AHFS Final Determination of Medical Acceptance: Off-label Use of Bortezomib in Combination with Cyclophosphamide and Dexamethasone as Induction Therapy for Newly Diagnosed Multiple Myeloma in Transplant-eligible Patients

Drug/Drug Combination: Bortezomib in combination with cyclophosphamide and dexamethasone

Off-label Use: Induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients

Criteria Used in Selection of Off-label Use for Review:

- Periodic review of prior Final Determination for the purpose of updating medical acceptance. The current Final Determination supersedes the past determination originally published in January 2009. At the time of the original review, the use of bortezomib in combination with cyclophosphamide and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients undergoing a stem-cell transplant (SCT) was not fully established.

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Overall response rate

Grade of Recommendation: Reasonable choice (Accepted, with possible conditions):

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 of each 4-week cycle for 4 cycles *(Reeder et al [reference 10019])*

Bortezomib 1.5 mg/m^2 IV and cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 of each 4-week cycle for 4 cycles along with dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 during cycles 1 and 2 and then 40 mg orally once weekly during cycles 3 and 4 *(Reeder et al [reference 10021])*

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with cyclophosphamide 300 mg/m^2 IV on days 1 and 8 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle during cycles 1–3 followed by bortezomib 1 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 100 mg orally daily and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle during cycles 4–6 *(Bensinger et al [reference 10029])*

Bortezomib 1.3 mg/m^2 by IV or subcutaneous injection on days 1, 4, 8, and 11 along with cyclophosphamide 900 mg/m^2 IV on day 1 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle for 3 cycles *(GMMG-MM5 [reference 10028])*

Narrative Summary:

Bortezomib, Dexamethasone, and Cyclophosphamide:

Efficacy and safety of bortezomib in combination with cyclophosphamide and dexamethasone† (bortezomib-cyclophosphamide-dexamethasone) as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients† have been studied in 2 noncomparative phase 2 studies and an open-label, randomized phase 3 study (GMMG-MM5).[10006, 10007, 10008, 10019, 10021, 10022, 10029]

In the first phase 2 study, patients with newly diagnosed multiple myeloma receiving bortezomib in combination with cyclophosphamide and dexamethasone were compared with a historical control group (34 patients who received lenalidomide 25 mg orally on days 1–21 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 during each 28-day cycle for 4 cycles).[10019, 10031] In this study, 33 patients received bortezomib 1.3 mg/m^2 as an IV injection twice weekly (days 1, 4, 8, and 11) along with cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 during each 28-day cycle for 4 cycles.[10019] The mean age of patients enrolled in the study was 60 years; 48% were female and 30% had International Staging System (ISS) stage III disease.[10019] Among patients for whom cytogenetic tests were performed, 50, 18, or 13% had del(13q), t(4;14) translocation, or del(17) chromosomal abnormalities, respectively.[10019] The overall response rate and rate of very good partial response or better after 4 cycles of therapy were 88 and 61%, respectively, in patients who received bortezomib-cyclophosphamide-dexamethasone compared with 91 and 44%, respectively, in the historical control group based on intent-to-treat analysis.[10019] Among patients who underwent stem cell transplantation following bortezomib-cyclophosphamide-dexamethasone induction therapy, the posttransplant complete or near-complete response rate was 70%.[10019]

Patients from this study (twice-weekly bortezomib; cohort 1) also were compared with a subsequent cohort of 30 patients who received bortezomib 1.5 mg/m^2 as an IV injection once weekly (days 1, 8, 15, and 22) along with cyclophosphamide (same dosage as in cohort 1) and dexamethasone (same dosage as in cohort 1 during cycles 1 and 2, followed by 40 mg once weekly during cycles 3 and 4).[10019, 10021] Comparison of the 2 cohorts suggested that overall response rates and rates of very good partial response or better for the regimens containing once-weekly (93 and 60%, respectively) or twice-weekly (88 and 61%, respectively) bortezomib were similar;[10021] however, the incidences of grade 3 or 4 thrombocytopenia (0 versus 25%), neutropenia (7 versus 13%), anemia (0 versus 12%), and peripheral neuropathy (0 versus 7%) were lower in patients receiving the regimen containing once-weekly bortezomib compared with those receiving the regimen containing twice-weekly bortezomib.[10019, 10021] Analysis of pooled data for the 2 cohorts indicated a median progression-free survival of 40 months; in addition, 5-year progression-free and overall survival rates for the 2 cohorts combined were 42 and 70%, respectively.[10022] Although the overall response rate was similar in patients with high-risk cytogenetic features and those with standard-risk cytogenetic features, median progression-free survival was shorter and 5-year progression-free and overall survival rates were lower in patients with high-risk cytogenetic features (27.6 months, 33%, and 54%, respectively) compared with those with standard-risk cytogenetic features (55.7 months, 48%, and 81%, respectively).[10022]

In another phase 2 study, patients with newly diagnosed multiple myeloma received the combination of bortezomib-cyclophosphamide-dexamethasone followed by bortezomib-thalidomide-dexamethasone to determine if sequential combination therapy could improve response rates and tolerability.[10008, 10029] In this study, 44 patients received bortezomib 1.3 mg/m^2 as an IV injection on days 1, 4, 8, and 11 along with cyclophosphamide 300 mg/m^2 IV on days 1 and 8 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 during each 21-day cycle for 3 cycles (cycles 1–3) followed by bortezomib 1 mg/m^2 as an IV injection

on days 1, 4, 8, and 11 along with thalidomide 100 mg orally daily and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 during each 21-day cycle for 3 cycles (cycles 4–6).[10029] The median age of patients enrolled in the study was 58 years, and the median Karnofsky performance status was 90%; 60% of patients had ISS stage II or III disease, 49% had a baseline β_2-microglobulin concentration of 3.5 mg/L or greater, and 7 patients had cytogenetic abnormalities, including t(4;14) translocation, del(17p), and/or del(13) chromosomal abnormalities.[10029] Very good partial response or better was observed in 31 or 57% of 42 evaluable patients following 3 cycles of bortezomib-cyclophosphamide-dexamethasone or 6 cycles of sequential combination therapy, respectively; near-complete response or better was observed following 3 or 6 cycles of therapy in 2 or 36% of patients, respectively.[10029] At a median follow-up of 20.9 months, median event-free and overall survival had not been reached; however, estimated 1-year event-free and overall survival rates were 81 and 91%, respectively.[10029]

In the GMMG-MM5 study, 502 patients with newly diagnosed multiple myeloma were randomized to receive bortezomib in combination with either cyclophosphamide and dexamethasone or doxorubicin and dexamethasone.[10028] Patients receiving bortezomib-cyclophosphamide-dexamethasone received bortezomib 1.3 mg/m^2 as an IV injection on days 1, 4, 8, and 11 along with cyclophosphamide 900 mg/m^2 IV on day 1 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 during each 21-day cycle.[10028] Those receiving bortezomib-doxorubicin-dexamethasone received the same dosage of bortezomib along with doxorubicin hydrochloride 9 mg/m^2 IV per day on days 1–4 and dexamethasone 20 mg orally on days 1–4, 9–12, and 17–20 of each 28-day cycle.[10028] Both regimens were continued for a total of 3 cycles.[10028] The route of administration for bortezomib was changed from IV to subcutaneous injection when data from a prior study in patients with relapsed multiple myeloma demonstrated no apparent loss in efficacy or increase in toxicity with subcutaneous administration.[10028] The median age of patients enrolled in the GMMG-MM5 study was 59 years, and 29% had ISS stage III disease.[10028] Among patients for whom cytogenetic tests were performed, 11, 11, or 40% had del(17p), t(4;14) translocation, or chromosome 1q21 duplication (i.e., 1q21 gain) abnormalities, respectively.[10028] The primary measure of efficacy was the rate of very good partial response or better, as assessed according to the International Myeloma Working Group Uniform Response criteria, following induction therapy.[10028]

Rates of overall response (78.1 versus 72.1%, respectively) and very good partial response or better (37 versus 34.3%, respectively) in the GMMG-MM5 study did not differ significantly between patients receiving bortezomib-cyclophosphamide-dexamethasone and those receiving bortezomib-doxorubicin-dexamethasone.[10028] In subgroups of patients with poor prognostic factors (i.e., t(4;14) translocation, del(17p), and/or 1q21 gain; renal impairment [serum creatinine concentration of 2 mg/dL or higher]), response rates attained with bortezomib-cyclophosphamide-dexamethasone appeared to be at least as high as those attained with bortezomib-doxorubicin-dexamethasone; the rate of progressive disease in patients with high-risk cytogenetic features, ISS stage III disease, or renal impairment appeared to be higher in those receiving bortezomib-doxorubicin-dexamethasone compared with those receiving bortezomib-cyclophosphamide-dexamethasone.[10028] In an exploratory analysis, overall response rates were similar with IV or subcutaneous injection of bortezomib, including in patients with poor prognostic factors.[10030] Grade 3 or greater leukopenia and/or neutropenia (35.2 versus 11.3%) occurred more frequently in patients receiving bortezomib-cyclophosphamide-dexamethasone, while grade 2 or greater neuropathy (14.9 versus 8.4%) occurred more frequently in patients receiving bortezomib-doxorubicin-dexamethasone.[10028]

Based on current evidence,[10019, 10021, 10022, 10028, 10029] use of bortezomib in combination with cyclophosphamide and dexamethasone may be considered a reasonable choice (accepted, with possible conditions) as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients; factors

that should be considered when selecting a combination chemotherapy regimen for use as induction therapy include cytogenetic features, performance status, preexisting conditions (e.g., peripheral neuropathy), and tolerability.

Dosage:

Bortezomib has been used in several regimens in combination with cyclophosphamide and dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients.[10019, 10021, 10028, 10029]

When bortezomib has been used in combination with cyclophosphamide and dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients, bortezomib 1.3 mg/m^2 has been administered by IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 of each 28-day cycle for 4 cycles.[10019]

Bortezomib 1.5 mg/m^2 also has been administered by IV injection once weekly (days 1, 8, 15, and 22) along with cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 of each 28-day cycle for 4 cycles, with dexamethasone 40 mg administered orally on days 1–4, 9–12, and 17–20 during cycles 1 and 2 and then once weekly during cycles 3 and 4.[10021]

Bortezomib 1.3 mg/m^2 also has been administered by IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with cyclophosphamide 300 mg/m^2 IV on days 1 and 8 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for 3 cycles (cycles 1–3) followed by bortezomib 1 mg/m^2 by IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with thalidomide 100 mg orally daily and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for 3 cycles (cycles 4–6).[10029]

Bortezomib 1.3 mg/m^2 also has been administered by subcutaneous or IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with cyclophosphamide 900 mg/m^2 IV on day 1 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for 3 cycles.[10028]

References:

10006. Reeder CB, Stewart AK, Hentz JG et al. Efficacy of induction with CyBorD in newly diagnosed multiple myeloma. *J Clin Oncol.* 2008; 26: Abstract 8517 (presented at the 44th Annual ASCO meeting. Chicago, IL: 2008 May 31).

10007. Reeder C, Reece D, Fonseca R et al. A phase II trial of myeloma induction therapy with cyclophosphamide, bortezomib and dexamethasone (Cybor-D): improved response over historical lenalidomide-dexamethasone controls. *Blood.* 2007; 110: Abstract No. 3601.

10008. Jagannath S, Bensinger B, Vescio R et al. A phase II study of bortezomib (Velcade®), cyclophosphamide (Cytoxan®), thalidomide and dexamethasone as first-line therapy for multiple myeloma. *Blood.* 2007; 110: Abstract 188 (presented at the 49th annual ASH meeting. Atlanta, GA: 2007 Dec 10).

10019. Reeder CB, Reece DE, Kukreti V et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia.* 2009; 23:1337-41.

10021. Reeder CB, Reece DE, Kukreti V et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood.* 2010; 115:3416-7.

10022. Reeder CB, Reece DE, Kukreti V et al. Long-term survival with cyclophosphamide, bortezomib and dexamethasone induction therapy in patients with newly diagnosed multiple myeloma. *Br J Haematol.* 2014; 167:563-5.

10028. Mai EK, Bertsch U, Dürig J et al. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. *Leukemia.* 2015; 29:1721-9.

10029. Bensinger WI, Jagannath S, Vescio R et al. Phase 2 study of two sequential three-drug combinations containing bortezomib, cyclophosphamide and dexamethasone, followed by bortezomib, thalidomide and dexamethasone as frontline therapy for multiple myeloma. *Br J Haematol*. 2010; 148:562-8.

10030. Merz M, Salwender H, Haenel M et al. Subcutaneous versus intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial. *Haematologica*. 2015; 100:964-9.

10031. Lacy MQ, Gertz MA, Dispenzieri A et al. Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. *Mayo Clin Proc*. 2007; 82:1179-84.

Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); overall response rate

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 of each 4-week cycle for 4 cycles (Reeder et al [reference 10019]):

Recommended use (Accepted): 2 votes

Reasonable choice (Accepted, treatment option): 3 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Bortezomib 1.5 mg/m^2 IV and cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 of each 4-week cycle for 4 cycles along with dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 during cycles 1 and 2 and then 40 mg orally once weekly during cycles 3 and 4 (Reeder et al [reference 10021]):

Recommended use (Accepted): 1 vote

Reasonable choice (Accepted, treatment option): 4 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with cyclophosphamide 300 mg/m^2 IV on days 1 and 8 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle during cycles 1–3 followed by bortezomib 1 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 100 mg orally once daily and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle during cycles 4–6 (Bensinger et al [reference 10029]):

Recommended use (Accepted): 1 vote

Reasonable choice (Accepted, treatment option): 4 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Bortezomib 1.3 mg/m^2 by IV or subcutaneous injection on days 1, 4, 8, and 11 along with cyclophosphamide 900 mg/m^2 IV on day 1 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle for 3 cycles (GMMG-MM5 [reference 10028]):

Recommended use (Accepted): 1 vote

Reasonable choice (Accepted, treatment option): 3 votes

Not fully established (Unclear risk/benefit or equivocal): 1 vote

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Based on current evidence,[10019, 10021, 10022, 10028, 10029] use of bortezomib in combination with cyclophosphamide and dexamethasone may be considered a reasonable choice (accepted, with possible conditions) as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients; factors that should be considered when selecting a combination chemotherapy regimen for use as induction therapy include cytogenetic features, performance status, preexisting conditions (e.g., peripheral neuropathy), and tolerability.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Reviewer #2: [General] 500 mg/m^2 dosing of cyclophosphamide (*Blood.* 2012; 119: 4375-82).

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 of each 4-week cycle for 4 cycles (Reeder et al [reference 10019]:

Reviewer #3: [Specific patient population] Those without high risk genetics may have more benefit.

Bortezomib 1.5 mg/m^2 IV and cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 of each 4-week cycle for 4 cycles along with dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 during cycles 1 and 2 and then 40 mg orally once weekly during cycles 3 and 4 (Reeder et al (reference 10021):

Reviewer #3: [Specific patient population] Those patients with higher risk of worsening neuropathy, as well as thrombosis.

Reviewer #4: [Specific patient population] Patients with peripheral neuropathy.

Reviewer #5: [Grade of recommendation] Only retrospective, nonrandomized comparison available for once vs twice weekly bortezomib (Reeder et al. *Blood.* 2010; 115:3416-7).

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with cyclophosphamide 300 mg/m^2 IV on days 1 and 8 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle during cycles 1–3 followed by bortezomib 1 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 100 mg orally once daily and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle during cycles 4–6 (Bensinger et al [reference 10029]):

None submitted.

Bortezomib 1.3 mg/m^2 by IV or subcutaneous injection on days 1, 4, 8, and 11 along with cyclophosphamide 900 mg/m^2 IV on day 1 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle for 3 cycles (GMMG-MM5 [reference 10028]):

Reviewer #3: [Grade of recommendation] Subcutaneous administration shown to be as effective as IV with decreased side effects.

Reviewer #5: [Grade of recommendation] Compared to other bortezomib/cyclophosphamide/dexamethasone studies, rates of very good partial response (VGPR) or greater appear lower; as stated in the article, this could be due to lower cyclophosphamide dose per cycle or less number of cycles (3 vs 4). Therefore, at the doses and cycle number listed here, there are better options.

Comments on Draft Narrative Summary:

None submitted.

Comments on Proposed Consensus Recommendation:

None submitted.

Participants:

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AHFS Oncology Expert Committee Members (reviewing and voting): Marc Earl, Pharm.D., BCOP; Mandy Gatesman, Pharm.D., BCOP; Christine Gegeckas, RPh, BCOP; Rowena Schwartz, Pharm.D., BCOP; Ron Walters, M.D., MBA, MHA, MS

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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