original article

Annals of Oncology 22: 1622–1627, 2011
doi:10.1093/annonc/mdq626
Published online 12 January 2011

An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma

T. E. Witzig[1]*, J. M. Vose[2], P. L. Zinzani[3], C. B. Reeder[4], R. Buckstein[5], J. A. Polikoff[6], R. Bouabdallah[7], C. Haioun[8], H. Tilly[9], P. Guo[10], D. Pietronigro[10], A. L. Ervin-Haynes[10] & M. S. Czuczman[11]

[1]*Department of Medicine, Division of Hematology, Mayo Clinic, Rochester;* [2]*Section of Hematology/Oncology, University of Nebraska, Omaha, USA;* [3]*Institute of Hematology and Oncology Seragnoli, University of Bologna, Bologna, Italy;* [4]*Department of Medicine, Division of Hematology, Mayo Clinic, Scottsdale, USA;* [5]*Department of Hematology, Sunnybrook Odette Cancer Center, Toronto, Canada;* [6]*Department of Hematology/Oncology, Kaiser Permanente Medical Group, San Diego, USA;* [7]*Department of Hematology, Institut Paoli Calmettes, Marseilles;* [8]*Department of Hôpital Henri Mondor-AP-HP, Créteil;* [9]*Department of Centre Henri Becquerel, Rouen, France;* [10]*Department of Celgene Corporation, Summit;* [11]*Department of Medicine, Lymphoma/Myeloma Service, Roswell Park Cancer Institute, Buffalo, USA*

Received 17 March 2010; revised 1 July 2010; accepted 22 September 2010

Background: Lenalidomide is an immunomodulatory agent with antitumor activity in B-cell malignancies. This phase II trial aimed to demonstrate the safety and efficacy of lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular grade 3 lymphoma (FL-III), or transformed lymphoma (TL).

Methods: Patients received oral lenalidomide 25 mg on days 1–21 every 28 days as tolerated or until progression. The primary end point was overall response rate (ORR).

Results: Two hundred and seventeen patients enrolled and received lenalidomide. The ORR was 35% (77/217), with 13% (29/217) complete remission (CR), 22% (48/217) partial remission, and 21% (45/217) with stable disease. The ORR for DLBCL was 28% (30/108), 42% (24/57) for MCL, 42% (8/19) for FL-III, and 45% (15/33) for TL. Median progression-free survival for all 217 patients was 3.7 months [95% confidence interval (CI) 2.7–5.1]. For 77 responders, the median response duration lasted 10.6 months (95% CI 7.0–NR). Median response duration was not reached in 29 patients who achieved a CR and in responding patients with FL-III or MCL. The most common adverse event was myelosuppression with grade 4 neutropenia and thrombocytopenia in 17% and 6%, respectively.

Conclusion: Lenalidomide is well tolerated and produces durable responses in patients with relapsed or refractory aggressive non-Hodgkin's lymphoma.

Key words: large cell lymphoma, lenalidomide, mantle cell lymphoma

introduction

Non-Hodgkin's lymphoma (NHL) is the fifth most common cancer in the United States, with nearly 66 000 new cases and 19 000 deaths each year [1]. The most common types of aggressive NHL include diffuse large B-Cell lymphoma (DLBCL), transformed lymphoma (TL), mantle cell lymphoma (MCL), and grade 3 follicular lymphoma (FL-III). Survival rates for aggressive NHL are variable. In DLBCL, treatment with R-CHOP has increased the cure rate; however, up to 40% of patients are not cured with initial therapy [2, 3]. For patients not responding to salvage regimens or stem-cell transplantation (SCT), the 1-year overall survival (OS) rate is ∼22% [4].

Improving survival has also been a challenge for patients with MCL. Although new intensive treatment regimens and salvage programs can achieve overall response rates (ORRs) of up to 90%, many patients still relapse [5]. The Nordic group recently reported a 96% ORR with induction chemoimmunotherapy followed by high-dose chemotherapy and SCT [6]. During follow-up, the patients received preemptive rituximab at signs of increasing minimal residual disease. With such a proactive approach, 65% of patients are projected to be progression free at 6 years. Many MCL patients are older adults and not candidates for this type of SCT-based therapy. When such patients relapse, the outlook is poor with median response durations lasting ∼6 months and median OS of 1–2 years [7–10]. Current treatment options also have limited efficacy for patients with TL. In a recent population-based analysis of 600 TL patients treated in the pre-rituximab era, the median OS was only 1.7 years [11].

Correspondence to: Dr T. E. Witzig, Hematology, Mayo Clinic, Stabile 628, 200 First Street SW, Rochester, MN 55905 USA. Tel: +1-507-266-2040; Fax: +1-507-266-9277; E-mail: witzig@mayo.edu

The survival results obtained with current treatment options for patients with relapsed or refractory aggressive NHL clearly indicate that new agents and approaches are needed. This is particularly important for the older adult patient population who are not SCT candidates and do not tolerate aggressive salvage regimens but are able and willing to accept treatments with mild or moderate toxic effects.

Lenalidomide (Revlimid; Celgene Corporation, Summit, NJ) is an immunomodulatory agent with multiple mechanisms of action that have the potential to interfere with aggressive NHL growth and survival. Lenalidomide can alter the tumor cell microenvironment and stimulate the activity of effector cells such as cytotoxic T and natural killer cells, [12, 13] and enhance the cytolytic action of T cells [14, 15]. *In vitro* studies show that lenalidomide exhibits both antiproliferative and antiangiogenic activity through up-regulation of tumor suppressor genes, which induce G1 growth arrest and inhibition cell signaling [16, 17].

There have been two prior pilot studies of single-agent lenalidomide for NHL. In NHL-001, 43 patients with relapsed or refractory indolent NHL treated with lenalidomide achieved a 23% ORR and a median response duration of >16.5 months [18]. Conducted exclusively in the United States, NHL-002 was a pilot study to assess the ORR to 12 months of single-agent lenalidomide in 49 patients with relapsed or refractory aggressive NHL [19]. Responses were observed in 35% of all patients and 53% in the subset of 15 patients with relapsed MCL [20]. Based on these encouraging preliminary results, we initiated a large international phase II trial (NHL-003; NCT00413036) to evaluate the clinical utility of single-agent lenalidomide in relapsed or refractory aggressive NHL.

patients and methods

This protocol was approved by the responsible Institutional Review Board or Ethics Committee at each participating center in accordance with local rules and regulations. All patients provided written informed consent before enrollment. The study was conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization Guidelines, and Title 21 of the US Code of Federal Regulations.

study design

This was a phase II, multicenter, single-arm, open-label study during which patients with relapsed or refractory aggressive NHL self-administered oral lenalidomide 25 mg once daily on days 1–21 of every 28-day cycle until disease progression or unacceptable adverse events. Patients were evaluated for toxicity each cycle and for response every two cycles until progression or when the patient went off-study for other reasons. All patients who discontinued treatment without progression were followed until progression or until the next NHL treatment was given. An internal data monitoring committee reviewed the safety data on an ongoing basis throughout the study.

patients

Eligible patients were 18 years or older with biopsy-proven relapsed or refractory aggressive NHL confirmed as DLBCL, MCL, FL-III, or TL. The disease was required to be ≥2 cm in a single dimension as measured by computerized tomography (CT). Other eligibility criteria were an Eastern Cooperative Oncology Group performance status score of zero, one, or two, a life expectancy of ≥90 days, off standard or experimental treatment for ≥28 days, absolute neutrophil count (ANC) ≥1500 cells/mm^3 (1.5×10^9/l), platelet count ≥60 000/mm^3 (60×10^9/l), calculated creatinine clearance (i.e. Cockroft–Gault formula) ≥50 ml/min, serum creatinine ≤2.5 mg/dl (221 μmol/l), serum aspartate aminotransferase or alanine aminotransferase ≤5.0 × upper limit of normal, and serum total bilirubin ≤2.0 mg/dl (34 μmol/l). Exclusion criteria were as follows: patients who were candidates and willing to undergo autologous SCT; active central nervous system disease; known infection with the HIV, pregnant, or lactating; active infection including hepatitis B or C; other active malignancies; serious cardiac conditions such as class III or IV heart failure or a clinically significant cardiac arrhythmia that was symptomatic or required treatment; prior allergic or cutaneous reaction to thalidomide; prior lenalidomide treatment; or grade ≥2 neuropathy.

response and safety assessments

Tumor response to lenalidomide was evaluated by the local investigator using the International Workshop Lymphoma Response Criteria [21]. When evaluating response to the most recent therapy a patient received before study enrollment, the following definitions were used: stable disease (SD) was defined as having a lesser response than a partial response (PR) without indications of progressive disease (PD) while on study treatment. A complete remission (CR) was defined as the complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy and normalization of all biochemical abnormalities (e.g. lactate dehydrogenase) associated with NHL. An unconfirmed CR (CRu) fulfilled the criteria for a CR but exhibited either a residual lymph node mass >1.5 cm, which regressed by more than 75% in the sum of the products of the greatest diameters, or an indeterminate bone marrow. Refractory to last therapy was defined as a best response of either SD or PD to their most recent anti-NHL regimen. Patients with no response or a progression-free survival (PFS) of <6 months in response to their last rituximab treatment (single agent or part of a multidrug regimen) were categorized as rituximab refractory. Baseline and on-study methods for response assessment had to be identical and included CT and/or magnetic resonance imaging scanning of measurable lesions. Bone marrow biopsy was repeated only if the patient had marrow involvement at baseline and met all other criteria for CR. Safety assessments included blood pressure and pulse, hematology and chemistry laboratory evaluations, serum thyroid function tests, serum/urine beta-human chorionic gonadotropin (females of childbearing potential only), and adverse events.

statistical analyses

ORR was the primary end point, which was defined as the proportion of patients with a best response of either a CR/CRu or PR. Secondary end points included response duration, time to progression (TTP), PFS, and safety. Adverse events and their severity were classified using the National Cancer Institute—Common Terminology Criteria for Adverse Events version 3.0. Estimates for ORR are provided using exact two-sided 95% confidence intervals (CIs), which are also provided for each corresponding variable assessing a median time-to-event. Kaplan–Meier estimates were used to characterize PFS, TTP, and duration of response. A one-stage binomial design was used to test the null hypothesis that the ORR was ≤20% versus the alternative hypothesis that ORR was ≥30%. For a planned sample size of 180 subjects evaluable for efficacy, at least 45 responses would reject the null hypothesis in favor of the alternative, with a lower limit of the 95% one-sided CI of >20%. Assuming that 10% of patients would not be evaluable for efficacy, the target for total enrollment was 200.

results

patient demographics

Between November 2006 and March 2008, 217 patients were enrolled and received lenalidomide (Table 1). Of the 48 participating centers, 17 were in the United States, 28 were in Europe (UK, Spain, Germany, France, and Italy), and 3 were in Canada.

response

The ORR for all 217 patients was 35% (77/217; 95% CI 29.1–42.2), with 13% CR/CRu (29/217; 95% CI 9.1–18.6), 22% PR (48/217; 95% CI 16.78–28.24), and 21% SD (45/217; 95% CI 15.55–26.75). Responses were observed across all the disease types (Table 2). Among 108 patients with DLBCL, 28% responded and 7% achieved a CR. The ORR was notably higher in the non-DLBCL disease types, with 42% for patients with FL-III or MCL achieving a response. This trial also had a sizeable group ($n = 33$) of patients with TL and the ORR was highest in this type at 45% with 21% CR. Responses occurred in 41% (43/105) of patients who entered the trial with relapsed disease and in 29.2% (28/96) of patients refractory to their last therapy.

Response to lenalidomide therapy was independent of the number and type of prior treatments and tumor burden.

Table 1. Patient characteristics at study entry

Characteristic	Patients ($N = 217$)
Median age, years (range)	66 (21–87)
Males, *n* (%)	140 (64.5)
Median time from diagnosis to first dose of lenalidomide, years (range)	2.7 (0.2–20.6)
Disease types, *n* (%)	
Diffuse large B-cell lymphoma	108 (49.8)
Mantle cell lymphoma	57 (26.3)
Transformed large B-cell lymphoma	33 (15.2)
Follicular lymphoma, grade III	19 (8.8)
IPI at study entry, *n* (%)	
Low risk (0–1)	44 (20.3)
Intermediate risk (2–3)	136 (62.7)
High risk (4–5)	37 (17.1)
ECOG performance status, *n* (%)	
0	90 (41.5)
1	100 (46.1)
2	25 (11.5)
Missing	2 (0.9)
Median prior treatment regimens, *n* (range)	3 (1–13)
Refractory to last therapy, *n* (%)	96 (44.2)
Refractory to rituximab, *n* (%)	117 (53.9)
Type of prior treatment regimens, *n* (%)	
Rituximab + combination chemotherapy	192 (88.5)
Combination chemotherapy	135 (62.2)
Rituximab	205 (94.5)
Bortezomib	20 (9.2)
Stem-cell transplantation	73 (33.6)

ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index.

Patients with a prior SCT had a 37% (27/73) ORR. The ORR was 33% (39/117) for rituximab refractory patients and 50% (10/20) in patients who had received prior bortezomib [50% (9/18) ORR in patients with MCL]. The International Prognostic Index (IPI) also did not significantly affect the ORR. In 60 patients with an intermediate or high IPI, the ORR was 37% and 27%, respectively. Among responders to lenalidomide, median time to response was 1.9 months (range 1.4–11.5 months), and median time to achieving a CR/CRu was 4.9 months (range 1.6–14.7 months). Thirty percent of patients achieving SD at their first disease assessment went on to achieve a response, while 25% of patients who achieved PR at their first assessment went on to achieve CR/CRu.

survival

The median PFS for all patients was 3.7 months (95% CI 2.7–5.1; Figure 1A). The 77 patients who responded to therapy achieved a median response duration lasting 10.6 months (95% CI 7.0–NR; Figure 2A). For 29 patients who achieved a CR/CRu, the median response duration has not been reached (95% CI 15.0–not reached) at a median follow-up of 9.2 months. In 48 patients with a PR, the median PFS and response duration were 7.7 months (95% CI 6.3–10.7) and 4.6 months (95% CI 3.2–8.9), respectively.

Survival end points were also assessed for each disease type (Figure 1B; Table 2). Patients with DLBCL had the shortest median PFS and response duration at 2.7 and 4.6 months, respectively. In contrast, patients with large cell NHL of the TL type had substantially better results, with a median PFS of 5.4 months and median response duration of 12.8 months. Patients with FL-III and MCL had a median PFS of 8.9 months and 5.7 months, respectively. It is notable that the median duration of response has not yet been reached for the lenalidomide responders with FL-III and MCL at a median follow-up of 6.4 and 7.1 months, respectively (Figure 2B).

safety

Lenalidomide was well tolerated by this heavily pretreated patient population. Although the median daily dose of lenalidomide was 25 mg (range 7.1–25 mg), 117 patients (53.9%) required at least one dose reduction or interruption. The median time to first dose reduction or interruption was 33 days. Among 31% (67/217) of patients who required dose reductions, 37 patients required only one reduction to 20 mg, 11 patients had two dose reductions to 15 mg, 9 patients had three dose reductions to 10 mg, and 10 patients had four dose reductions to a 5 mg daily dose. The most common reasons for dose reduction were neutropenia (56%) and thrombocytopenia (31%). Tolerability-related treatment interruptions were typically brief, lasting a median of 7 days. At data cut-off, 44 patients (20%) remain on study and 39 (18%) are still receiving study medication.

The most common adverse event of any grade or cause was reversible myelosuppression. Most common treatment-related grade 3 or 4 adverse events included neutropenia (41%), thrombocytopenia (19%), and anemia (9.2%) (Table 3). Grade 3 or 4 febrile neutropenia occurred in only 2% (5/217) of

Table 2. Response, median response duration, and median progression-free survival (PFS) achieved with lenalidomide in patients with relapsed or refractory aggressive non-Hodgkin's lymphoma by disease type

Disease type	*N*	Response, *n* (%)					Median PFS (months)	Median response duration (months)
		ORR	CR/CRu	PR	SD	PD[a]		
All patients	217	77 (35)	29 (13)	48 (22)	45	67	3.7	10.6
DLBCL	108	30 (28)	8 (7)	22 (20)	23	40	2.7	4.6
MCL	57	24 (42)	12 (21)	12 (21)	14	12	5.7	Not reached
TL	33	15 (45)	7 (21)	8 (24)	2	12	5.4	12.8
FL-III	19	8 (42)	2 (11)	6 (32)	6	3	8.9	Not reached

[a]There are an additional 28 patients who had no response assessment and are counted as nonresponders in the response rate calculations.
CR, complete remission; CRu, complete remission unconfirmed; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

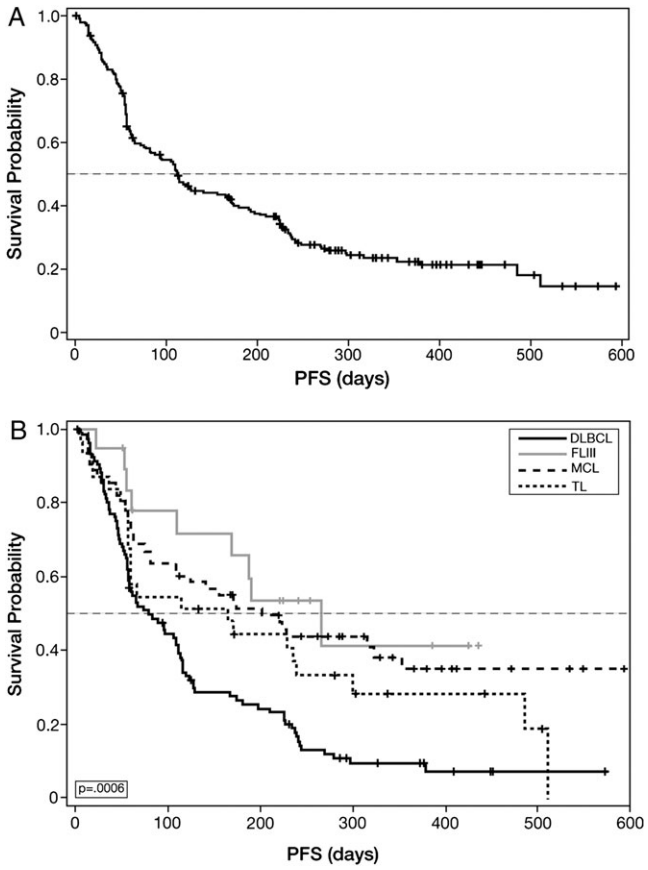

Figure 1. Kaplan–Meier estimate of progression-free survival (PFS) for all 217 patients (A) and by disease type (B). DLBCL, diffuse large B-cell lymphoma; FL-III, follicular grade 3 lymphoma; MCL, mantle cell lymphoma; TL, transformed lymphoma.

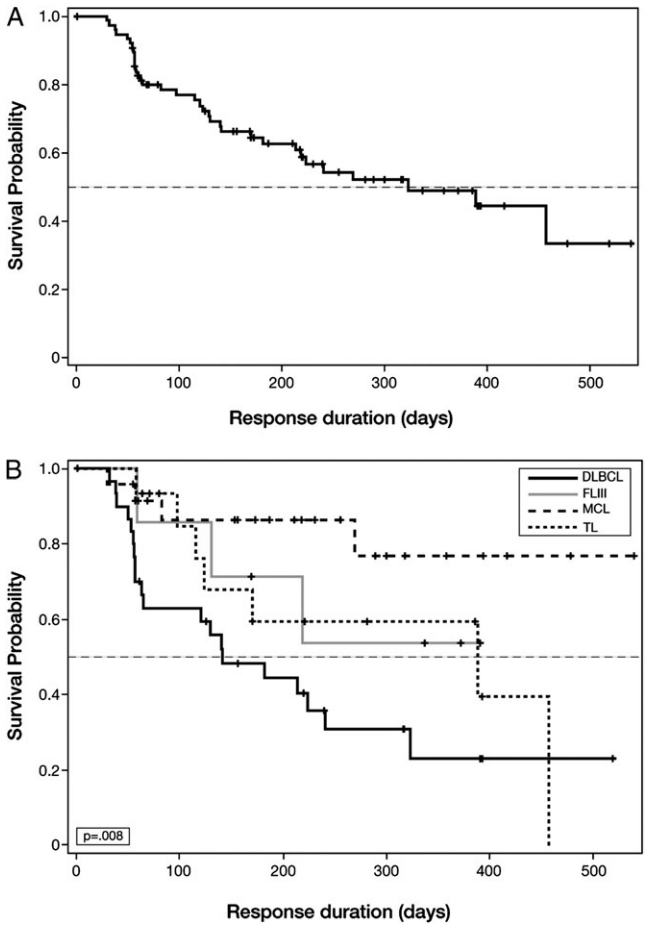

Figure 2. Kaplan–Meier estimate for response duration for all responders to lenalidomide (A) and for responders to lenalidomide within each disease type (B). DLBCL, diffuse large B-cell lymphoma; FL-III, follicular grade 3 lymphoma; MCL, mantle cell lymphoma; TL, transformed lymphoma.

patients. Myeloid growth factors were not mandated but were permitted and were administered to 54 patients (25%) during the study. Adverse events led to discontinuation from study treatment in 49 patients (23%). Tumor flares occurred in 7 patients, 4 (1.8%) with grade 1 or 2, and 3 with grade 3. Common nonhematologic events of all grades irrespective of attribution to lenalidomide included gastrointestinal events (61.3%), rash (18.0%), and fatigue (28%), the majority of which were grade 1 or 2.

discussion

This large international study of 217 patients demonstrates that single-agent lenalidomide has antitumor activity in patients with relapsed or refractory aggressive NHL based on an ORR of 35% with 13% CR/CRu. Although the median PFS for all 217 patients was relatively short at 3.7 months, the response

Table 3. Treatment-related grade 3 or 4 adverse events occurring in at least five patients

Adverse event	Grade 3, *n* (%)	Grade 4, *n* (%)
Neutropenia	52 (24)	37 (17.1)
Febrile neutropenia	2 (0.9)	3 (1.4)
Thrombocytopenia	29 (13.4)	13 (6.0)
Anemia	18 (8.3)	2 (0.9)
Leukopenia	12 (5.5)	4 (1.8)
Asthenia	9 (4.1)	3 (1.4)
Dyspnea	10 (4.6)	2 (0.9)
Back pain	9 (4.1)	1 (0.5)
Fatigue	10 (4.6)	0
Abdominal pain	8 (3.7)	0
Pain	8 (3.7)	0
Pneumonia	6 (2.8)	1 (0.5)
Pleural effusion	3 (1.4)	3 (1.4)
Dehydration	6 (2.8)	0
Cancer pain	4 (1.8)	1 (0.5)
Deep vein thrombosis	5 (2.3)	0
Hypokalemia	5 (2.3)	0

duration for responders was substantial with a median of 10.6 months. These results support earlier findings from a smaller North American study of lenalidomide in 49 patients with similar eligibility [19]. After longer follow-up of that study, the median PFS was 3.6 months and the duration of response was 10.2 months (data on file, Celgene Corporation).

This large study offers a unique opportunity to evaluate responses in the various types of aggressive NHL. It demonstrates that ORR in the DLBCL type is actually the lowest with substantially higher ORRs in the other types. We found an ORR of 42% in 57 patients with relapsed MCL and 12 (21%) of these patients attained a CR/CRu. Median PFS for the entire MCL cohort was 5.7 months and the median response duration in responders has not been reached. This is consistent with results from the earlier pilot trial (NHL-002) of lenalidomide where the subset of patients with relapsed MCL achieved a 53% ORR, 20% CR/CRu, and a median response duration of 13.7 months [20]. Given the typically poor survival outcomes of patients with relapsed or refractory MCL, the promising results from these two studies compare favorably relative to other single agent therapies. For example, recent studies evaluated the safety and efficacy of the mammalian target of rapamycin (mTOR) inhibitor temsirolimus in a MCL patient population similar to the studies with lenalidomide. The phase II studies of temsirolimus showed ORRs of 38%–41%, with median response durations of 6–7 months [8, 9]. This led to a randomized phase III trial comparing single-agent temsirolimus to other single-agent chemotherapies [22]. At the higher temsirolimus dose level evaluated (75 mg), the ORR was 22% with a median PFS of 4.8 months [22]. Preliminary results from a phase II study of everolimus, another mTOR inhibitor, in relapsed aggressive NHL reported a 29% ORR among patients with MCL [23]. Two phase II studies of bortezomib have been conducted in patients with relapsed MCL. In the first, patients had a median of one prior therapy and achieved a 33% ORR and a median response duration lasting 9.2 months [7]. In the second report, the ORR was 41% with a median response duration of 6.2 months [24].

A substantial number ($n = 33$) of patients with relapsed TL and FL-III ($n = 19$) were treated and the ORRs were 45% and 42%, respectively. Although median PFS was 5.4 months for all TL patients, responders to lenalidomide did particularly well with a median response duration of 12.8 months. In the FL-III patients, the median PFS was 8.9 months and the median duration of response is not yet reached. Other studies for relapsed TL have been small making it difficult to compare with our results. Bendamustine produced a 66% (10/15) ORR for TL, with a median response duration of 2.3 months [25]. In a prior study of bortezomib monotherapy, none of the three TL patients enrolled responded [24]. A median PFS of ~1 year has been reported with radioimmunotherapy, although again, these studies had few patients with TL [26, 27].

Response to lenalidomide among patients with DLBCL was 28%. This ORR is similar to or better than those achieved with other single agents. For example, bortezomib produced an ORR of only 8% in 12 patients with relapsed DLBCL, with a median TTP of 3.6 months [24]. Temsirolimus treatment of 82 patients with relapsed or refractory DLBCL resulted in an ORR of 32% [28]. A comparable ORR of 30% was also reported for the DLBCL patient subset from a phase II study of everolimus [23]. Studies of rituximab monotherapy have reported response rates ranging from 31% to 38%, with a median event-free or PFS of 2.0–3.8 months [29–31]. Median TTP to rituximab was 3.5 months for all patients and 8.2 months for responders. Finally, among patients with relapsed but rituximab-naïve aggressive NHL, gemcitabine monotherapy yielded an ORR of 20% with a median response duration lasting 6 months [32].

There is a substantial unmet need for new therapies for patients with relapsed aggressive NHL. Such patients are often older adults with substantial comorbidities making them ineligible for intensive chemotherapies and many are not eligible for SCT or relapse after SCT or other intensive chemotherapy regimens. This study demonstrated that lenalidomide is generally well tolerated by patients with relapsed or refractory disease, with only 23% of patients discontinuing therapy due to adverse events. In this study, lenalidomide was administered at the standard dose of 25 mg daily for 21 out of every 28-day cycle. Dose reductions to usually 20 mg and occasionally 15 mg or treatment interruptions were necessary in 31% of patients. It is not known if the ORR would be similar if lenalidomide was initiated at these lower doses. It is reasonable in future studies of lenalidomide for relapsed disease to initiate therapy with the 25 mg dose and reduce as tolerated. Although grade 3/4 neutropenia was frequent in this study, the rate of febrile neutropenia was very low.

The immunomodulatory drugs offer a new therapeutic option for this patient population and warrant further testing in combination with conventional chemo- and immunotherapy agents (NCT00670358). The demonstrated benefit in response duration, and a convenient oral formulation, has also prompted an exploration of lenalidomide in the maintenance setting for DLBCL (NCT00799513) and MCL (NCT01021423).

acknowledgements

The authors are fully responsible for the opinion and editorial content presented in this manuscript.

Contributors: TEW was the PI on the project and designed the study with DP, ALE-H, and MSC. TEW, JMV, CH, and MSC provided study material/patients, collection and assembly of data, and data analysis and interpretation. TEW wrote the manuscript with input and critical review from all the authors. DP and ALE-H provided collection and assembly of data, data analysis and interpretation, and critical review of the manuscript. PLZ, CR, RBu, JAP, RBo, and HT provided study material/patients and critical review of the manuscript.

funding

This study was financially supported and sponsored by Celgene Corporation.

disclosure

PG, DP, ALE-H are employees of Celgene and have received Celgene stock and stock options. RBu, CH, HT, and MSC have received consulting fees and research funding from Celgene. HT has also received honoraria from Celgene. TEW, JMV, and CR have received research support from Celgene to conduct this clinical trial. TEW is an occasional uncompensated advisor to Celgene.

references

1. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2009. CA Cancer J Clin 2009; 59: 225–249.
2. Habermann TM, Weller EA, Morrison VA et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006; 24: 3121–3127.
3. Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346: 235–242.
4. Philip T, Guglielmi C, Hagenbeek A et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma [see comments]. N Engl J Med 1995; 333: 1540–1545.
5. Herrmann A, Hoster E, Zwingers T et al. Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol 2009; 27: 511–518.
6. Geisler CH, Kolstad A, Laurell A et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008; 112: 2687–2693.
7. Fisher RI, Bernstein SH, Kahl BS et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006; 24: 4867–4874.
8. Witzig TE, Geyer SM, Ghobrial I et al. Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. J Clin Oncol 2005; 23: 5347–5356.
9. Ansell SM, Inwards DJ, Rowland KM Jr et al. Low-dose, single-agent temsirolimus for relapsed mantle cell lymphoma: a phase 2 trial in the North Central Cancer Treatment Group. Cancer 2008; 113: 508–514.
10. Kouroukis CT, Belch A, Crump M et al. Flavopiridol in untreated or relapsed mantle-cell lymphoma: results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2003; 21: 1740–1745.
11. Al-Tourah AJ, Gill KK, Chhanabhai M et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol 2008; 26: 5165–5169.
12. Zhu D, Corral LG, Fleming YW, Stein B. Immunomodulatory drugs Revlimid (lenalidomide) and CC-4047 induce apoptosis of both hematological and solid tumor cells through NK cell activation. Cancer Immunol Immunother 2008; 57: 1849–1859.
13. Wu L, Adams M, Carter T et al. lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. Clin Cancer Res 2008; 14: 4650–4657.
14. Gorgun G, Ramsay AG, Holderried TA et al. E(mu)-TCL1 mice represent a model for immunotherapeutic reversal of chronic lymphocytic leukemia-induced T-cell dysfunction. Proc Natl Acad Sci USA 2009; 106: 6250–6255.
15. Gaidarova S, Corral LG, Gleizer E et al. Lenalidomide enhances anti-tumor effect of {gamma}{delta} T Cells against mantle cell lymphoma. Blood 2008; 112: 2616 (ASH Annual Meeting Abstracts).
16. Gandhi AK, Kang J, Naziruddin S et al. Lenalidomide inhibits proliferation of Namalwa CSN.70 cells and interferes with Gab1 phosphorylation and adaptor protein complex assembly. Leuk Res 2006; 30: 849–858.
17. Verhelle D, Corral LG, Wong K et al. Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34+ progenitor cells. Cancer Res 2007; 67: 746–755.
18. Witzig TE, Wiernik PH, Moore T et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009; 27: 5404–5409.
19. Wiernik PH, Lossos IS, Tuscano JM et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008; 26: 4952–4957.
20. Habermann TM, Lossos IS, Justice G et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol 2009; 145: 344–349.
21. Cheson B, Horning S, Coiffier B et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphoma. J Clin Oncol 1999; 17: 1244–1253.
22. Hess G, Herbrecht R, Romaguera J et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol 2009; 27: 3822–3829.
23. Witzig TE, Habermann TM, Reeder C et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed non-Hodgkin's lymphoma and Hodgkin disease. Haematologia 2009; 94 (Suppl 2): 436 (Abstr 1081).
24. Goy A, Younes A, McLaughlin P et al. Phase II Study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2005; 23: 667–675.
25. Friedberg JW, Cohen P, Chen L et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008; 26: 204–210.
26. Kaminski MS, Estes J, Zasadny KR et al. Radioimmunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 2000; 96: 1259–1266.
27. Witzig TE, Flinn IW, Gordon LI et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002; 20: 3262–3269.
28. Smith SM, Pro B, Cisneros A et al. Activity of single agent temsirolimus (CCI-779) in non-mantle cell non-Hodgkin lymphoma subtypes. J Clin Oncol 2008; 26: (Abstr 8514).
29. Coiffier B, Haioun C, Ketterer N et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998; 92: 1927–1932.
30. Rothe A, Schulz H, Elter T et al. Rituximab monotherapy is effective in patients with poor risk refractory aggressive non-Hodgkin's lymphoma. Haematologica 2004; 89: 875–876.
31. Tobinai K, Igarashi T, Itoh K et al. Japanese multicenter phase II and pharmacokinetic study of rituximab in relapsed or refractory patients with aggressive B-cell lymphoma. Ann Oncol 2004; 15: 821–830.
32. Fossa A, Santoro A, Hiddemann W et al. Gemcitabine as a single agent in the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 1999; 17: 3786–3792.