



Bortezomib Administration in a Pregnant Woman Despite its Contraindication: A Case Report

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Abstract

Multiple myeloma (MM) is characterized by the malignant proliferation of monoclonal plasma cells in the bone marrow. Generally, it is a malignancy of older people, and its presentation before the age of 40 is rare. In addition, the incidence of MM during pregnancy is very rare. This case study reports a 38-year-old woman with a 1.5-year history of bone pain and diagnosis of immunoglobulin G and a kappa light-chain myeloma (Durie-Salmon stage IIIA, International Staging System III) and poor cytogenetic prognosis (del 11p, 46XX). The treatment plan included four courses of bortezomib, lenalidomide, and dexamethasone were planned as her treatment. At the end of the third course, it was revealed that she was in the 9th week of pregnancy, but her treatment continued as before because of refusing abortion and changing treatment modality. Despite continuing this treatment, a healthy boy was born without any malformations. Even in the next four-year follow-up, her son had normal growth and development. Regarding the contraindication of bortezomib during pregnancy, some data demonstrated that receiving bortezomib during pregnancy had no teratogenic effects on the fetus. This case study aimed to present this issue as well. Perhaps the declaration of bortezomib contraindication during pregnancy will become less in the future.

Keywords: Multiple myeloma, Bortezomib, Pregnancy

Background

Multiple myeloma (MM) is the neoplastic proliferation of plasma cells that produce monoclonal immunoglobulins. It starts in the spongy tissue inside the bone marrow and can cause bone pain, osteopenia, and osteolytic lesions.

The most common clinical presentations are bone pain in the back or chest with osteolytic lesions, increased levels of total serum protein, and anemia and fatigue as systemic signs, as well as hypercalcemia, acute renal failure (myeloma kidney), and neurologic issues due to spinal cord compression; splenomegaly and lymphadenopathy are less common.¹ Screening tests include serum and urine protein electrophoresis with immunofixation and free light chain (FLC) assay. To confirm the diagnosis of bone marrow aspiration and biopsy, a complete blood count with differentiation and imaging workups are necessary. Cross-sectional imaging is more sensitive than plain radiography for detecting skeletal lesions; whole-body dose computed tomography (CT) scan, magnetic resonance imaging, and positron emission tomography/CT may be used in different settings.²⁻⁴

Most patients with MM have an amount of M-protein secreted by malignant cells, which is detectable with serum protein electrophoresis and urine *protein electrophoresis*. These abnormal cells can produce immunoglobulin G (IgG), IgA, kappa, or lambda light chains only (Bence

Jones) and IgD.¹ Nearly 3% of patients have a normal serum and urine immunofixation known as non-secretory myeloma,¹ and in 60% of them, FLC can be detected in FLC assay.^{5,6} Although MM can appear in all geographic locations,⁷ it occurs 2-3 times more in African Americans and Blacks than Whites^{1,8,9} and it is more detectable in men.

The average age of a patient diagnosed with MM is 66; thus, this is a disease of older adults, and only 2% of cases are younger than 40 years.^{1,10} Patients with t (4;14), t (14;16), t (14;20), del 17p13, or gain 1 q by fluorescence in situ hybridization (FISH) technique and increased levels of lactate dehydrogenase are considered to have high-risk MM and shorter survival.^{11,12}

Based on risk stratification and eligibility for autologous hematopoietic cell transplantation, the treatment would be different. Patients eligible for hematopoietic stem cell transplantation receive a triplet regimen for 3-4 months before stem cell collection to reduce the number of malignant cells, whereas ineligible ones receive 8-12 cycles of a triplet regimen accompanied by maintenance therapy.

The first-line therapy for MM is bortezomib in combination with melphalan and prednisone.¹³ In addition, there are different kinds of regimens, such as Revlimid and Velcade and Dexamethasone (RVD), which is a combination of lenalidomide (Revlimid), bortezomib



(Velcade), and dexamethasone.¹⁴ This regimen was considered an effective induction regimen in both eligible and ineligible patients. Both bortezomib (a proteasome inhibitor) and lenalidomide (an immunomodulatory agent) can cause fetal harm if administered in pregnancy.¹⁵ This report discusses a patient who received bortezomib, lenalidomide, and dexamethasone during pregnancy to show no abnormalities occurred despite the administration of bortezomib during pregnancy.

Case Presentation

Our patient was a 38-year-old woman (G2 P2 ABO) with a 1.5-year history of bone pain, anemia, and elevated erythrocyte sedimentation rate. The results obtained in early laboratory tests are provided in Table 1.

She had no previous medical history of hypertension, diabetes mellitus, or hyperlipidemia. She expressed that she has been using nonsteroidal anti-inflammatory drugs such as diclofenac, ibuprofen, pro Re Nata (PRN), and ferrous sulfate once a day. In her physical examination, the auscultation of the lung and the heart was normal. She had pain in her long bones without arthralgia and low back pain with a decreased range of motion in her lumbar region.

Then, supplementary tests were performed because of the suspicion of MM. Serum protein electrophoresis revealed a monoclonal protein spike in the gamma globulin region. Serum immunofixation reported a high level of IgG (5747 mg/dL), IgM < 30 mg/dL, and IgA = 100

mg/dL (NL), accompanied by increased Bence-Jones protein (kappa light chain) in 24-hour urine. Serum kappa-FLC was elevated (920 mg/dL) in the FLC assay (within a normal amount of lambda-FLC). Similarly, there was an increase in beta2-microglobulin (5.4 mg/dL). Further, a bone survey delineated multiple lytic lesions in the skull and right hip. Bone marrow aspiration was performed, showing increased cellularity and myeloid erythroid (M/E) ratio (= 4-5/1). Furthermore, erythroid hyperplasia, diffuse plasma cell infiltration (80%), and adequate megakaryocytes were detected.

Cytogenetic bone marrow analysis in abnormal plasma cells was recognized (del 17p, 46xx); thus, she was diagnosed with symptomatic MM (Durie-Salmon stage IIIA, International Staging System III) and poor cytogenetic prognosis. At the end of the third course, she reported a delay in menstruation, and pregnancy was confirmed with the positive beta-hCG test. By ultrasound sonography, the fetal age was about 9 weeks and 5 days. Due to the risk of fetal defects and the teratogenicity of bortezomib and lenalidomide, it was recommended that abortion be induced or the initial anti-myeloma therapy be changed, but she refused these suggestions; therefore, the fourth course continued as before. Serial ultrasound screenings were performed during pregnancy; the fetus had normal growth without any abnormalities.

The patient received bortezomib and dexamethasone as her maintenance treatment. In the 38th week, she had an elective cesarean. A baby boy was born with a normal Apgar score and a weight of 3200 g without any abnormalities. There was no abnormality in the pediatric examination. Due to the necessity of maintenance therapy, the patient was prohibited from breastfeeding.

The Re-BMA report revealed normal cellularity in the bone marrow, with fewer than 5% of cells being plasma cells. Autologous hematopoietic stem cell transplantation was performed because of poor cytogenetic prognosis. In the next 4-year follow-up, she was in complete remission, and her son had normal growth and development. The last follow-up laboratory tests (4 years after diagnosis) are listed in Table 2.

Discussion

MM is a malignancy of plasma cells producing a monoclonal immunoglobulin and is the second most common hematologic cancer after non-Hodgkin lymphoma.^{16,17} MM is more common in men.¹⁸ Three groups of people are at a higher risk for myeloma, namely, older individuals, individuals with a family history of myeloma, and people with a personal history of monoclonal gammopathy of undetermined significance. MM is observed in older patients with an average age of 67–70 at diagnosis; it is a rare neoplasm before the age of 40; thus, the incidence of myeloma in pregnancy is uncommon.^{17,19} The most common symptoms of pregnant

Table 1. Results of Early Laboratory Tests

Laboratory Tests	Value
WBC	$6.4 \times 10^3/\text{mL}$
Hb	9.5 g/dL
MCV	86.3 fL
Plt	$320 \times 10^3/\text{mL}$
Ca	12.8 mg/dL
P	3.2 mg/dL
LDH	960 U/L
Uric acid	9.7 mg/dL
BUN	28 mg/dL
Cr	0.9 mg/dL
AST	23 U/L
ALT	41 U/L
ALP	490 IU/L
Total bilirubin	1.3 mg/dL
Direct bilirubin	0.6 mg/dL
ESR	110 mm/h
CRP	1 +

Note. WBC: White blood count; Hb: Hemoglobin; MCV: Mean corpuscular volume; Plt: Platelet; Ca: Calcium; P: Phosphorus; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; Cr: Creatinine; AST: Aspartate transferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 2. Last Follow-up Laboratory Tests (Four Years After Diagnosis)

Laboratory Tests	Value
WBC	4.5 × 10 ³ /mL
Hb	12.8 mg/dL
MCV	81 fL
Plt	321 × 10 ³ /mL
Ca	8.1 mg/dL
P	3.2 mg/dL
BUN	31 mg/dL
Cr	0.7 mg/dL
AST	27 U/L
ALT	21 U/L
Total bilirubin	1 mg/dL
Direct bilirubin	0.8 mg/dL
ESR	10 mm/h
CRP	Negative
FBS	97 mg/dL

Note. SPEP: Normal. Serum IgG: 970, Serum IgM: Normal; Serum IgA: Normal; Serum Kappa light chain: Normal; Serum Lambda light chain: Normal. Urine Kappa light chain: Normal; Urine Lambda light chain: Normal; WBC: White blood count; Hb: Hemoglobin; MCV: Mean corpuscular volume; Plt: Platelet; Ca: Calcium; P: Phosphorus; BUN: Blood urea nitrogen; Cr: Creatinine; AST: Aspartate transferase; ALT: Alanine transaminase; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; FBS: Fasting blood sugar.

women with MM are bone pain and anemia.^{20,21}

Myeloma cytogenetic data should be reported in pregnant females because chromosomal abnormalities determine myeloma prognosis²²; del 17p in our patient shows a poor prognosis. Due to the toxic impacts of anti-myeloma therapy on the fetus, four treatment methods are suggested for myeloma during pregnancy, including (1) abortion, (2) treatment with novel agents along with accepting fetal risks, (3) just observing and starting treatment after delivery, and (4) using steroids. In pregnancy, the selection of safe therapeutic agents for myeloma is challenging and limited, especially if the patient intends to continue her pregnancy.^{17,18} Induction therapy is the first phase of treatment in patients with symptomatic MM. Its appropriate approach is a combination of 2 or 3 drugs as an induction regimen; for example, one of the most effective induction regimens in these patients who are candidates for allogeneic stem cell transplantation is the “positive regimen”, including bortezomib, lenalidomide, and dexamethasone for 4–6 cycles.^{23,24}

Bortezomib is a proteasome inhibitor that activates cell-cycle arrest and apoptosis; its two different administration methods are *intravenous* and subcutaneous injection. Based on the mechanism of action and animal studies, its administration during pregnancy may have a teratogenic effect on the fetus; therefore, contraception during therapy and 7 months after treatment is mandatory. Bortezomib should be avoided during pregnancy, although some data are available about its safety, similar

to our case study that demonstrates this issue.^{22,25,26} Lenalidomide is an analog of thalidomide, acts as an immunomodulator, antiangiogenic, and antineoplastic agent, and can cause severe birth defects or fetal lethality; thus, it is contraindicated during pregnancy. Moreover, it is necessary to use effective contraception while taking lenalidomide. The drug must be discontinued if pregnancy occurs during treatment^{21,22}; of course, patient consent is also important in this regard.

Corticosteroids are assumed to be safe during pregnancy and can be used for controlling disease until delivery, as these drugs cause the pregnant woman to deliver a healthy baby.²¹ Moreover, dexamethasone is utilized for increasing the rate of lung maturation and has no undesirable effects on long-term prognosis.^{21,27}

The evaluation of a pregnant woman and her fetus is really important. In this way, serial fetal ultrasound screenings can be helpful^{22,28}; in our reviews, the fetus had normal growth.

Cesarean section is preferred in patients with MM due to worries about bone disease and pelvic stability.²¹ In our case study, a healthy son with a normal APGAR score was born; even subsequent follow-ups did not show any abnormalities up to 4 years old.

Conclusion

According to several studies as well as our case study, it seems that considering the contraindication and teratogenic effects of bortezomib, malformations resulting from its administration may less occur during pregnancy; of course, more extensive studies are needed to confirm this matter. Based on our case report, receiving bortezomib during pregnancy in a patient with MM was accompanied by no abnormalities in the baby (even in the long follow-up).

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Competing Interests

None declared.

Ethical Approval

The patient confidentiality was maintained throughout the presentation of this case report, and no experiments were conducted on human subjects.

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