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Addition of lenalidomide to rituximab, ifosfamide, carboplatin, etoposide (RICER) in first-relapse/primary refractory diffuse large B-cell lymphoma

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Summary

Relapsed/refractory diffuse large B-cell lymphoma (DLBCL) is associated with a poor prognosis. Outcomes are particularly poor following immunochemotherapy failure or relapse within 12 months of induction. We conducted a Phase I/II trial of lenalidomide plus RICE (rituximab, ifosfamide, carboplatin, and etoposide) (RICER) as a salvage regimen for first-relapse or primary refractory DLBCL. Dose-escalated lenalidomide was combined with RICE every 14 d. After three cycles of RICER, patients with chemosensitive disease underwent stem cell collection and consolidation with BEAM [BCNU (carmustine), etoposide, cytarabine, melphalan] followed by autologous stem cell transplantation (autoSCT). Patients who recovered from autoSCT toxicities within 90 d initiated maintenance treatment with lenalidomide 25 mg daily for 21 d every 28 d for 12 months. No dose-limiting or unexpected toxicities occurred with lenalidomide 25 mg plus RICE. Grade 3/4 haematological toxicities resolved appropriately, and planned dose density and dose intensity of RICER were preserved. No lenalidomide or RICE dose reductions were required in any of the three cycles. After two cycles of RICER, nine of 15 patients (60%) achieved a complete response, and two achieved a partial response (13%). Combining lenalidomide with RICE is feasible, and results in promising response rates (particularly complete response rates) in high-risk DLBCL patients.

Keywords: lenalidomide, diffuse large B-cell lymphoma, rituximab, salvage, bone marrow transplantation.

Diffuse large B-cell lymphomas (DLBCLs) are the most common subtype of lymphomas, accounting for over one-third of all non-Hodgkin lymphomas (NHLs) (Campo *et al*, 2011). There is clear evidence of heterogeneity within the DLBCL class, both at the molecular level and in terms of clinical outcomes. Molecular profiling has identified three main subtypes of DLBCL: germinal centre B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, and primary mediastinal B-cell lymphoma (Nogai *et al*, 2011), which are believed to originate from distinct cell types: GCB DLBCL from germinal centre B cells; ABC DLBCL from B-cells that are differentiating into plasma cells (post-germinal centre); and primary mediastinal B-cell lymphoma from thymus-derived B cells. Patient prognosis and response to treatment are also influenced by a number of additional molecular features, including the MKI67 (Ki67) proliferation index and expression of *TP53* (p53), *MYC* (c-Myc), *BCL2*, or *BCL6*. Emerging entities, such as double- and triple-hit DLBCL (for example, those involving *BCL2-MYC* rearrangement and/or overexpression), are associated with very poor outcomes and are frequently resistant to conventional chemotherapy (Green *et al*, 2012; Kobayashi *et al*, 2012).

Chemoimmunotherapy using rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (R-CHOP) has markedly improved the outcome of DLBCL over the last decade, with over 50% of patients achieving long-term survival. However 10–15% of patients fail R-CHOP initially and 20–25% relapse, with 80% of the failures occurring within the first 18 months of treatment and very few late relapses being reported (Gisselbrecht, 2012).

Patients with relapsed or primary refractory DLBCL generally receive salvage therapy with either rituximab, ifosfamide,

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carboplatin and etoposide (RICE) or other regimens, such as rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP), followed by consolidation with high-dose therapy (HDT) and autologous stem cell transplantation (autoSCT) in patients who demonstrate chemosensitive disease. The inclusion of rituximab in these salvage regimens has increased the response rate in comparison with non-rituximab-containing regimens, thus enabling more patients to undergo HDT/autoSCT (Kewalramani *et al*, 2004; Mey *et al*, 2006). However, despite these improved response rates, only approximately 50% of patients are able to proceed to autoSCT (Gisselbrecht, 2012) and only approximately half of these achieve durable remission post-transplant (Mounier *et al*, 2012). Several factors appear to be associated with these particularly poor outcomes and secondary failures, including prior exposure to rituximab in the first-line setting and/or relapse within 12 months of induction therapy (Gisselbrecht, 2012). New strategies are needed to improve response rates – particularly complete response (CR) rates prior to autoSCT – and to prevent recurrence following transplantation. Accordingly, the US National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend that patients with relapsed/refractory DLBCL should be considered for inclusion in clinical trials (NCCN, 2013).

The immunomodulatory agent lenalidomide has demonstrated direct tumouricidal and antiproliferative effects in lymphoma, and clinical activity and tolerability in Phase II studies in aggressive NHLs. Interestingly, in the single-agent setting, lenalidomide has shown preferential activity in the ABC subtype (Hernandez-Ilizaliturri *et al*, 2011), which is found in a higher percentage of relapsed/refractory DLBCL patients and is associated with worse outcomes than other subtypes (Hernandez-Ilizaliturri *et al*, 2011). Preliminary data obtained with lenalidomide plus R–CHOP in the frontline setting appear very promising and, in particular, suggest efficacy in non-GCB DLBCL (outcomes in patients with non-GCB DLBCL were similar to those in patients with GCB DLBCL) (Nowakowski *et al*, 2011; Chiappella *et al*, 2013). However, to date, studies in relapsed or refractory lymphoma have only evaluated single-agent lenalidomide, lenalidomide in combination with either rituximab or dexamethasone, or lenalidomide in combination with rituximab and bendamustine (Nowakowski *et al*, 2011; Witzig *et al*, 2011; Zinzani *et al*, 2011; Eve *et al*, 2012; Wang *et al*, 2012; Zaja *et al*, 2012; Hitz *et al*, 2013). The inclusion of lenalidomide in rituximab–chemotherapy salvage regimens that involve a range of agents with differing mechanisms of action could increase the response rate and quality of response. This, in turn, would allow more patients to proceed to HDT/autoSCT, but the risk remains that such regimens could also be associated with increased toxicity. To investigate the possibility of improving response rates by incorporating lenalidomide into rituximab-containing regimens, while maintaining acceptable toxicity, we conducted a Phase I/II trial combining lenalidomide with RICE (RICER) as a salvage regimen in first-relapse or primary refractory DLBCL. Here, we report the Phase I results of the study, which evaluated the safety and tolerability of the regimen.

Materials and methods

Study design

This multi-institution, Phase I/II, single-arm, open-label dose escalation study comprises three stages. The first stage, which is reported here, determined the maximum tolerated dose (MTD) and safety of RICER for the treatment of patients with DLBCL either in first-relapse or with primary refractory disease. The second stage will evaluate the efficacy and safety of RICER in this patient population, including its effect on the ability to adequately mobilize and collect $CD34^+$ cells prior to autoSCT. The third stage will evaluate the efficacy and safety of post–autoSCT lenalidomide maintenance in these patients.

The protocol was approved by the institutional review board/ethics committee of the participating centres. The study is being conducted in accordance with the Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01241734).

Patients

Eligible patients were aged ≥18 years, with histologically confirmed DLBCL that had relapsed or was refractory after one prior therapeutic treatment, and had either measurable disease or confirmed bone marrow involvement by DLBCL without measurable disease. Patients were required to be deemed eligible for autoSCT.

Immunohistochemical and molecular staining

Immunohistochemical and molecular staining were performed on pathology samples. The pathologist was blinded to the clinical outcomes of patients. Assignment of GCB and non–GCB phenotypes was based on the Hans algorithm (Hans *et al*, 2004). MYC staining was performed retrospectively using immunohistochemical and fluorescence *in situ* hybridization methodology. Haematoxylin and eosin-stained slides were reviewed for each case. One representative section containing the highest density of viable tumour cells was selected for MYC (Clone: Y69; prediluted; Ventana Medical Systems, Tucson, AZ, USA) immunohistochemical staining. Stains were performed on 4-μm sections with an automated stainer (Ventana Medical Systems), as per manufacturer protocol. Appropriate positive and negative controls were used for each antibody. A positive cut-off value was defined as 40% nuclear expression for MYC staining.

Treatment

Four dose levels of lenalidomide were evaluated in the Phase I part of the study: 10 mg, 15 mg, 20 mg and 25 mg, given

orally for 7 d (days 1–7), together with RICE [rituximab 375 mg/m^2 intravenously (IV) on day 1; ifosfamide 5 g/m^2 over 24 h mixed with mesna 5 g/m^2 IV on day 2; carboplatin area under the curve of 5 IV on day 2; etoposide 100 mg/m^2 IV on days 2–4]. Prophylactic antibiotics and growth factors were used according to the participating institutions' policy. Aspirin, 81 mg daily, was administered from day 1 until platelet counts dropped below 50 × 10^9/l. For patients who could not take aspirin, low-dose low–molecular-weight heparin was permitted. Dose interruptions/modifications due to adverse events were permitted during all stages of the study.

For the MTD part of the trial, a 3 × 3 dose-escalation design was used, in which a cohort of three consecutive patients was assigned initially to the lowest dose of lenalidomide in combination with RICE. If no patient developed a dose-limiting toxicity (DLT) during cycle 1 (one cycle being 14 d), the subsequent cohort of three patients would be assigned to the next dose. If any patient in any cohort developed a DLT, that cohort would be expanded by another three patients. In the absence of a DLT being identified, the 25 mg cohort was expanded to a total of six patients.

Restaging was performed after two cycles of RICER, and response to treatment was assessed using the revised International Working Group Criteria for malignant lymphoma (Cheson *et al*, 2007). Subjects with stable or progressive disease were removed from the study, while those who responded received a third cycle followed by stem cell collection within 10–14 d of the third cycle. Following recovery from stem cell mobilization, patients received high-dose consolidation with BEAM [BCNU (carmustine), etoposide, cytarabine, melphalan] followed by autoSCT. Involved-field radiation to the sites of bulky disease was allowed prior to high-dose consolidation myeloablative therapy.

Patients who recovered from autoSCT toxicities within 90 d started maintenance therapy with lenalidomide 25 mg daily for 21 d every 28 d, and continued on this regimen for up to 12 months. The maintenance dose could be reduced by 5 mg in the next cycle if grade 3 neutropenia was observed during a cycle or if a dose delay was required because of grade 3 neutropenia or thrombocytopenia. The minimum lenalidomide dose was 5 mg.

Recovery from autoSCT was defined as two consecutive laboratory values at weekly intervals and at least one physical assessment demonstrating all of the following: an absolute neutrophil count (ANC) ≥1·5 × 10^9/l; platelet count ≥75 × 10^9/l; Eastern Cooperative Oncology Group performance status ≤2; and no evidence of disease progression, by imaging. In addition, any rash or neuropathy that was encountered from prior treatments was required to have resolved to grade ≤1 severity. Any other adverse events that were encountered from prior treatments were required to have resolved to grade ≤2 severity.

Study endpoints

Primary endpoints for stage 1 of the trial were safety and tolerability, with a secondary endpoint of incidence of DLT for determination of the MTD to be used in stage 2.

Assessments

Response assessments. Efficacy assessments were conducted after two cycles of RICER, 28 d after BEAM autoSCT, and every 3 months during maintenance. Response assessment included: physical examination; radiographic evaluation by computerized tomography and [^{18}F] fluorodeoxyglucose-positron emission tomography (FDG-PET), using the 2007 revised response criteria for malignant lymphoma (Cheson *et al*, 2007); and bone marrow biopsy and aspiration assessment if bone marrow was involved at relapse diagnosis. All patients who had at least one post-treatment restaging were considered evaluable for response.

Safety assessments. All adverse clinical experiences, whether observed by the investigator or reported by the patient, were recorded, together with details of the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4) (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReferen ce_8.5x11.pdf). Adverse-event queries, serum biochemistry and complete blood count were evaluated on days 1–4 during each cycle.

Dose-limiting toxicity was defined as any of the following: any grade 5 toxicity; grade 4 thrombocytopenia or absolute neutropenia lasting >14 d; desquamating rash; life–threatening deep-vein thrombosis or sepsis; or failure of platelet recovery to 50 × 10^9/l or neutrophil recovery to 1·0 × 10^9/l by day 29 of the first cycle.

Statistical analysis

Descriptive statistics were used to evaluate patient baseline characteristics, disease course, disease stage, CD34$^+$ cell counts, and autoSCT procedure data.

Results

Patients

Sixteen patients were enrolled between 14 October, 2010 and 14 December, 2012, and received treatment with RICER. Patient characteristics at baseline are shown in Table I. In total, seven patients (44%) had primary refractory DLBCL, and seven patients relapsed within 12 months of initial therapy. All patients had previously received rituximab.

Table I. Patient demographics and baseline disease characteristics (n = 16).

Characteristic	Value
Median age, years (range)	61·5 (41–75)
Male, *n* (%)	13 (81)
Stage at relapse, *n* (%)	
Stage I,II	6 (38)
Stage III	3 (19)
Stage IV	7 (44)
GCB vs non-GCB subtype, *n* (%)	5 (31)/11 (69)
Relapse IPI, *n* (%)	
Low, low–intermediate	8 (50)
High–intermediate, high	8 (50)
Primary refractory, *n* (%)	7 (44)
Relapse occurred <12 months after initial therapy	7 (44)
Relapse occurred >12 months after initial therapy	2 (13)
Initial therapy, *n* (%)	
R-CHOP	12 (75)
R-HCVAD	3 (19)
R-CODOX-M/IVAC	1 (6)

GCB, germinal B-cell; IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-HCVAD, rituximab, fractionated cyclophosphamide, vincristine, Adriamycin (doxorubicin), dexamethasone; R-CODOX-M/IVAC, rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/etoposide, ifosfamide, cytarabine.

Disposition

One patient was withdrawn because of a rapid decrease in performance status and disease progression before the second cycle of RICER could be administered. This patient's data were censored.

RICER salvage therapy: safety and tolerability

No dose reductions of lenalidomide, ifosfamide, carboplatin or etoposide were required. Although the protocol–prescribed frequency of RICER was every 14 d, RICER was given every 21 d in eight patients and every 14 d in seven patients. One patient delayed treatment to 28 d because of respiratory syncytial virus (RSV) infection. The delay was imposed in order to observe for RSV complications; however, none occurred, and the patient was able to proceed with treatment.

Dose-limiting toxicity was not seen with lenalidomide 25 mg during RICER salvage treatment, and this was selected as the dose for use in stage II. The tolerability of lenalidomide plus RICE when used as a salvage therapy is shown in Table II. Based on simple observations, there was no apparent dose relationship between lenalidomide dose and the incidence of adverse events during cycle 1. Grade 3/4 toxicities were all haematological and resolved appropriately, and the planned dose density and dose intensity of RICER were preserved. There were no dose reductions of lenalidomide or rituximab, ifosfamide, carboplatin or etoposide in any of the three cycles. Three episodes of febrile neutropenia occurred during RICER administration. Two patients had a history of prior deep-vein thrombosis; however, no new cases of deep-vein thrombosis were reported during RICER administration.

Table II. Adverse events associated with lenalidomide in combination with RICE during cycle 1 (n = 15).

Common adverse events, *n* (%)	Grade 1	Grade 2	Grade 3	Grade 4
Neuropathy	1 (7)	1 (7)	–	–
Rash	1 (7)	1 (7)	–	–
Fatigue	2 (13)	–	–	–
Diarrhoea	–	–	–	–
Cytopenias, *n* (%)				
Anaemia	6 (40)	6 (40)	3 (20)	–
Thrombocytopenia	4 (27)	2 (13)	5 (33)	3 (20)
Neutropenia	1 (7)	1 (7)	2 (13)	6 (40)

RICE, rituximab, ifosfamide, carboplatin, etoposide.

RICER salvage therapy: response

Of the 15 patients evaluable for response at the initial assessment following two cycles of RICER, 11 (73%) achieved a response, of whom nine (60%) achieved CRs and two (13%) achieved partial responses (PRs) (Table III). Of these 11 patients, eight had previously responded to first-line therapy (three responses lasted >1 year; five responses lasted <1 year), while three patients were refractory to first-line therapy. All four non-responders to RICER had primary refractory disease or relapsed within 4 months of initial chemotherapy.

Correlation between response and immunohistochemical and molecular staining findings

All five of the GCB subjects (100%) had a response to therapy, while six of the 10 non-GCB subjects responded (60%). *MYC* expression was analyzed by fluorescence *in situ* hybridization (FISH) and immunohistochemistry in five and 14 samples, respectively. Five patients had MYC-positive disease by immunohistochemistry, and one by FISH. Four of the five patients who overexpressed *MYC* (80%) responded to RICER.

As of December 2013, six non-GCB and one GCB subjects are in continuous remission. All three relapses in post-auto-SCT period had GCB.

Autologous stem cell transplantation

Stem cell collection was achieved in all but one of the 11 patients who responded to RICER (Table IV). An attempt was made to collect stem cells from that patient, but the total number of cells collected ($1{\cdot}21 \times 10^6$) was inadequate for auto-SCT. Bacteraemia at the time of collection, as well as diminished bone marrow reserve due to a first-line high-dose

Table III. Characteristics of responders and non-responders to RICER (n = 15).

Characteristic	Responders	Non-responders
Patients, *N*	11	4
Subtype, *n*		
GCB DLBCL	5	0
Non-GCB DLBCL	6	4
First-line therapy, *n*		
R-CHOP	9	3
High-dose therapy	2	1
Response to first-line therapy, *n*		
No response	3	3
Response (duration)	8 (3 > 12 months; 5 < 12 months)	1 (4 months)

RICER, rituximab, ifosfamide, carboplatin, etoposide, lenalidomide; DLBCL, diffuse large B-cell lymphoma; GCB, germinal B-cell-like; R-CHOP, rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone.

chemotherapy regimen [CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, cytarabine)] within 6 months of RICER salvage, could have contributed to stem cell mobilization failure. The remaining 10 patients who were successfully mobilized underwent BEAM consolidation followed by autoSCT.

No unexpected toxicities were observed in the 30 d post-transplantation, and there was no delay in engraftment compared to historical controls: median number of days to ANC >0·5 × 10^9/l was 10 d (range 9–12), and to platelet count >20 × 10^9/l, unsupported by transfusion, was 13 d (range 8–14).

Maintenance lenalidomide: safety and tolerability

As of December 2013, eight of the 10 patients who completed autoSCT had received post–transplantation maintenance lenalidomide (Table V). In one patient the platelet count had not recovered (≥75 × 10^9/l) within 90 d post-autoSCT, and thus maintenance lenalidomide was not started. A second patient was found to have a gastric mass on restaging PET scan and underwent HDT-autoSCT, but did not continue on maintenance lenalidomide because he needed major surgery.

Two patients started maintenance lenalidomide but relapsed during cycle 4 and cycle 2 respectively, and subsequently died. Both had primary refractory disease. One patient started lenalidomide but became noncompliant after the first cycle and was lost to follow-up. One patient completed nine cycles of maintenance, had disease progression and was taken out of the study. One patient completed eight cycles with grade 2/3 neutropenia in each cycle and lenalidomide was subsequently stopped. One patient completed all 12 cycles at 5 mg daily. Two patients are still actively participating in the study and receiving lenalidomide at 5 mg and 15 mg during cycles 10 and 7, respectively.

Table IV. autoSCT characteristics.

Characteristic	
Patients completing stem cell harvest, *n/N* (%)	10/15 (67)
Patients completing BEAM + autoSCT, *n/N* (%)	10/15 (67)
Use of plerixafor, *n*	
Yes	2
No	8
Median stem cell harvest, ×10^6/kg (range)	6·41 (3·37–12·83)
Median number of collection days (range)	5 (2–7)
Engraftment	
Median time to ANC >0·5 × 10^9/l, days (range)	10 (9–12)
Median time to platelet count recovery to 20 × 10^9/l without transfusional support, days (range)	13 (8–14)

ANC, absolute neutrophil count; autoSCT, autologous stem cell transplantation; BEAM, BCNU (carmustine), etoposide, cytarabine, melphalan.

Neutropenia was the most commonly observed toxicity with lenalidomide in the post-transplant period. There were no infections in the lenalidomide maintenance period. Grade 1 and 2 thrombocytopenias were observed, but did not lead to delays or dose reductions. When lenalidomide was stopped, prompt recovery of haemoglobin, white blood cell and platelet counts to normal limits was observed. There were no new cases of deep vein thrombosis.

In summary, as of December 2013, out of 11 subjects who had objective response to RICER, 10 underwent autoSCT. The disease status is as follows: six are in complete remission post-autoSCT (range 11–36 months); one patient was lost to follow up; one patient who responded to RICER but failed stem cell collection is in complete remission 22 months later; three patients relapsed within the first year after auto-SCT: two died from progressive disease, and one is alive in partial remission after adoptive T cell therapy with autologous chimeric antigen receptor 19 T cell (autoCART19).

Discussion

We describe the first study, to our knowledge, evaluating the feasibility and safety of the immunomodulatory agent lenalidomide in combination with RICE as a salvage regimen in refractory/relapsed DLBCL, prior to HDT plus autoSCT, and followed by lenalidomide maintenance. Overall, our findings indicate that combining lenalidomide at a dose of 25 mg with RICE is feasible, resulting in a promising response rate in this DLBCL population. Grade 3/4 adverse events observed in the study were all haematological (Table II) and did not differ significantly from expected RICE-related toxicities.

Single-agent lenalidomide has been shown to produce durable responses in patients with relapsed or refractory aggressive lymphoma, and combinations of lenalidomide

Table V. Lenalidomide maintenance post-autoSCT (starting dose 25 mg daily for 21 d every 28 d).

Age, years	Sex	Total number of cycles	Maximum tolerated maintenance dose (mg)	Comment
71	Female	4	20	Relapsed within 6 months of autoSCT while on lenalidomide, and died from disease progression
61	Male	2	20	Relapsed within 3 months of autoSCT while on lenalidomide, and died from disease progression
63	Male	8	0	Alive, in CR
65	Female	12	5	Completed maintenance stage; alive, in CR
54	Male	2	25	Removed from study due to noncompliance, alive
65	Male	9	–	Removed from study secondary to disease progression, alive
69	Male	10	5	In maintenance phase, in CR
51	Male	7	15	In maintenance phase, in CR

autoSCT, autologous stem cell transplantation; CR, complete remission.

with rituximab or with rituximab and bendamustine are active in elderly patients with relapsed/refractory DLBCL (Nowakowski *et al*, 2011; Witzig *et al*, 2011; Zinzani *et al*, 2011; Eve *et al*, 2012; Wang *et al*, 2012; Zaja *et al*, 2012; Hitz *et al*, 2013). Preclinical data suggest synergy between lenalidomide and rituximab (Wu *et al*, 2008; Zhang *et al*, 2009). The combination of rituximab with the most commonly used salvage regimen, ifosfamide, carboplatin and etoposide (ICE), produced CR rates of 38–53%, and PR rates of 25–27%. However, in patients with prior rituximab exposure or early relapse (<12 months), the overall response rate (ORR) is around 45%, with event-free survival at 3 years being only 20% (Gisselbrecht *et al*, 2010). With the small patient numbers in the current study, it is not possible to establish whether lenalidomide provides additional benefit in terms of patients' ability to proceed to autoSCT. However, the CR rate of 60% in a poor risk group is encouraging, and merits further investigation in a larger Phase II trial.

Interestingly, previously published data suggest that single-agent lenalidomide demonstrates differential activity between GCB and non-GCB DLBCL subtypes. In a series of 40 patients with relapsed/refractory DLBCL, the ORR was 8·7% vs. 52·9% ($P = 0{\cdot}006$) and median progression-free survival was 1·7 months vs. 6·2 months ($P = 0{\cdot}004$) in patients with GCB ($n = 23$) versus those with non-GCB ($n = 17$) DLBCL (Hernandez-Ilizaliturri *et al*, 2011). In our study, although the numbers were smaller, we saw a 100% response rate in the five patients with GCB DLBCL, and a 60% response rate in the 10 evaluable patients with non-GCB disease. Interestingly, most patients with *MYC*-overexpressing disease responded to RICER. Our data in a poor risk population is promising and warrants further investigation. Although it is premature to make conclusions regarding maintenance lenalidomide in the post-transplant setting, myelotoxicity was the most common side effect leading to dose reduction.

We conclude that the addition of lenalidomide to the widely used RICE salvage regimen is feasible, is not associated with an increased toxicity burden, and results in promising response rates in this DLBCL population that included a number of patients with refractory disease. Further studies are needed to evaluate the efficacy of this regimen, particularly in high-risk GCB and *MYC*-overexpressing patient populations.

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