Refractory Multiple Myeloma

A Case Study

Case: #1
48-Year-Old Male Presented to the ER with Fatigue and Acute Severe Lower Back Pain

Patient assessment:

- X-ray of lumbar spine: L4 compression fracture, lytic disease in L2 and L5
- Blood work: Hb 9.5 mg/L, platelets 178/mm^3, creatinine 4.0 mg/dL, albumin 3.5 mg/dL, Ca 12 mg/dL, LDH 250 U/L
- Hospitalized for acute renal failure, pain control, hypercalcemia and hem/onc consultation

ER=emergency room; Hb=hemoglobin; Ca=calcium; LDH=lactate dehydrogenase; hem/onc=hematology/oncology

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- Additional labs: Serum β2-M 6.0 mg/L, PEP M-protein 4.5 g/dL, IgG lambda, IgG 5200 mg/dL, IgA 35 g/L, IgM 25 g/L, UPEP + lambda light chains
- Bone marrow: 40% plasma cells, cytogenetics normal; FISH: no t(4;14), t(14;16), or del(17p)
- Skeletal survey: multiple lytic lesions; severe L4 compression fracture
- Staging ISS III; Durie-Salmon IIIB
- Patient management plan:
  - Hydration (hydrate but don't drown)
  - Steroids
  - Diuretics???
  - Bisphosphonates?
  - Pain control: morphine 2 mg IV every 2-4 hours PRN pain
  - Treat the disease: IgG lambda multiple myeloma (MM), ISS stage III
    - Disease burden is significant, prognosis is comparatively poor, historic median survival 29 months compared to 62 months for ISS stage I or 44 months for ISS stage II

PEP=protein electrophoresis; Ig=immunoglobulin; UPEP=urine protein electrophoresis; FISH= fluorescence in situ hybridization; ISS=International Staging System; PRN=as needed

Greipp PR, et al. *J Clin Oncol*. 2005;23(15):3412-3420.; Durie BG, et al. *Cancer*. 1975;36(3):842-854.

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- The patient was initially hydrated, treated with bortezomib + dexamethasone [NCCN Guidelines preferred regimens (category 1)] followed by zoledronic acid [NCCN Guidelines: all patients receiving primary therapy should be given bisphosphonates (Category 1)]. Lenalidomide was added during the second cycle after normalization of creatinine [NCCN Guidelines preferred regimens (category 2A)] . The patient underwent HDM and transplant and was placed on lenalidomide maintenance [NCCN Guidelines preferred regimens (category 1)]
- He relapsed after 1.6 years of maintenance (new right femur lesion) and was at that time placed on bortezomib with vorinostat an HDAC inhibitor,* [NCCN Guidelines listed other regimens (category 2A)]. He achieved a PR

*Vorinostat is not US FDA approved for the treatment of multiple myeloma
HDM=high-dose melphalan; HDAC=histone deacetylases; PR=partial remission
National Comprehensive Cancer Network (NCCN) Guidelines Multiple Myeloma Version 2.2013.

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- However, 6 months into therapy he developed grade 2 neuropathy and presented with significant boney progression
- The patient also had an ANC of 800 and platelets of 35,000
- Patient is refractory to current treatment since progression occurred on therapy

- Next steps

ANC=absolute neutrophil count

Major Factors That Influence Choice of Therapy

DISEASE-RELATED[1]	REGIMEN-RELATED[1]	PATIENT-RELATED[1]
DOR to initial therapy	Prior drug exposure	Pre-existing toxicity
FISH/cytogenetics	Toxicity of regimen	Comorbidities
	Mode of administration	Age
	Previous SCT	Performance status

- Non-progressive disease for 1.6 years on maintenance; DOR was good; no high-risk features by FISH/cytogenetics; placed on Bort+vorinostat. Duration of response was poor - 6 months
- Bort/Len/Dex, HDM-ASCT primary therapy followed by lenalidomide maintenance until disease progression; placed on Bort+vorinostat but progressed on therapy with symptoms of peripheral neuropathy, neutropenia and new bone lesions
- Bone lesions- disease related; Young, peripheral neuropathy, likely reversible

Patient is now considered bortezomib refractory and is also lenalidomide refractory

DOR=duration of response; SCT=stem cell transplant; Bort= bortezomib; Len=lenalidomide; Dex=dexamethasone; HDM-ASCT= high-dose melphalan therapy with autologous stem cell transplantation

[1]Lonial SL. ASH Educational Book, 2010..

2013 NCCN Guidelines for Relapsed Myeloma

Preferred Regimens	Other Regimens
•Repeat primary induction therapy (if relapse at >6 months) •Bortezomib (category 1) •Bortezomib/dexamethasone •Bortezomib/lenalidomide/dexamethasone •Bortezomib/liposomal doxorubicin (category 1) •Bortezomib/thalidomide/dexamethasone •**Carfilzomib*** •Cyclophosphamide/lenalidomide/dexamethasone •Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) •Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)±bortezomib (VTD-PACE) •High-dose cyclophosphamide •Lenalidomide/dexamethasone (category 1) •Pomalidomide*/dexamethasone •Thalidomide/dexamethasone	•**Bendamustine** •**~~Bortezomib/~~** •**~~vorinostat~~** •**Lenalidomide/bendamustine/dexamethasone**

*Indicated for patients that have received at least two prior therapies including bortezomib and an IMiD and have demonstrated disease progression on or within 60 days of completion of the last therapy.

[1]NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.2.2013

Selection and Sequencing Rationale

Chosen regimen: Carfilzomib

- Patient has new lytic lesions with relapse significant marrow compromise; previous experienced neuropathy; refractory to combinations of bortezomib and lenalidomide plus dexamethasone, refractory to bortezomib plus HDAC
- Carfilzomib may have advantage in having antiresorptive and bone anabolic activity though this evidence is primarily from in vivo studies and mouse models

Hurchla MA, et al. *Blood* (ASH Annual Abstracts) 2011;Abstract 2906.