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A Phase II trial of Bendamustine in combination with Rituximab in older patients with previously untreated Diffuse Large B-Cell Lymphoma

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Summary

Bendamustine in combination with rituximab (BR) has been associated with high response rates and acceptable toxicity in older patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Evaluation of BR is warranted in the front-line setting for DLBCL patients not eligible for anthracyclines or for the elderly. In this phase II study, we enrolled DLBCL patients aged 65 years who were poor candidates for R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) to determine the efficacy and safety of BR in previously untreated stage II–IV DLBCL. Twenty-three patients were enrolled with a median age of 80 years. 52% of patients presented with poor functional status (Eastern Cooperative Oncology Group performance score of 2). The overall response rate was 78% with 12 complete responses (52%). At a median follow up of 29 months, the median overall survival was 10.2 months and the median progression-free survival was 5.4 months. The most common grade 3/4 adverse events were haematological. Combination therapy with BR demonstrates high response rates as front-line therapy in frail older

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patients with DLBCL, but survival rates were low. BR should be used with caution in future clinical trials involving older DLBCL patients with poor functional status.

Keywords

DLBCL; elderly patients; bendamustine; rituximab; lymphoma

Introduction

Non-Hodgkin lymphoma (NHL) is the seventh most common type of cancer with over 70,000 new cases of NHL diagnosed annually in the United States (Siegel, *et al* 2015). Diffuse large B-cell lymphoma (DLBCL), an aggressive sub-type of lymphoma, is the most common type of NHL and is a disease of the elderly, with a median age of 70 years at diagnosis (Smith, *et al* 2011). A major advance in the therapy of NHL has been the development of monoclonal antibodies, such as rituximab, a chimeric anti-CD20 antibody. Chemo-immunotherapy with R-CHOP [rituximab combined with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)] has been shown to be more effective in the treatment of elderly patients with DLBCL than CHOP alone, without added toxicity (Coiffier, *et al* 2002, Feugier, *et al* 2005, Habermann, *et al* 2006), with one study showing a complete response (CR) rate of 75% and a 5-year progression-free survival (PFS) of 54% in patients receiving R-CHOP (Coiffier, *et al* 2002, Feugier, *et al* 2005). However, there were still a significant number of patients with severe adverse events in these studies including a treatment-associated death rate of up to 14% (Feugier, *et al* 2005). Given this level of toxicity associated with R-CHOP, even in a selected group of older DLBCL patients with good baseline performance status, novel therapeutic strategies are urgently needed to improve survival outcomes, especially in older patients who may not tolerate aggressive chemotherapy, such as R-CHOP.

Bendamustine is an alkylating agent with properties of a purine analogue and is approved by the U.S. Food and Drug Administration (FDA) for treatment of chronic lymphocytic leukaemia (CLL) and indolent NHL. The success of bendamustine combined with rituximab (BR) in indolent NHL (Robinson, *et al* 2008, Rummel, *et al* 2013) generated interest in the study of this combination in aggressive NHL. A phase 1 study of BR in patients with relapsed or refractory aggressive B-cell NHL found a maximum tolerated dose of 120 mg/m^2 on a 21-day cycle and showed the combination to be well tolerated with promising efficacy (Ogura, *et al* 2011). Several phase II studies of BR in patients with relapsed or refractory DLBCL who were not eligible for autologous stem cell transplant showed promising efficacy with overall good tolerance of this regimen in the salvage setting (Ohmachi, *et al* 2013, Vacirca, *et al* 2014).

Based on the promising clinical data summarized above, we conducted a phase II trial using bendamustine 90 to 120 mg/m^2/day on days 1 and 2, depending on Eastern Cooperative Oncology Group (ECOG) performance status (PS), in combination with rituximab 375 mg/m^2 on day 1 every 21 days for treatment of older patients (aged 65 years) with previously untreated stages II–IV DLBCL who were deemed to be poor candidates for R-

CHOP. The purpose of this study was to determine whether BR is a safe, feasible and effective treatment option for these patients. In addition, we conducted a geriatric assessment (Hurria, *et al* 2005) at baseline to further investigate other factors associated with toxicity and outcome in older DLBCL patients treated with chemotherapy.

Methods

Study Design and Objectives

This single arm phase II trial was designed to investigate the efficacy and safety of BR in previously untreated older patients with stage II–IV DLBCL (ClinicalTrials.gov NCT01234467). The primary end point was CR rate. Secondary end points were overall response rate (ORR), disease-free survival (DFS), PFS and overall survival (OS) at 3 years, toxicity and tolerability, and geriatric assessment (GA) at baseline.

Patient Eligibility

Patients aged 65 years or older with ECOG PS 0–3 and previously untreated histologically confirmed CD20^{+} DLBCL were eligible for the study. Patients were required to have measurable disease, either by lesions that could be accurately measured in 2 dimensions by computerized tomography with a greatest transverse diameter of 1 cm or greater or by bone marrow histopathology. Patients were required to be deemed a poor candidate for R-CHOP due to ejection fraction 45%, ECOG PS 2, or based on the treating physician's discretion. Baseline laboratory parameters included haemoglobin >80 g/l, absolute neutrophil count (ANC) >1.0 cells $\times$ 10^9/l, platelet count $> 75 \times 10^9$/l and adequate hepatic and renal function, demonstrated by aspartate aminotransferase (AST) < 2.5 x upper limit normal (ULN), total serum bilirubin < 2.5 x ULN, and serum creatinine < 1.5 x ULN. Patients with a history of hepatitis or with central nervous system involvement by lymphoma were excluded from the study. Patients from several different community sites across the state were included in this protocol through the University of North Carolina Cancer Network. All patients signed an institutional review board (IRB)-approved informed consent document for this protocol.

Treatment

Patients received bendamustine at a dose of 120 mg/m^2 infused over 60 min on days 1 and 2 of each 21-day cycle along with rituximab 375 mg/m^2 after bendamustine on day 1 of each cycle. Patients with ECOG PS of 3 at baseline were allowed to receive bendamustine at a dose of 90 mg/m^2 daily, with a dose increase to 120 mg/m^2 daily if their ECOG PS improved to 2 after 3 cycles of BR. Pre-phase steroid therapy with prednisone 100 mg/day for five days was permitted prior to the initiation of BR in patients with poor functional status at the initial presentation (Pfreundschuh, *et al* 2004). Primary prophylaxis with granulocyte colony-stimulating factor (pegfilgastrim or filgastrim) was administered as part of the protocol.

National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/ CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), were used to assess toxicity. If

patients developed grade 4 haematological or grade 3 or higher non-haematological toxicities, the cycle was prolonged to 28 days. If further toxicity occurred at the reduced dose level, the bendamustine dose was reduced to 90 mg/m^2 in patients who were receiving 120 mg/m^2. For patients who were already at 90 mg/m^2 when further toxicity occurred, study treatment was discontinued. Toxicities must have resolved to grade 2 or lower before beginning the next cycle. Treatment was postponed if ANC had not recovered to at least 1.0 $\times 10^9$/l and platelets to at least 75 $\times 10^9$/l by the time of the next cycle. If therapy was held for 14 or more days, the protocol directed treatment was discontinued.

Patients were treated for up to 8 cycles and patients were assessed for response after 3 cycles. If they had CR, they were treated for 3 additional cycles. If they failed to achieve a partial response (PR), they were removed from the protocol. If they achieved PR, they were treated for 3–5 additional cycles. Treatment was discontinued in patients with disease progression, concomitant illness preventing further treatment administration, unacceptable adverse events, or at the discretion of the patient or investigator.

Patients were also asked to complete a geriatric assessment using the tool developed by Hurria *et al* (2005) at baseline. The geriatric assessment consists of both an external evaluation completed with the assistance of research associates and a patient questionnaire. The external evaluation consists of the Blessed Orientation-Memory-Concentration (BOMC) test (Katzman, *et al* 1983, Kawas, *et al* 1995), which includes questions to screen for macroscopic cognitive impairment, the Karnofsky Performance Status tool (KPS) and the Timed Up and Go (TUG) test (Podsiadlo and Richardson 1991, Shumway-Cook, *et al* 2000). Patients completed a questionnaire which includes assessments designed to evaluate functional status including the Instrumental Activities of Daily Living (IADL), a subscale of the Multidimensional Functional Assessment Questionnaire (MFAQ): Older American Resources and Services (OARS) (Fillenbaum and Smyer 1981), and the Activities of Daily Living (ADL) subscale of the Medical Outcomes Study (MOS) Physical Health. The patient questionnaire also includes a self-reporting version of the KPS as well as a question asking patients to report the number of times they have fallen in the last 6 months (Teno, *et al* 1990), a co-morbidity scale (the Physical Health Section of the OARS) (Extermann, *et al* 1998), a request for patients to list all current medications they are taking (Lees and Chan 2011), an assessment of psychological distress and well-being (Kelly, *et al* 2008, Rumpf, *et al* 2001, Trainor, *et al* 2013), and evaluations of social functioning and social support (Sherbourne 1991).

Patients were evaluated every 6 months for 3 years after completion of treatment or until death. Patients removed from the study for adverse events were followed until resolution or stabilization of the adverse event and then subsequently for 3 years after discontinuation of treatment or until death.

Assessment of Efficacy

The primary endpoint for the trial was the rate of CR. Response rates were evaluated as defined by the International Harmonization Project for Response Criteria (Cheson, *et al* 2007). DFS was measured from the time of occurrence of disease-free state or attainment of CR to disease recurrence or death as a result of lymphoma or acute toxicity of treatment.

PFS was defined as the time from the start of treatment until lymphoma progression or death as a result of any cause. OS was defined as the time from start of treatment until death as a result of any cause.

Statistical Methods

Sample size was determined using historical data and the null hypothesis that the CR rate is 50% or less tested against a one-sided alternative. The trial used a Simon-like two-stage design with relaxed stopping for futility (Ivanova and Deal 2016) using CR for primary analysis and both PR and CR for futility analysis. A total sample size of 37 would be required to achieve 80% power if the true CR rate was 70% with plan to reject the null hypothesis if 24 or more patients responded out of 37. If the number of CRs plus PRs in the first 23 patients was less than 13, the trial would be stopped for futility. The type I error rate is at most 0.05, assuming a CR rate of 50% and a PR rate of at most 20%. There was a mandatory interim analysis for futility after enrolment of the first 23 patients.

An intention to treat approach was followed in all data summaries and analyses. The CR and ORR rates were estimated and 95% confidence interval (CI) computed. PFS and OS were summarized using the Kaplan-Meier method. All demographic and analytic data were summarized by descriptive statistics. P-values < 0.05 were considered statistically significant. Patients who were enrolled in the study but who voluntarily withdrew prior to treatment or never initiated treatment due to the development of inter-current illness or death were not included in the analysis.

Results

Patients

Patient characteristics are summarized in Table I. Twenty-eight patients were assessed for eligibility; 4 patients were excluded for not meeting the inclusion criteria and 1 patient eventually declined to participate. Twenty-three patients were enrolled between March 2011 and May 2013 with the majority (82%) having stage III or IV disease at baseline. The median age was 80 years (range 65–89) and 79% of patients had IPI score of ≥3. More than half the patients (52%) presented with poor functional status with ECOG score of ≥2 prior to therapy, including 6 patients with ECOG score of 3. DLBCL subtype was determined by immunohistochemistry with 7 patients with germinal centre B-cell like (GCB) subtype, 12 patients with non-GCB subtype and 4 patients not able to be classified(Hans, *et al* 2004). MYC, BCL2, and BCL6 status by fluorescence in situ hybridization (FISH) or immunohistochemistry analyses were not available at the time of enrolment in the majority of patients. Although patients with transformed lymphoma were not excluded from this study, there was only one patient enrolled in the trial with a history of previously untreated follicular lymphoma. Baseline geriatric assessment characteristics of the patients are listed in Supplementary Table 1. Of note, 4 of 18 patients (22%) experienced 2 or more falls in the past 6 months, 12 of 18 patients (67%) had impairments in their IADL, and 11 of 18 patients (61%) had a TUG score of 14 s or more or were unable to do the test.

The median number of cycles completed per patient was 6. Three out of 23 patients received an initial dose of 90 mg/m^2. Out of 23 patients included in the study, 11 patients completed treatment per protocol, 3 patients discontinued therapy secondary to adverse events, 2 patients died while receiving therapy, 2 patients withdrew from the study, 2 patients discontinued therapy because of disease progression while receiving treatment, 1 patient discontinued therapy because of clinical deterioration, 1 patient discontinued therapy due to other complicating disease (stroke) and 1 patient withdrew due to physician preference. This study represents the data after inclusion of the first 23 patients at the planned interim analysis. The data analysis was performed prior to the previously determined 3-year follow-up period because the study did not reach the initially planned sample size to determine the survival rates in a statistically significant manner as secondary objectives.

Safety/Toxicity

The major grade 3 or higher adverse events were haematological toxicities and are summarized in Table II. Common non-haematological toxicities included fatigue (70%), anorexia (52%), nausea (39%), hypoalbuminemia (30%), elevated AST (30%) and elevated alkaline phosphatase (30%) and were mostly grade 1 or 2. Three patients discontinued treatment because of adverse events: 1 patient had prolonged thrombocytopenia, 1 patient had weakness and failure to thrive and 1 patient had persistent grade 3 toxicities including infections and an overall failure to thrive.

Sixteen out of 23 patients died during the study period (Table III). Four deaths were felt to be treatment-related, five deaths were felt to be disease-related and seven deaths were secondary to other causes not considered by the investigators to be related to study treatment (see Table III for more details).

Efficacy/Response

The ORR was 78%, with 12 CRs (52%, 95% CI: 30.6%–73.2%) and six partial responses (26%, 95% CI: 10.2%–48.4%). One patient had stable disease. Progressive disease was documented in one patient and three patients were not evaluable for disease progression due to early deaths.

At the median follow-up of 29 months, the median OS was 10.2 months (95% CI, 3.8–13.3 months) and the median PFS was 5.4 months (95% CI, 3.8–10.2 months) (Figure 1). For patients with ECOG score ≥ 2, the median OS was 3.7 months compared to median OS of 10.4 months for patients with ECOG score 0–1, although this difference was not statistically significant (p=0.17). There was no significant difference in OS between patients aged 80 years and older and patients younger than 80 years (6.4 months vs 10.2 months, respectively, p = 0.43). There were also some sustained responses seen in patients, with 6 out of 7 patients who were alive at last evaluation without evidence of disease progression. The maximum PFS was 41.9 months and 3 other patients had PFS over 2 years at the time of data cut-off.

The only baseline geriatric assessment measure associated with OS and PFS was number of falls. Four out of 18 patients who had 2 or more falls in the 6 months prior to initiation had a median OS of 4.0 months compared to a median OS of 10.7 months in the 14 patients with 0 or 1 fall (p= 0.001) (Figure 2).

Four out of 9 evaluable patients (44%) with non-GCB subtype and 5 out of 7 (71%) patients with GCB subtype had CR, but this difference was not statistically significant (p=0.36). There was no significant difference in OS based on pathology subtype with mean OS of 10.5 months (95% CI: 2.6-NR) in non-GCB subtype and 9.9 months (95% CI: 2.7-NR) in GCB subtype.

Discussion

This study aimed to find a tolerable and efficacious treatment for elderly, frail patients with DLBCL.

There have been a few phase II trials investigating the safety and efficacy of BR in patients with relapsed and refractory DLBCL which showed overall good response and tolerance, with one study showing an ORR of 45.8% (Vacirca, *et al* 2014) and the other study showing an ORR of 62.7% (Ohmachi, *et al* 2013). The most frequently observed grade 3 or 4 toxicities in both studies were haematological with the non-haematological toxicities being mostly grade 1 or 2 in severity. Given the promising results and safety profile of BR in the relapsed/refractory setting, we proposed a phase II trial of BR in elderly patients with DLBCL in the first line setting. We used a dosing regimen of 120 mg/m^2 of bendamustine and a 21-day cycle to maximize response rates based on the data by Ohmachi et al (2013), which showed promising efficacy and tolerability in patients with relapsed/refractory DLBCL.

This is the first prospective trial investigating the safety and efficacy of BR specifically in patients with previously untreated DLBCL. Although the response rates were high with ORR greater than 75% and a CR rate of 52%, OS rates were low with a median of less than one year in the current study.

The results of our study are comparable to recently published retrospective studies of BR in the elderly. The safety and efficacy of BR was retrospectively assessed in 20 consecutive patients with aggressive lymphoma in the first line or relapsed/refractory setting (Horn, *et al* 2012). The ORR was 55% with a median PFS and OS of 8.3 and 19.4 months, respectively. This was a younger population than that of our study with a median age of 72 years. In addition, patients in this study received a lower dose of bendamustine, 90 mg/m^2 in a 28-day cycle. In another retrospective analysis, 13 patients with DLBCL who received BR as first line therapy were evaluated for response, with an ORR of 62% and median PFS and OS of 6 and 9 months, respectively (Walter, *et al* 2012). There has been one other phase II trial investigating the safety and efficacy of BR in the first line setting, but this trial included patients with several different types of aggressive B-cell lymphoma, as opposed to DLBCL alone (Weidmann, *et al* 2011). This trial enrolled 14 patients who were aged 80 years or older (median age of 85 years) with aggressive B-cell lymphomas who did not qualify for treatment with R-CHOP. The CR rate was 54% with a 15% PR rate and median OS and PFS of 7.7 months.

The toxicity profile of the BR combination in our study was similar to that seen in other investigations of this regimen, with haematological toxicities being the most common

adverse events. There were, however, four deaths that were felt to be treatment-related and an overall high number of deaths with 16 patients dying during the evaluation period. At the time of the mandatory interim analysis for futility, the one-year PFS was 26% with 95% CI of 13% to 52%. Because this PFS rate was predictive of lower than a 2 or 3 year-PFS of around 50% or higher seen in historical controls of elderly with DLBCL treated with other regimens (Alvarez, *et al* 2014, Hainsworth, *et al* 2010, Jung, *et al* 2015, Kasahara, *et al* 2011, Kreher, *et al* 2014, Meguro, *et al* 2012, Peyrade, *et al* 2011), the decision was made to terminate the trial at the time of interim analysis. The lower survival rates in our study are probably related to the fact that the population in the present trial was more "unfit" and frail than the other populations studied with the presence of a high IPI, an average age of 80 years, and more than half of the patients having a performance status of 2 or 3. In addition, a large proportion of our patients had significant impairments, as demonstrated by their baseline geriatric assessment (Table S1). These patients had significant comorbidities at baseline, which explains the higher number of unrelated deaths during or after therapy. However, it is important to note that this population may be more representative of the older and frail population commonly seen in clinical practice. In addition, as part of the University of North Carolina Cancer Network, this study was able to recruit patients from a variety of practice settings across the state, which also suggests that the patients in this study may be a more accurate representation of patients seen in the actual clinical setting.

There have been several studies investigating dose variations of R-CHOP in elderly or frail patients as an alternative therapy for DLBCL. A phase 2 study of rituximab combined with low-dose CHOP (R-mini-CHOP) in patients greater than 80 years old had a median OS of 29 months, which, is more favourable than that seen in this study (Peyrade, *et al* 2011). The median age of 83 years in the R-mini-CHOP study is comparable to that in the present study, but it included a much more "fit" elderly population with the majority of patients having an ECOG PS of 0 and 1 and no significant comorbidities, including contraindication to receiving doxorubicin. The results of a retrospective study of patients with newly diagnosed DLBCL who were felt to be unfit to receive R-CHOP and instead received either R-mini-CHOP or BR showed a more limited survival (Hammersen, *et al* 2014). The ORR for BR was 64% with a median PFS and OS of 6 and 15 months, respectively. The results for R-mini-CHOP in the same study were comparable to the BR group with an ORR of 60% and median PFS and OS of 6 and 8 months, respectively. These patients had a median age greater than 80 years and were less "fit" than those in the other studies discussed, with about one third of patients having an ECOG score of 2 or greater. The results of the above studies suggest that dose variations of R-CHOP may be a feasible alternative regimen in carefully selected elderly patients with a good performance status. Whether the results with such an approach would be an improvement over those described in this report with BR is unknown.

Lastly, a geriatric assessment was utilized in this study, and a recent history of a fall was predictive of worse survival in a statistically significant manner. Obtaining a history of falls is a relatively simple intervention and it may serve as a strong predictive measure of outcome when considering any potentially morbid chemotherapy regimen in elderly patients with DLBCL. This study was limited by a small sample size because it was terminated prematurely at the time of interim analysis. In addition, more complete post-treatment

geriatric assessment data at the time of follow-up would have strengthened the geriatric assessment analysis.

In summary, combination therapy with BR demonstrated high response rates in the first-line setting in an elderly population with DLBCL who were deemed poor candidates for R-CHOP therapy, but survival rates were still low. Therefore, BR, especially with high dose bendamustine, should be used with caution in future clinical trials involving older patients with DLBCL with poor functional status. Nevertheless, high response rates and sustained responses in some of the responders are encouraging, and use of this regimen with lower doses of drugs, fewer cycles of therapy, or in combination with a novel agent may be worth consideration in this less robust population. Notably, patients enrolled in this trial were more representative of the actual clinical setting, which makes this study highly relevant for clinical practice. There is currently no standard of care in the treatment of elderly and less fit patients with DLBCL, and more clinical trials of alternative therapies are urgently needed to improve survival outcomes in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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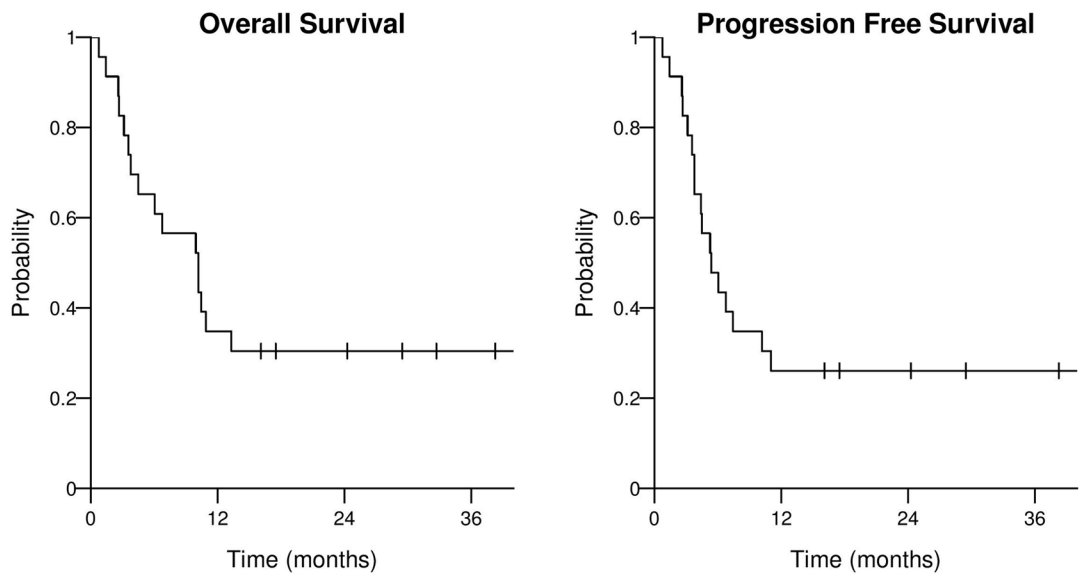
Figure 1.
Kaplan-Meier estimates of median overall survival (OS) and progression-free survival (PFS). The median OS was 10.2 months (95% confidence interval [CI]: 3.8–13.3). The median PFS was 5.4 months (95% CI: 3.8, 10.2).
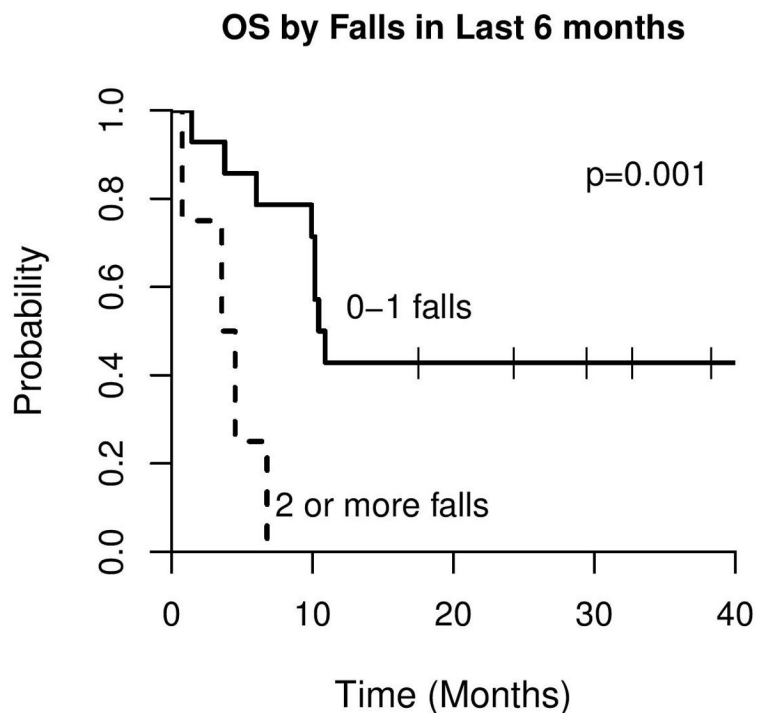
Figure 2.
Kaplan-Meier estimates of median overall survival (OS) based on number of falls. The median OS was 4.0 months (95% confidence interval [CI]: 0.77, 6.8) for patients with 2 or more falls and 10.7 months (95% CI: 6.0, not reached) for patients with 0 or 1 falls.

Table I

Patient Characteristics (N=23)

Variable	N (%)
Age, years (median, range)	80 (65–89)
Gender	
Male	12 (52%)
Female	11 (48%)
Race	
White	21 (91%)
Other	2 (9%)
Stage	
II	4 (17%)
III	7 (30%)
IV	12 (52%)
ECOG Performance Status	
0	2 (9%)
1	9 (39%)
2	6 (26%)
3	6 (26%)
International Prognostic Index	
2	5 (22%)
3	5 (22%)
4	8 (35%)
5	5 (22%)
Lactate dehydrogenase	
Normal	8 (35%)
Elevated	15 (65%)
Pathology Subtype	
Non-Germinal Centre	12 (52%)
Germinal Centre	7 (30%)
Not classified	4 (17%)

ECOG, Eastern Cooperative Oncology Group

Table II

Toxicity

TOXICITY	Number of Patients with Grade 3	Number of Patients with Grade 4	Percentage of all patients with grade 3
Haematological Toxicities			
Lymphopenia	8	8	70%
Anaemia	6	0	26%
Neutropenia	1	3	17%
Thrombocytopenia	1	3	17%
Lymphocytosis	1	0	4%
Non-Haematological Toxicities			
Fatigue	3	0	13%
Anorexia	0	2	9%
Hyperglycaemia	2	0	9%
Urinary tract infection	2	0	9%
Arthralgia	1	0	4%
Atrial fibrillation	1	0	4%
Cognitive disturbance	1	0	4%
Generalized muscle weakness	1	0	4%
Heart failure	0	1	4%
Hypoalbuminaemia	1	0	4%
Hyponatraemia	1	0	4%
Infusion related reaction	1	0	4%
Myalgia	1	0	4%
Nausea	1	0	4%
Pleural effusion	1	0	4%
Maculopapular rash	1	0	4%
Sepsis	0	1	4%
Skin infection	1	0	4%

Table III

Cause of Death.

Age (years)	Sex	Response	Cycles completed (n)	Description
Treatment-Related				
81	F	PR	3	Anorexia[1]
69	M	NE	3	Pneumonia
78	F	PR	6	Pneumonia
79	F	CR	5	Anorexia[1]
Disease-Related				
78	M	PR	5	Disease progression after 5 cycles
85	F	PD	2	Disease progression after 2 cycles
72	M	PR	6	Disease progression after 6 cycles
83	F	CR	6	Disease progression after 6 cycles
84	M	CR	6	Disease progression after 6 cycles
Non-Treatment or Disease Related				
73	M	CR	6	Acute cerebral vascular accident after completion of therapy
86	F	SD	2	Congestive heart failure with underlying heart disease
87	F	CR	4	Femoral neck fracture
88	M	NE	1	Treatment stopped after cerebral vascular accident
87	M	CR	3	Unknown. Patient withdrew from the study
85	M	NE	2	Unknown. Sudden death at home
65	F	CR	6	Respiratory failure secondary to pneumonia after treatment completed

M= male, F= female, CR = Complete response, PR = Partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

[1] A potential causal relationship was determined between treatment and anorexia, although this was not definitive.