84% of patients were responsive to the last prior therapy (31% in our study) and the median number of prior therapies was 3 (5 in our study). Two new drugs have recently been approved by the Food and Drug Administration (FDA) for the treatment of these patients: brentuximab vedotin and panobinostat. In a pivotal phase-II study that enrolled 102 patients (58% responsive to the last prior therapy, with a median of 3.5 prior therapies) [20],

brentuximab vedotin achieved an ORR of 75% and a CR rate of 34%; the median time to progression was 5.6 months, and, importantly, the median duration of CR was 20 months, with a significantly lower toxicity than that reported with GVD. Panobinostat achieved an ORR of 27% (CR rate 4%) and a median PFS of 6 months in 129 patients who had received a median of 4 prior therapies (59% had responded to the last prior therapy). Toxicity was significant, with a 79% rate of grade 3-4 thrombocytopenia per patient [21]. Other histone deacetylase inhibitors were more toxic (mocetinostat) [22] or less active (vorinostat) [23] than panobinostat.

Two other drugs have achieved interesting results in patients with cHL relapsed or refractory after ASCT: everolimus and bendamustine. In a phase-II study, the mTOR inhibitor everolimus achieved an ORR of 47% in 19 patients [24]. A confirmatory study, not yet reported, enrolled 57 patients and achieved an ORR of 42% [25]. The use of everolimus in patients with heavily pretreated cHL requires close monitoring of pulmonary function, as severe pulmonary toxicity was reported for 4 of the 19 patients enrolled in the first study [24]. Bendamustine was examined at a dose of 120 mg/m^2 for two days (with granulocyte growth factor support) every 3 weeks in a phase-II study that enrolled 36 patients. ORR was 53%, CR rate was 33%, and median PFS was less than 6 months [26]. Data from a recent Italian retrospective study suggest that bendamustine may achieve similar efficacy when administered every 4 weeks [27].

In this setting, lenalidomide appears to be marginally active in patients with cHL relapsed or refractory after ASCT. However, the lenalidomide-cyclophosphamide combination achieved acceptable results (38% ORR, clinical benefit rate of 62%, median PFS of 7 months) even though the prognostic factors in our study population were more unfavorable that those of patients enrolled in the other studies reviewed (5 prior therapies, median progression after ASCT at 5 months, and 69% refractory to the last prior therapy). In this regard, a response was achieved by 4 of the 5 patients who were not refractory to the last prior therapy. Unfortunately, we could not confirm these results in a larger population.

The choice of treatment for cHL relapsed or refractory after ASCT depends on the goal of treatment and patient preference. In a young patient with good performance status, usually the goal is to achieve a complete response for consolidation with allogeneic transplantation. In that case, brentuximab vedotin appears to be the treatment of choice, and bendamustine or the GVD regimen are options worth considering. In patients ineligible for allogeneic transplantation, the goal should be to prolong survival with good quality of life. In this scenario, brentuximab vedotin currently remains the drug of choice, but the lenalidomide-cyclophosphamide combination might be an acceptable option after

failure to brentuximab if the results are confirmed in other studies with larger numbers of patients.

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DISCLOSURE:

REFERENCES

1.- Josting A, Müller H, Borchmann P, et al. Dose intensity of chemotherapy in patients with relapsed Hodgkin's lymphoma. J Clin Oncol 2010; 28: 5074-5080.

2.- Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol 2009; 146(2): 158-163.

3.- Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012; 30: 2183-2189.

4.- Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study. J Clin Oncol 2012; 30: 2197-2203.

5.- Krönke J, Udeshi ND, Narla A, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science 2014; 343: 301-305.

6.- Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science 2014; 343: 305-309.

7.- Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002; 100: 3063-3067.

8.- Haslett PA, Hanekom WA, Muller G, Kaplan G. Thalidomide and a thalidomide analogue drug costimulate virus-specific CD-8 + T cells in vitro. J Infect Dis 2003; 187: 946-955.

9.- Zhang H, Vakil V, Braunstein M, et al. Circulating endothelial progenitor cell in multiple myeloma: implications and significance. Blood 2005; 105: 3286-3294.

10.- Colleoni M, Rocca A, Sandri MT, et al. Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. Ann Oncol 2002; 13: 73-80.

11.- Man S, Bocci G, Francia G, et al. Antitumor effects in mice of low-dose (metronomic) cyclophosphamide administered continously through the drinkin water. Cancer Res 2002; 62: 2731-2735.

12.- Buckstein R, Kerbel RS, Shaked Y, et al. High-dose celecoxib and metronomic " low-dose" cyclophosphamide is an effective and safe therapy in patients with relapsed and refractory aggressive histology non-Hodgkin´s lymphoma. Clin Cancer Res 2006; 12: 5190-5198.

13.- Young SD, Whissell M, Noble JC, Cano PO, Lopez PG, Germond CJ. Phase II clinical trial results involving treatment with low-dose daily oral cyclophosphamide, weekly

vinblastine, and rofecoxib in patients with advanced solid tumors. Clin Cancer Res 2006; 12: 3092-3098.

14.- Blansfield JA, Caragacianu D, Alexander HR, et al. Combining agents that target the tumor microenvironment improves the efficacy of anticancer therapy. Clin Cancer Res 2008; 14: 270-280.

15.- Swerdlow S, Campo E, Harris NL, eds.; International Agency for Research on Cancer. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue. Geneva, Switzerland: World Health Organization; 2008.

16.- Cheson BD, Horning SJ, Coiffier B, et al: Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999; 17:1244-1253.

17.- Boll B, Borchmann P, Topp MS, et al. Lenalidomide in patients with refractory or multiple relapsed Hodgkin lymphoma. British Journal of Haematology 2009; 148: 480-490.

18.- Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood 2011; 118: 5119-5125.

19.- Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol 2007; 18: 1071-1079.

20.- Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012; 30: 2183-2189.

21.- Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study. J Clin Oncol 2012; 30: 2197-2203.

22.- Younes A, Oki Y, Bociek RG, et al. Mocetinostat for relapsed classical Hodgkin's lymphoma: an open-label, single-arm, phase 2 trial. Lancet Oncol 2011; 12: 1222-1228.

23.- Kirschbaum MH, Goldman BH, Zain JM, et al. A phase 2 study of vorinostat for treatment of relapsed or refractory Hodgkin lymphoma: Southwest Oncology Group Study S0517. Leuk Lymphoma 2012; 53: 259-262.

24.- Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. Am J Hematol 2010; 85: 320-324.

25.- Johnston PB, Pinter-Brown L, Rogerio J, Warsi G, Chau Q, Ramchandren R. Everolimus for relapsed/refractory classical Hodgkin lymphoma: multicenter, open-label, single-arm, phase 2 study [abstract]. Blood (ASH Annual Meeting Abstracts). 2012; 120: 2740.

26.- Moskowitz AJ, Hamlin PA Jr, Perales MA, et al. Phase II Study of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol 2013; 31: 456-460.
27.- Anastasia A, Carlo-Stella C, Corradini P, et al. Bendamustine for Hodgkin lymphoma patients failing autologous or autologous and allogeneic stem cell transplantation: a retrospective study of the Fondazione Italiana Linfomi. Br J Haematol 2014 Mar 7. doi: 10.1111/bjh.12821. [Epub ahead of print].

TABLES AND FIGURES LEGEND

Table 1.

Number of patients at each dose level of lenalidomide.

Table 2.

Patient characteristics.

Table 3.

Worst toxicity per patient.

Table 4.

Response rate.

Figure 1.

Progression free survival.

Figure 2.

Overall survival.

Table 1. Lenalidomide dose levels.

Level	mg/day every 28 days	Patients in cycle 1 (n)	Patients in cycle 2 (n)	Patients in cycle 3 (n)	Patients in last cycle (n)
2	25 mg for 28 days	0	0	7	6
1	20 mg for 28 days	0	9	2	1
0	20 mg for 21 days	16	7	7	5
- 1	15 mg for 21 days	0	0	0	2
- 2	10 mg for 21 days	0	0	0	2
- 3	5 mg for 21 days	0	0	0	0

Table 2. Patient characteristics.

Sex	Male	10 (62%)	Age (years)	Median	34
	Female	6 (38%)		Range	18-77
Initial stage	I	1 (6%)	Stage at inclusion	I	0 (0%)
	II	8 (50%)		II	2 (12.5%)
	III	5 (31%)		III	2 (12.5%)
	IV	2 (13%)		IV	12 (75%)
Primary refractory	Yes	10 (62%)	Refractory to last therapy	Yes	11 (69%)
	No	6 (38%)		No	5 (31%)
Number of previous lines	Median	5	Number of lines pre ASCT	Median	3
	Range	2-6		Range	2-4
Previous ASCT	Yes	12 (75%)	Previous allotransplant	Yes	5 (31%)
	No	4 (25%)		No	11 (69%)
TTP after ASCT (months)	Median	5	Time from dx to inclusion (months)	Median	58
	Range	3-23		Range	13-128
Performance status	ECOG 0	6 (38%)	Hemoglobin (gr/dl)	> 12	6 (38%)
	ECOG 1	9 (56%)		10.5-12	2 (12%)
	ECOG 2	1 (6%)		< 10.5	8 (50%)
B symptoms	Yes	5 (31%)	Bulky disease	Yes	6 (38%)
	No	11 (69%)		No	10 (62%)
Extranodal disease	Yes	12 (75%)	Albumin (gr/dl)	> 40	10 (62%)
	No	4 (25%)		< 40	6 (38%)
Leucocytes	> 15000/µL	4 (25%)	Lymphocytes	> 600/µL	11 (69%)
	< 15000/µL	12 (75%)		< 600/µL	5 (31%)

ASCT: autologous stem cell transplantation; **TTP**: time to progression; **dx:** diagnosis; ECOG: Eastern Cooperative Oncology Group performance status scale.

Table 3. Worst toxicity per patient

Type	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neuropathy	15 (94%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Constipation	14 (87%)	1 (6%)	1 (6%)	0 (0%)	0 (0%)
Skin rush	12 (75%)	0 (0%)	4 (25%)	0 (0%)	0 (0%)
Asthenia	13 (81%)	0 (0%)	3 (19%)	0 (0%)	0 (0%)
Vomits	15 (94%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)
Arthralgia	15 (94%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)
Anxiety	15 (94%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)
Liver	13 (81%)	0 (0%)	1 (6%)	1 (6%)	1 (6%)
Neutropenia	6 (38%)	0 (0%)	1 (6%)	8 (50%)	1 (6%)
Lymphopenia	13 (81%)	0 (0%)	0 (0%)	2 (13%)	1 (6%)
Thrombocytopenia	9 (56%)	0 (0%)	2 (12.5%)	3 (19%)	2 (12.5%)
Anemia	8 (50%)	0 (0%)	4 (25%)	3 (19%)	1 (6%)
Infections*	9 (56%)	0 (0%)	3 (19%)	3 (19%)	0 (0%)

* 1 grade 5 (6%): a non-neutropenic patient developed pneumonia that rapidly progressed to septic shock and respiratory failure that led to the patient's death.

Table 4. Response rate.

Response	Cycle 2	Cycle 4	Beyond the 4th cycle
Complete	1 (6%)*	0 (0%)	1 (6%)
Partial	5 (31%)	5 (31%)	5 (31%)
Stabilization	6 (38%)	6 (38%)	5 (31%)
Progression	4 (25%)	5 (31%)	5 (31%)

*One patient achieved a complete response after the second cycle but progressed after the fourth.

Figure 1. Progression free survival

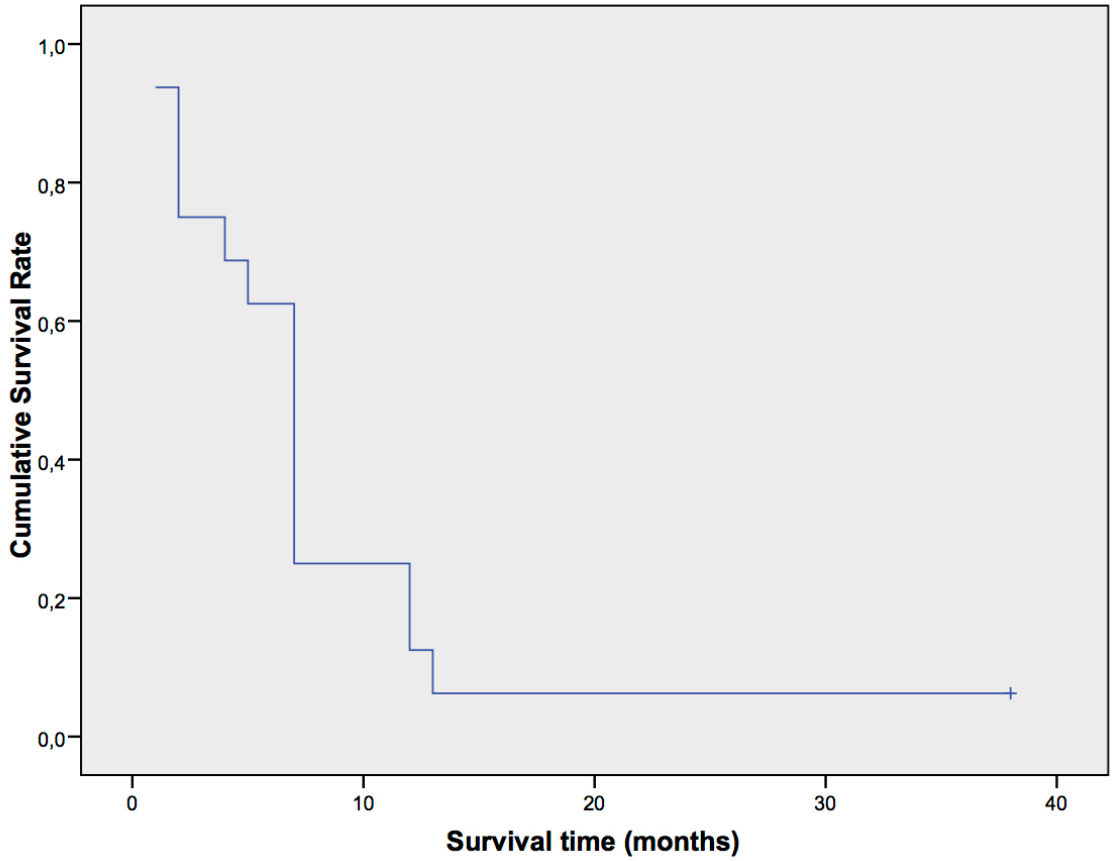

Figure 2. Overall survival.