L-PROBe: A Novel Non-anthracycline Combination Chemotherapy Regimen for Aggressive B Cell Non-Hodgkin Lymphoma in Elderly Patients

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Abstract The management of aggressive B cell lymphomas in elderly patients is associated with poor tolerability of commonly used chemotherapeutic agents. The safety and tolerability of a novel combination chemotherapy regimen utilizing rituximab, lenalidomide, bendamustine, vincristine and prednisolone was assessed in a series of elderly patients with new onset or relapsed/refractory aggressive B cell lymphoma and inability to receive conventional chemotherapy due to poor performance status and/or significant comorbidities. Ten patients (7 male, 3 female) with a median age of 72 years (range 58–79 years) received therapy with lenalidomide (10 mg/day on days 1–14), rituximab (375 mg/m² on day 1), bendamustine (90 mg/m² on days 1 and 2), vincristine (1.4 mg/m² on day 1) and prednisolone (60 mg/m²/day on days 1–5) with cycles repeated every 28 days. Grade 3/4 hematological toxicities included neutropenia (30 %), anemia (30 %) and thrombocytopenia (10 %). An overall response rate of 40 % was observed with a median survival of 120 days (range 14–286 days). Three of the patients who responded achieved complete remission at the end of six cycles of therapy. This combination chemotherapy appears to be well tolerated and effective in elderly patients with poor performance status. Larger controlled studies are indicated to clearly demonstrate applicability of this novel regimen.

Keywords Lymphoma · Lenalidomide · Bendamustine · Rituximab · Elderly

Introduction

Aggressive B cell Non-Hodgkin Lymphoma (NHL) is not uncommon in elderly patients. Chemotherapy regimens such as R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) are considered the standard of care in aggressive B cell lymphomas however usage of these chemotherapy protocols in patients with severe debility due to advanced age and extensive disease can lead to unacceptable toxicities and difficulty in management. Elderly patients, due to their advanced age, comorbid illnesses, and higher propensity of chemotherapy induced neutropenia are at increased risk of developing complications with standard dose regimen like RCHOP [1]. Of particular importance is the higher incidence of cardiac toxicity in this group of patients. As a result, elderly patients with poor performance status are either treated with reduced dose regimen or at times with best supportive care alone.

New therapeutic approaches are needed in order to effectively manage this group of individuals and combination of effective and safe conventional agents with novel drugs and targeted therapy is an enticing prospect. The limitation of toxicity without compromising efficacy remains the goal of therapy in these patients.

The use of the alkylating agent bendamustine in chronic lymphocytic leukaemia and relapsed indolent lymphomas has been extensively studied and combination therapy with rituximab has been associated with encouraging results [2]. The use of bendamustine alone as well as in combination with rituximab has been studied in indolent B Lymphoid

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malignancies and in relapsed/refractory cases of aggressive NHL [3–5].

These reports illustrate the utility of bendamustine based chemotherapeutic regimens as a safer but still efficacious modality for the treatment of NHL particularly in subgroups of patients with poor performance status and bad prognostic markers. Studies have shown the potential benefit of the use of lenalidomide in cases of relapsed NHL both as monotherapy as well as in combination with other agents [6–10]. Hence, the addition of lenalidomide is expected to improve the outcomes in elderly patient with newly diagnosed B NHL by virtue of its novel mechanism of action and immunomodulatory effects.

Keeping this in mind, we attempted to devise a new combination chemotherapy regimen by utilizing certain conventional agents with proven efficacy and safety, especially in terms of myelosuppression, and adding newer agents with novel mechanisms of actions in order to create an effective and safe composite regimen.

Any effective chemotherapy regimen requires the use of a mixture of agents with varied and complimentary actions without significant overlapping toxicities. In this intent, a combination of rituximab, vincristine and prednisolone in combination with bendamustine was designed. Lenalidomide was added to this combination in view of its potent immunomodulatory activity and antineoplastic action.

This combination was devised in order to limit toxicity by omitting potent but potentially toxic agents such as doxorubicin and cyclophosphamide without compromising efficacy by introducing novel agents such as rituximab and lenalidomide.

In this study the feasibility of this novel regimen, designated by the acronym L-PROBe (Lenalidomide, Prednisolone, Rituximab, Vincristine, and Bendamustine); regimen was assessed in elderly patients with special attention paid to tolerability and safety.

Materials and Methods

The study was conducted at the Postgraduate Institute of Medical Education and Research, a tertiary care centre situated in Chandigarh, northern India. The period of study was from July 2012 to April 2014. The protocol was designed as a pilot study in order to assess feasibility.

Inclusion and Exclusion Criteria

Patients aged ≥ 55 years with a confirmed diagnosis of aggressive B cell Non-Hodgkin Lymphoma (Diffuse Large B Cell Lymphoma or Follicular Lymphoma, grade 3) that

were considered unfit for standard chemotherapy due to poor performance status or relapse/progression of disease. Younger patients, critically ill patients and those unable to provide informed consent were not considered eligible for the study.

Assessment

All patients underwent detailed history and physical examination. Histopathological examination with immunohistochemistry was mandatory for all patients, as was a complete radiological survey involving PET-CT scan, and a bone marrow aspiration with trephine biopsy. Pre chemotherapy cardiac evaluation involving MUGA (Multiple Gated Acquisition) radionuclide imaging and, if needed, 2Dimensional Echocardiography was done in all cases. Renal and Liver function tests were done at baseline in all cases. Lactate Dehydrogenase and $\beta 2$ microglobulin were measured at baseline in all cases.

Chemotherapy Protocol

The protocol was designated by the acronym L-PROBe.

L = Capsule Lenalidomide 10 mg once daily from D1–D14; P = Tablet Prednisolone 60 mg/m² from D1–5 (Maximum dose 100 mg); R = Injection Rituximab 375 mg/m² I/v on D1; O = Injection Vincristine 1.4 mg/m² I/v on D1 (Maximum dose 2 mg); Be = Injection Bendamustine 90 mg/m² I/v on D1 and 2; Cycles were repeated at intervals of 28 days.

Supportive measures including administration of allopurinol and the use of granulocyte growth factors, prophylactic antibiotics, and aspirin 100 mg/day were permitted.

Follow Up Assessment

Each patient was reviewed weekly with complete blood counts and clinical examination. Renal and liver function tests were monitored weekly in the first cycle and monthly henceforth. PET-CT scan was repeated at the end of four cycles and at the end of treatment (6 cycles).

Any adverse events were recorded at each follow up visit. Severity of adverse events was graded as per the NCI (National Cancer Institute) toxicity classification scheme. Patients were given the option to withdraw from the trial at any point in the study. They were offered palliative or metronomic chemotherapy in the event that they no longer wished to receive the L-PROBe regimen.

Patients who did not respond after four cycles of chemotherapy or progressed at any point during the trial received treatment for relapsed or refractory disease as per existing protocols.

Statistical Analysis

Univariate analysis was done using Student 't' test for continuous variables and Chi square test for categorical variables if data was normally distributed. A *p* value of <0.05 was considered significant. OS was defined as the time from study entry until death due to any cause, or until the last survival date if still alive. The Kaplan–Meier method was used to estimate survival curves. The log-rank test was used for comparisons and the Cox proportional hazards model with a step wise backward variable selection approach (*p* < 0.1) for multivariate analysis and to obtain hazard ratios with confidence intervals.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical clearance was obtained from the institute's ethics committee.

Results

The baseline characteristics of the patients are depicted in Table 1. Ten patients were included in this study of which seven were males and three were females. The median age was 72 years (range 58–79 years). The patient group included seven patients with DLBCL and three patients with high grade follicular lymphoma. Four patients had relapsed disease including one patient who had progressive disease on three chemotherapy regimens prior to enrolment in this trial. Significant comorbid illnesses were present in all patients. Four patients each had type 2 diabetes mellitus or hypertension. Two patients had established coronary artery disease. One patient had deep venous thrombosis at the time of enrolment and was treated with enoxaparin. One patient had a prior history of adenocarcinoma of the ascending colon and had undergone surgery and chemotherapy prior to enrolment in the trial. ECOG performance status was III or IV in three quarters of the patients enrolled. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score was calculated for all patients [11]. For the purposes of this study, a chemotherapy toxicity score equivalent to CHOP chemotherapy was utilized. All patients had medium–high or high scores (median 8, range 7–11). The Revised International Prognostic Index and the Follicular Lymphoma International Prognostic Index was assessed in patients with DLBCL and follicular lymphoma respectively. Only one patient had a low FLIPI out of the enrolled patients. Eight patients either had intermediate or high risk

Table 1 Baseline demographic and clinical characteristics

Parameter	N = 10
<i>Sex [n (%)]</i>	
Female	3 (30)
Male	7 (70)
Age (years), median (min, max)	72 (58, 79)
<i>ECOG performance status [n (%)]</i>	
1	2 (20)
2	2 (20)
3	1 (10)
4	5 (50)
<i>CRASH Score</i>	
Low	0 (0)
Medium–High	9 (90)
High	1 (10)
<i>Stage (Ann Arbor staging) [n (%)]</i>	
I	1 (10)
II	1 (10)
III	3 (30)
IV	5 (50)
<i>B symptoms [n (%)]</i>	
No	2 (20)
Yes	8 (80)
<i>IPI/FLIPI [n (%)]</i>	
2	2 (20)
3	4 (40)
4	2 (20)
5	2 (20)
<i>Primary diagnosis</i>	
DLBCL	7 (70)
FL3b	3 (30)
New onset disease	6 (60)
Relapsed disease	4 (40)
Median number of prior chemotherapy regimens	2
<i>Prior regimens^a</i>	
R-CHOP	3 (30)
R-CVP	1 (10)
BR	1 (10)
R-MINE	1 (10)
R-ICE	1 (10)

CRASH Chemotherapy Risk Assessment Scale for High-Age Patients, IPI International Prognostic Index, FLIPI Follicular Lymphoma International Prognostic Index, DLBCL Diffuse Large B cell Lymphoma, FL3b Follicular Lymphoma Type 3b, R-CHOP Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone, R-CVP Rituximab, Cyclophosphamide, Vincristine, Prednisolone, BR Bendamustine, Rituximab, R-MINE Rituximab, Mesna, Ifosfamide, Mitoxantrone, Etoposide, R-ICE Rituximab, Ifosfamide, Cisplatin, Etoposide

^a Some patients received more than one chemotherapy regimen

prognostic indices. The patients included in the trial were either ineligible for standard RCHOP chemotherapy due to significant additional systemic illnesses (such as coronary artery disease with impaired left ventricular ejection fraction), extreme frailty or had progressive disease or relapse after previous treatment with standard chemotherapy regimens. In the absence of this chemotherapy protocol, these patients would have received either palliative care or metronomic therapy.

All patients received the L-PROBe protocol as described without any dose reductions. Thirty-three cycles of chemotherapy were administered to the ten patients available for analysis. Three patients were able to control the full course of six cycles of chemotherapy. One patient received four cycles and was eligible for interim assessment. One patient with primary progressive DLBCL progressed after two cycles of L-PROBe chemotherapy as well and moved on to palliative radiation therapy, eventually succumbing to progressive disease. One patient withdrew consent after three cycles of chemotherapy complicated by the development of cryptococcal meningitis. The patient eventually succumbed to complications related to progressive disease and sepsis. One patient withdrew consent after one cycle of chemotherapy due to severe debility. Two patients died while on chemotherapy due to cardiovascular complications. Both patients sustained myocardial infarction.

The four patients that were able to complete four cycles of chemotherapy and were eligible for interim assessment by PET-CT scan showed favourable responses to chemotherapy in the form of disappearance of FDG avid lesions and reduction in the size and number of involved nodal or extranodal areas, indicating an overall response rate of 40 %. Three patients (30 %) who completed six cycles of chemotherapy fulfilled criteria for complete remission (CR).

Tolerance and Safety

The most common haematological toxicity observed was neutropenia (60 %) patients and was grade 3–4 in 30 % cases. Three patients required inpatient care for febrile neutropenia along with growth factor support. All cases of febrile neutropenia occurred after three or more cycles of L-PROBe chemotherapy. Of note, two of these patients had bone marrow involvement at the baseline. The appearance of neutropenia was noted in two patients only towards the end of their treatment schedules. This may indicate a role for up front use of growth factors in such cases, as is frequently seen in patients undergoing standard chemotherapy regimens. Grade 3 anaemia was also seen in the same group of patients towards the end of their treatment courses. Thrombocytopenia was noted in only one patient after

the sixth cycle of chemotherapy and was present in conjunction with grade 3 neutropenia and anaemia. Neutropenia is a major cause for morbidity and mortality in elderly patients undergoing chemotherapy for aggressive lymphoma. Growth factor support is frequently required in such cases from the first cycle of chemotherapy itself. Alternative regimens such as bendamustine-rituximab are not associated with significant neutropenia. Grade 3–4 neutropenia was seen in 29 % of elderly patients with indolent or mantle cell lymphoma treated with bendamustine-rituximab versus 69 % in patients treated with RCHOP in an open-label, multicentre, randomised, phase 3 non-inferiority trial conducted in Germany [12]. The lenalidomide-bendamustine-rituximab combination studied in elderly patients with aggressive lymphoma was associated with grade 3–4 neutropenia in 23 % patients [9]. In the combination of lenalidomide with RCHOP, the rate of grade 3–4 neutropenia was 28 % and G-CSF was used in 89 % of cycles administered [13]. The incidence of grade 3–4 neutropenia in the present study may have been higher due to the presence of bone marrow involvement in 50 % of the cases. The presence of an already compromised bone marrow reserve, advanced age and general debility may have resulted in a reduced tolerance to the myelosuppressive effect of lenalidomide. Delayed neutropenia has also been described in some patients receiving rituximab and may have contributed to the development of neutropenia in this set of patients.

No fresh thrombotic events were seen in any of the study population. All patients received prophylaxis with 100 mg of aspirin from enrolment to one month after the last dose of lenalidomide. One patient had deep venous thrombosis at baseline and received therapeutic dose enoxaparin instead of aspirin.

Non haematological toxicities were seen in all patients. Nausea and vomiting were universal but mild (grade 1) and well tolerated in all cases. Anorexia was also seen in all patients however this was also mild and transient. No parenteral nutrition or nasogastric feeding was required in any patient. Constipation was seen in nine patients (90 %) and was grade 3–4 in two patients (20 %). This is likely to be due to the concomitant use of lenalidomide and vincristine. Vincristine is associated with the development of autonomic neuropathy that may present as severe constipation [14]. Constipation was seen in 30 % of patients treated with lenalidomide and rituximab for relapsed/refractory lymphoma [15]. Chronic constipation is a common problem in elderly patients due to reduced gut motility and low residue diet. This is likely to worsen when drugs that are known to cause constipation are used. The prophylactic use of stool softeners and laxatives reduced the morbidity due to constipation and provided symptomatic relief. Paralytic ileus was not seen in any of the patients.

Alopecia was seen in all patients but was manifested by thinning of hair or patchy hair loss (grade 1). Although chemotherapy induced alopecia is not a life-threatening adverse event, it can have profound psychosocial and quality-of-life consequences, resulting in anxiety, depression, negative body image, lowered self-esteem, and a reduced sense of well-being. The alopecia noted in the present series is likely to be due to the use of vincristine. Rash or other dermatological adverse events were not seen in any patient.

Fatigue was seen in all patients and was grade 3–4 in the majority (60 %). This finding is similar to that noted by Wang et al. [16] in a trial of lenalidomide and rituximab in elderly patients with relapsed or refractory lymphoma where the total incidence was 81 %. The high incidence of grade 3–4 fatigue in the present study may reflect the poorer performance status in this set of patients wherein 60 % had a performance status of 3 or greater whereas the patients included in the lenalidomide-rituximab trial had performance status of 2 or less. The poorer performance status in the group studied may explain the proportionately greater severity of this and other non-haematological adverse events.

Outcomes

Despite there being only four patients available for interim analysis of response, all patients who completed four cycles of chemotherapy demonstrated encouraging responses to L-PROBe chemotherapy, with an overall response rate of 40 % and a median survival of 120 days (range 14–286 days). The response rates reported in two similar trials incorporating lenalidomide with bendamustine-rituximab and RCHOP in aggressive lymphomas were 37.5 and 91 % respectively [9, 13]. The patients belonging to the LRCHOP21 group had better performance status than the patients in the BRL group which were specifically chosen as they were unfit to receive anthracycline based therapy. The type of patients selected for the present trial included elderly patients that had either progressed or relapsed after standard chemotherapy containing anthracyclines or were unable to receive standard chemotherapy. The proportion of patients with poor performance status in the present study was also higher than that incorporated in both the above studies where patients had performance statuses of 2 or less. These factors may explain the similar response rates in the present study and the trial by Hitz et al. [9] utilising a similar chemotherapy regimen. We compared the outcomes of patients with high CRASH scores (≥ 8) to those with lower scores (< 8). Of the three patients with lower CRASH scores, two were able to complete the chemotherapy course. One patient had progressive disease refractory to

multiple lines of chemotherapy and progressed while on L-PROBe as well. Five of the remaining eight patients were unable to complete therapy due to complications like sepsis, progression of disease or severe debility.

Encouragingly, two out of the three patients with previously treated disease responded to L-PROBe and were able to achieve remission. One patient had primary progressive disease and did not respond to any treatment.

Discussion

The treatment of elderly patients with aggressive lymphoma is challenging. Due to improvements in basic healthcare and an ageing population, the focus has shifted to this expanding group of individuals that, until recently, was relegated to receive palliative care or reduced toxicity regimens due to intolerance to standard chemotherapeutic agents. The advent of better supportive care including the use of growth factors has enabled the use of regimens such as RCHOP even in elderly patients [17]. Despite these advances, elderly patients are often not considered suitable for standard chemotherapy regimens due to the presence of significant comorbid illnesses especially cardiovascular disease, which precludes the use of anthracyclines such as doxorubicin. In order to treat these individuals effectively while simultaneously limiting serious chemotoxicity, alternative regimens such as the combination of bendamustine and rituximab have been developed. Despite displaying impressive activity in indolent lymphomas, the reports in aggressive or relapsed disease have been less encouraging. The addition of the immunomodulatory agent lenalidomide to these regimens has been studied in small series recently. There have been encouraging reports of the efficacy of lenalidomide in patients with relapsed and refractory disease, as well as in those patients with new onset disease who are unable to receive standard chemotherapy.

Bendamustine has been shown to retain activity even in patients previously treated and refractory to rituximab, making it an important drug in this subset of patients. Lenalidomide has also been shown to have potent antitumor activity in patients with refractory or relapsed aggressive lymphoma [18]. The combination of lenalidomide with rituximab is active in elderly patients with relapsed/refractory diffuse large B cell lymphoma with a high proportion of patients achieving a complete remission (CR) with lenalidomide maintenance [8]. The potential synergistic activity of lenalidomide with bendamustine was assessed in a phase I trial of bendamustine, rituximab and lenalidomide in a small group of elderly patients with aggressive B cell lymphoma who were not eligible for anthracycline based therapy [9]. Although prior regimens

utilising bendamustine in doses of 120 mg/m² have been described, this trial included a bendamustine dosage of 75 mg/m². An intermediate dose of 90 mg/m² was used in our trial. This dosage has been described in combination with rituximab in a phase II study in fourteen elderly patients (≥ 80 years) with aggressive B-cell lymphomas who were not eligible for R-CHOP or who did not agree to aggressive treatment [19]. The rationale for using an intermediate dose in our study was the potential for cytopenias when used in combination with another potentially myelosuppressive agent such as lenalidomide. The dose of lenalidomide was also reduced in our study to 10 mg per day for 14 days as opposed to the usual monotherapy dose of 20 mg per day [6]. The duration of therapy was also reduced to 14 days as opposed to 21 days in order to permit sufficient time for marrow recovery and limit the toxicity. A similar protocol was used in a phase I trial of lenalidomide in combination with RCHOP in elderly, untreated patients with DLBCL [13]. Vincristine was included in our trial as it has potent antitumor activity without causing significant myelosuppression. The combination of lenalidomide, rituximab, bendamustine, vincristine and prednisolone was therefore considered an acceptable alternative to conventional chemotherapy in elderly patients with aggressive Non-Hodgkin Lymphoma. Thus, a combination of two safe and effective older agents (vincristine and prednisolone) with a chemotherapy agent with a novel mechanism of action and efficacy in relapsed disease (bendamustine), an immunomodulatory drug with antineoplastic activity (lenalidomide) and an immunotherapeutic agent (rituximab) was considered optimal for the purpose defined. The response rate noted in this trial was less than that seen in other trials in comparable populations. A phase I trial of lenalidomide in combination with rituximab and bendamustine in elderly patients showed a partial response in 25 % patients and a complete response in 12.5 % patients [9]. A phase I study of lenalidomide in combination with RCHOP in elderly patients with DLBCL showed a remarkable response rate of 90 % however haematological toxicities were significant [13]. Studies conducted in relapsed and refractory disease showed worse outcomes with overall response rates of 37.5 and 35 % in patients treated with lenalidomide-rituximab-bendamustine and lenalidomide-rituximab respectively [8, 9]. One possible reason for the lower response rate in the present series of patients may be due to the selection of cases, particularly the inclusion of patients with relapsed and progressive disease in addition to those with new onset disease. The inclusion of patients with significant cardiovascular disease may have contributed to mortality in two cases that may have otherwise been eligible for assessment of response.

Another intriguing facet that may have affected outcomes has been the differential outcomes noted in patients

with non-germinal centre B-cell (GCB) phenotype DLBCL. Immunohistochemistry algorithms and recently, gene expression profiling (GEP) has divided DLBCL into distinct subgroups, the Germinal Centre B-Cell phenotype (GCB) and non-GCB variants (referred to as Activated B-Cell in GEP studies) [20, 21]. Patients with non-GCB phenotypes have been found to have inferior outcomes when compared with GCB phenotype DLBCLs [20]. Lenalidomide appears to have higher activity in this subtype of DLBCL when used as a single agent in relapsed/refractory DLBCL [22]. This effect is based on the synthetic lethality of lenalidomide in non-GCB tumour cells, wherein enhanced interferon β production leads to cell death [23]. Other mechanisms of action in this tumour type include cereblon dependent downregulation of transcription factors such as IRF4 and SPIB. Studies of lenalidomide in combination with other chemotherapeutic agents have also shown similar outcomes, with there being significant improvement in progression free and overall survival in patients with non-GCB phenotype DLBCL treated with RCHOP versus R2CHOP [10, 24]. A large randomized phase II clinical trial comparing RCHOP to R2CHOP in DLBCL classified on the basis of GEP is currently recruiting participants (NCT01856192).

This study incorporated patients with poor performance status, relapsed and/or refractory disease and advanced age in order to demonstrate the utility of this novel chemotherapy protocol even in patients who would be thought to be unable to receive intensive chemotherapy. Despite these factors, one-third of the patients enrolled responded well to therapy. The haematological adverse events noted were primarily related to neutropenic fever and its complications. The prophylactic use of G-CSF in patients considered to be at high risk for neutropenia may reduce the incidence of this complication.

Non Haematological toxicity was seen in all patients. Constipation and fatigue caused significant morbidity in these patients and was likely to be related to the poor performance status and pre-existing gut dysmotility. The concomitant use of lenalidomide and vincristine, both known to cause constipation, is likely to have contributed to the severity of this condition. Prophylactic usage of stool softeners or laxatives may be useful in these cases. Severe fatigue was present in most patients at the baseline. Lenalidomide has been associated with significant fatigue and likely worsened this complaint in the enrolled patients.

The use of this novel chemotherapy regimen in a larger series of patients may provide more encouraging results, especially in the context of patients with very poor performance status and high risk disease. Further studies are indicated utilizing this regimen in patients with better performance status and less comorbidity.

Limitations

The sample size was small in the present study and therefore robust statistical information cannot be generated from the current data. The selection of patients with advanced age, aggressive disease and poor performance status was instrumental in there being a smaller cohort of patients available for enrolment. In the present scenario, most patients with this combination of factors would not be considered for standard chemotherapy regimens and would instead receive palliative care or reduced intensity regimens. In attempting to provide a chemotherapy regimen with an acceptable safety profile without compromising on efficacy, the overall response rate of 40 % can be considered encouraging. The propensity for lenalidomide to cause myelosuppression especially after multiple cycles remains an important factor requiring careful consideration in these patients. The routine use of growth factor support in this subset has been described in more intensive chemotherapy regimens such as RCHOP-21 and LRCHOP-21. It is feasible that such preventive administration of G-CSF may avoid episodes of grade 3–4 neutropenia in elderly or frail patients.

Another limitation of this study has been our inability to classify patients into GCB or non-GCB phenotypes. Logistical constraints and the availability of adequate tissue in the DLBCL patients did not permit accurate subgroup classification. It is likely that patients with a non-GCB phenotype would have responded better on a lenalidomide containing chemotherapy regimen. A forthcoming study based on the same chemotherapy regimen is likely to address this deficiency.

Conclusion

L-PROBe is a novel and effective chemotherapy agent for use in elderly patients with relapsed or refractory aggressive B-cell lymphomas with an acceptable tolerability. Survival rates are similar to other chemotherapy combinations in this setting.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

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