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

Drug/Drug Combination: Bortezomib in combination with 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 dexamethasone as front-line, induction therapy for standard- and high-risk patients undergoing an autologous stem-cell transplant was a reasonable choice (accepted).

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

Strength of Study End Point(s): Complete response plus near-complete response

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

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 of each 3-week cycle for 4 cycles and dexamethasone 40 mg orally on days 1−4 and 9−12 during cycles 1 and 2 and then on days 1−4 during cycles 3 and 4

Narrative Summary:

Bortezomib and Dexamethasone:

Efficacy and safety of bortezomib in combination with dexamethasone† as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients† have been studied in an open-label, randomized phase 3 study (IFM 2005-01).[10002, 10012]

In the IFM 2005-01 study, 482 patients with previously untreated multiple myeloma were randomized to receive bortezomib in combination with dexamethasone (bortezomib-dexamethasone) or the combination of vincristine, doxorubicin, and dexamethasone (vincristine-doxorubicin-dexamethasone) as an induction regimen; both regimens were administered with or without dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation therapy.[10002, 10012] Patients receiving the bortezomib-dexamethasone induction regimen received bortezomib 1.3 mg/m^2 as an IV injection on days 1, 4, 8, and 11 of each 3-week cycle for 4 cycles along with dexamethasone 40 mg orally on days 1–4 and 9–12 during cycles 1 and 2 and then on days 1–4 of cycles 3 and 4.[10002, 10012] Those receiving the vincristine-doxorubicin-dexamethasone induction regimen received vincristine sulfate 0.4 mg and doxorubicin hydrochloride 9 mg/m^2 per day by continuous IV infusion on days 1–4 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 on days 1–4 of cycles 3 and 4.[10012] The median age of patients enrolled in

the study was 57.1 years; 22% had International Staging System (ISS) stage III disease, 57.5% had a baseline β_2-microglobulin concentration exceeding 3 mg/L, 42.3% had chromosome 13 deletion (del(13)), and 14.3% had t(4;14) translocation with or without chromosome 17p deletion (del(17p)).[10012]

The primary measure of efficacy was complete plus near-complete response rate following induction therapy.[10012] Tumor responses were assessed using European Group for Blood and Marrow Transplantation (EBMT) response criteria.[10012] The postinduction complete plus near-complete response rate (14.8 versus 6.4%) and the postinduction overall response rate (78.5 versus 62.8%) were higher in patients receiving bortezomib-dexamethasone compared with those receiving vincristine-doxorubicin-dexamethasone.[10012] The complete plus near-complete response rate also was higher following initial transplantation (35 versus 18.4%) and overall (39.5 versus 22.5%), including responses following second transplants when required, in patients receiving bortezomib-dexamethasone compared with those receiving vincristine-doxorubicin-dexamethasone.[10012] Postinduction response rates were higher in patients receiving bortezomib-dexamethasone compared with those receiving vincristine-doxorubicin-dexamethasone regardless of disease stage or presence of high-risk cytogenetic features (i.e., del(13), t(4;14) translocation and/or del(17p) chromosomal abnormality).[10012] Among patients who received bortezomib-dexamethasone induction therapy, rates of attaining a very good partial response or better were similar regardless of disease stage, use of consolidation therapy, or presence of the t(4;14) translocation with or without del(17p), but were slightly higher in patients with del(13) compared with those without this chromosomal abnormality.[10012] Following initial autologous stem cell transplantation, 38.6% of patients who had received bortezomib-dexamethasone induction therapy required a second stem cell transplant compared with 56% of those who had received vincristine-doxorubicin-dexamethasone.[10012] Although median overall survival had not been reached at a median follow-up of 32.2 months, median progression-free survival at a median follow-up of 31.2 months was numerically, but not significantly, longer in patients who received induction therapy with bortezomib-dexamethasone compared with those who received vincristine-doxorubicin-dexamethasone (36 versus 29.7 months).[10012]

Infection (48.1 versus 38.1%), peripheral neuropathy (45.6 versus 28%), thrombocytopenia (10.9 versus 4.6%), and herpes zoster infection (9.2 versus 2.1%) occurred more frequently in patients receiving bortezomib-dexamethasone, while neutropenia (13.8 versus 8%) and thrombosis (12.1 versus 4.6%) occurred more frequently in patients receiving vincristine-doxorubicin-dexamethasone.[10012]

Based on current evidence,[10012] use of bortezomib in combination with 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 performance status and preexisting conditions (e.g., peripheral neuropathy).

Dosage:

When bortezomib has been used in combination with 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) followed by a 10-day rest period (days 12–21) of each 21-day cycle for 4 cycles.[10002, 10012] In cycles 1 and 2, dexamethasone 40 mg was administered orally on days 1–4 and 9–12; in cycles 3 and 4, dexamethasone 40 mg was administered orally on days 1–4.[10002, 10012]

References:

10002. Harousseau JL, Mathiot C, Attal M et al. Velcade/Dexamethasone (Vel/D) versus VAD as induction treatment prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM): updated results of the IFM 2005/01 trial. *Blood.* 2007; 110: Abstract 450 (presented at the 49th annual ASH

meeting. Atlanta, GA: 2007 Dec 10).

10012. Harousseau JL, Attal M, Avet-Loiseau H et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol.* 2010; 28:4621-9.

Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); complete response plus near-complete response

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

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

Proposed Consensus Recommendation:

Based on current evidence,[10012] use of bortezomib in combination with 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 performance status and preexisting conditions (e.g., peripheral neuropathy).

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: [Specific patient population] Performance status of 2 or less. Meets inclusion criteria of trial.

Reviewer #5: [Specific patient population] Elderly or patients with extensive comorbidities.

Reviewer #5: [Grade of recommendation] Randomized clinical trial showing benefit in patients for induction [therapy] of multiple myeloma. Other options exist which may be more efficacious in certain patients which lead to it as a reasonable choice for these patients.

Comments on Draft Narrative Summary:

None submitted.

Comments on Proposed Consensus Recommendation:

Reviewer #3: Subcutaneous bortezomib is equally efficacious as IV bortezomib with less peripheral neuropathy and thus represents an alternative route of administration.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Marc Earl, Pharm.D., BCOP; Raymond Hohl, M.D., Ph.D.; LeAnne Kennedy, Pharm.D., BCOP; LeAnn Norris, Pharm.D., BCPS, 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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