Supplemental to Siegel et al, Integrated safety profile of single-agent carfilzomib of 526 patients from 4 phase 2 trials

Supplemental Methods

Guidelines for the prevention and management of tumor lysis syndrome (TLS) were provided for 003-A1, 004, and 005. Prophylactic antiviral therapy was optional for all patients but required in accordance with institutional guidelines for any patients with a history of herpes zoster or simplex for 003-A1 and in the cohort of patients receiving low-dose dexamethasone in 005.

In addition to the grouped analyses, laboratory data were analyzed for trends, duration, and degree of worsening, standardized by analyzing the maximum change from each patient's baseline value for hematologic, renal, and hepatic evaluations. Routine echocardiograms were not performed. Worsening renal function was defined by a doubling or more from baseline of serum creatinine, and an episode of worsening renal function was defined as resolved (thus, transient) at the point at which the serum creatinine first returned to within 20% of baseline. Grade shift analyses were performed for hematologic and renal AEs. Neurologic assessments included history and baseline neuropathy status; additional events related to or indicative of neuropathy were also analyzed.

More detailed analyses were performed for the following select organ toxicities: cardiac, renal, pulmonary, and hepatic. AEs were analyzed by cycle, but not in respect to timing of the dose, except for an analysis of AEs within 1 day of dosing. An analysis comparing baseline cardiac risk to mortality (cardiac risk defined as a patient who reported use of at least 1 cardiovascular or antidiabetic medication prior to study entry) was performed. In the analysis of renal events an evaluation was performed to correlate renal AE presentation to progressive disease (PD), with PD determined by the Independent Review Committee or by PI at end of treatment. Within the analysis of pulmonary events,

dyspnea refined analyses were performed including time-to-event and duration-of-event analyses, pulmonary toxicity was analyzed across System Organ Classes (SOCs), and an analysis was performed to identify respiratory infection AEs. In addition to evaluating hepatic AEs, liver function test (LFT) laboratory data were used to assess evidence of drug-induced liver injury; Hy's law criteria per the US Food and Drug Administration Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation was used to identify and evaluate patients who had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3× ULN and a total bilirubin ≥2× ULN at any time. Finally, reported events of TLS were evaluated based on criteria described in the literature for laboratory TLS[1] and clinical TLS.[2] For the manifestations associated with TLS, individual patient clinical course and laboratory values were compared with baseline values in conjunction with evidence of disease response to evaluate diagnosis.

Supplemental Results and Discussion

Gastrointestinal

Gastrointestinal (GI) AEs were reported for 381 patients (72.4%) with similar rates across the studies. The most common (>20%) GI AEs were nausea (44.9%), diarrhea (32.7%), vomiting (22.2%), and constipation (20.9%), the majority of which were Grade 1 and 2 (42.8% and 25.9%) and managed with standard therapy. GI AEs of Grade 3 were reported in 3.6% of patients, including nausea (1.3%), vomiting (1.0%), diarrhea (0.8%), and constipation (0.4%), and in 1 patient each (0.2%) with Grade 3 abdominal pain, dyspepsia, abdominal discomfort, and anorexia. In general, significant weight loss was not reported across the studies. A total of 15 patients (2.9%) experienced serious GI events, all of which resolved with either concomitant medication or hospitalization. Five patients (1.0%) had a dose reduction due to a GI event and 2 patients (0.4%) discontinued study treatment due to a GI AE. These

results of carfilzomib are comparable to bortezomib and lenalidomide in relation to nausea, diarrhea, and constipation, particularly for ≥Grade 3 events.[3-7]

Hepatic

Any hepatic event was reported for 99 patients (18.8%), the most frequent being increased AST in 66 patients (12.5%) and increased ALT in 43 patients (8.2%). Other hepatic AEs included hepatic failure (0.6%), hepatic encephalopathy (0.2%), and veno-occlusive liver disease (0.2%). Grade 3 events were reported in 33 patients (6.3%), the majority of which were increased AST (2.9%) and increased ALT (2.7%), and 2 patients with Grade 4 events (1 AST increased and 1 transaminase increased). Grade 5 events of hepatic failure were reported for 2 patients, both in the setting of disease progression in patients on multiple concomitant medications with 1 patient experiencing sepsis. Events resulting in clinical symptoms occurred in <1% of patients with most of the hepatic SMQ AEs reflecting laboratory abnormalities. Dose reduction was reported for 1 patient (0.2%), and 3 patients (0.6%) discontinued treatment. A Hy's law analysis was performed on all patients who received carfilzomib (N= 768) to identify patients who had both transaminase and total bilirubin elevations (n=7 including 3 patients with solid tumors) and no patient met the criteria for Hy's Law in that all patients had other plausible explanations for the liver function abnormalities such as obstructive jaundice, disease progression and/or multiple concomitant hepatotoxic medications. Hepatic events, while not common for patients with MM, can be potentially serious. In response to carfilzomib treatment, hepatic AEs were mostly mild to moderate elevations of transaminases, the majority of which were Grade 1 or 2 and did not result in study drug discontinuation or reduction.

Tumor lysis syndrome

Five patients (2 from 003-A0, 1 from 003-A1, and 2 from 004) experienced a TLS event as reported by the Investigator—3 of the 5 patients began treatment before prophylaxis guidelines were instituted, and an additional patient initiated treatment after the guidelines were implemented but did not receive the recommended prophylaxis. All 5 patients met at least some criteria for diagnosis of laboratory TLS, while 3 of 5 had evidence of clinical TLS. In 3 of 5 patients TLS resolved, while in the other 2 it was reported as continuing at the time of death (due to progressive disease for 1 patient and due to multiorgan failure for the other patient). All of the 5 patients with TLS had evidence of progressive disease with a relatively high tumor burden upon entry into the studies and were heavily pretreated, including autologous peripheral blood stem cell or bone marrow transplants before enrollment. Once prophylactic guidelines were added to the study protocols, TLS was reported in 1 of 613 patients (this patient is included in the cases discussed above) enrolled in phase 1 and phase 2 studies and hence proved to no longer be a major concern.[8, 9]

Herpes virus infection

Across the studies, 153 (29.1%) patients had a history of herpes virus infection. Two-thirds (62.7%) of all patients reported taking a concomitant antiviral medication while on study. During the studies, any herpes virus infection was reported in 25 patients (4.8%). Overall, herpes zoster events were reported in 2.3% of patients (12 total, with 8 of those patients having a prior history), and herpes simplex virus was reported in 2.7% of patients (14 total, with a prior history in 4 of those patients). All events were Grade 1 or 2 with the exception of 1 Grade 3 event of “pain secondary to shingles”. In contrast to bortezomib,[5] herpes virus infections were uncommon across the carfilzomib studies. Additionally, the episodes were predominantly mild or moderate in severity, rarely resulted in missed doses, and generally resolved in

the usual time course with standard medical management. Additionally, the risk of opportunistic viral infections was not increased by the lymphopenia reported in these studies.

Electrolyte disturbances

Electrolyte disturbances were noted in these studies. The most commonly reported all grade AEs of this type were hypomagnesemia (13.5%) and hypokalemia (13.7%) which were generally Grade 1 or 2. The most common electrolyte disturbances of Grade 3 or higher included hyponatremia (6.5%), hypophosphatemia (5.1%) and hypercalcemia (4.0%). Electrolyte disturbances ≥Grade 3 reported less often (2−4% of patients) included hyperglycemia, hypokalemia, decreased blood phosphorous, hypocalcemia, and hyperkalemia.

Supplemental Table

Treatment emergent AE onset by time period across the 4 phase 2 studies

AE, n (%)	Cycle 1 N=526	Cycle 2 N=444	Cycles 3-5 N=355	Cycles 6-8 N=221	Cycles 9-11 N=154	Cycles ≥12 N=100
Any cardiac	52 (9.9)	32 (7.2)	27 (7.6)	14 (6.3)	3 (1.9)	3 (3.0)
Any fatigue	137 (26.0)	75 (16.9)	100 (28.2)	40 (18.1)	14 (9.1)	3 (3.0)
Any thrombocytopenia	151 (28.7)	57 (12.8)	48 (13.5)	9 (4.1)	10 (6.5)	1 (1.0)
Any pulmonary infection	28 (5.3)	24 (5.4)	31(8.7)	10 (4.5)	9 (5.8)	3 (3.0)
Any dyspnea	104 (19.8)	54 (12.2)	68 (19.2)	26 (11.8)	18 (11.7)	6 (6.0)
Any PN	21 (4.0)	18 (4.1)	30 (8.5)	9 (4.1)	8 (5.2)	1 (1.0)

References

1. Sezer O, Vesole DH, Singhal S, Richardson P, Stadtmauer E, Jakob C, et al. Bortezomib-induced tumor lysis syndrome in multiple myeloma. Clin Lymphoma Myeloma. 2006;7(3):233-5.

2. Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. Am J Med. 1993;94(2):133-9.

3. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357(21):2133-42.

4. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352(24):2487-98.

5. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003;348(26):2609-17.

6. Revlimid® Prescribing Information. Celgene Corporation, Summit, NJ. 2012.

7. Velcade™ Prescribing Information. Millennium Pharmaceuticals, Cambridge, MA. 2012.

8. Alsina M, Trudel S, Furman RR, Rosen PJ, O'Connor OA, Comenzo RL, et al. A phase 1 single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma. Clin Cancer Res. 2012;18(17):4830-40.

9. Davies S, Pandian R, Bolos J, Castaner R. Carfilzomib. Drugs Future. 2009;34(9):708-16.