Renal Failure in the Multiple Myeloma Patient

A Case Study

65-year-old Male, Relapsed Refractory After HDT-ASCT and Achieving a CR

- 65-year-old male diagnosed 4 years ago
  - Initial induction therapy with CyBorD: achieved a VGPR
  - Consolidation with HDT: achieved a CR
  - Maintenance lenalidomide x 2 years, then discontinued due to fatigue
- Patient did well for 3 years (in CR)
- Last month was noted to have a monoclonal IgG of 1.5 g/dL with creatinine of 1.8 mg/dL

HDT-ASCT=high-dose therapy-autologous stem cell transplant; CR=complete response; CyBorD=cyclophosphamide, bortezomib, dexamethasone; VGPR=very good partial response; IgG=immunoglobulin G

Factors in Selecting Treatment for the Renal Impaired Patient

- Disease-related factors
  - Duration of response to initial therapy
  - FISH or cytogenetic profile (eg, t(4;14) or p53 deletion)
- Regimen-related factors
  - Prior drug exposure (relapsed vs refractory)
  - Toxicity of regimen (combination vs single agent)
  - Mode of administration (eg, oral or intravenous)
- Patient-related factors
  - Preexisting toxicities (eg, cumulative myelosuppression, peripheral neuropathy, performance status)

FISH=fluorescence in situ hybridization

Jakubowiak A. *Semin Hematol.* 2012;49 Suppl 1:S16-32.

Treating the Renally Impaired Patient

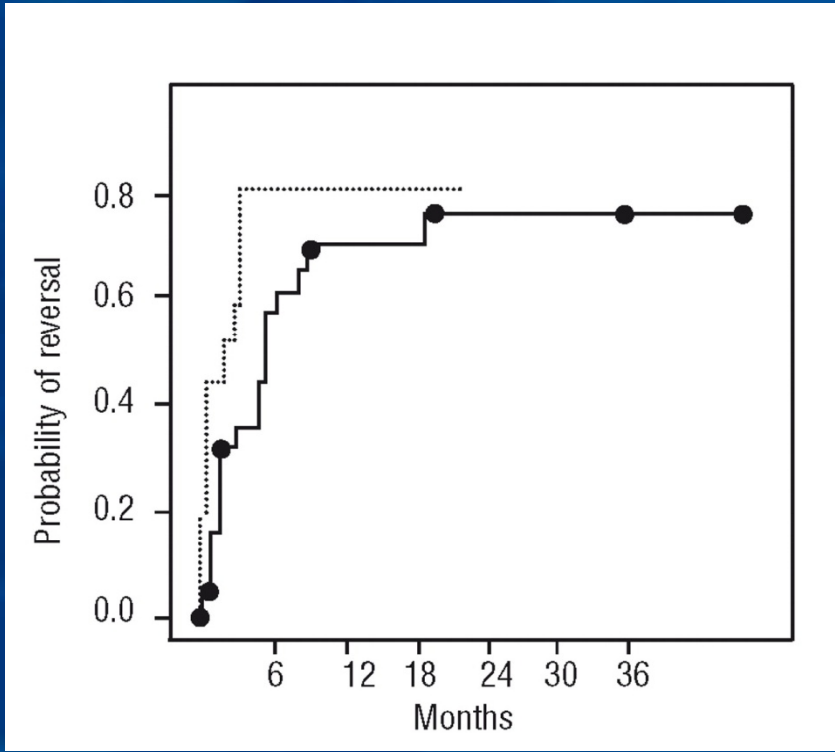
- Reversal of renal failure seen in up to 50% of newly diagnosed patients receiving bortezomib-based regimens (usually with dexamethasone +/- (liposomal) doxorubicin)
  - Can give at full doses
- Can use thalidomide, lenalidomide in renal failure
  - Little efficacy data reported on renal improvement rates
  - Dose-reduce lenalidomide due to increased myelosuppression:
    - CrCl 30-60 mL/min: 10 mg daily
    - CrCl <30 (not on dialysis): 15 mg every other day
    - CrCl <30 (on dialysis): 5 mg daily
- Consider dose-reduced oral melphalan

CrCl=creatinine clearance

Ludwig H, et al. *Haematologica.* 2007;92(10):1411-1414.; Ludwig H, et al. *Blood*. 2007;110:Abstract 3603.; Lenalidomide (Revlimid®) Prescribing information, Jan 2009.; Chanan-Khan AA, et al. *Clin Cancer Res*. 2012;18(8):2145-2163.

Probability of RF Reversal According to Treatment High-Dose Dexamethasone Plus New Agents

Thalidomide and/or Bortezomib



- Renal failure (RF) was reversed in 73% of all patients within a median of 1.9 months
- In patients treated with dexamethasone and novel agents (thalidomide and/or bortezomib) the reversibility rate was 80% within a median of 0.8 months
- Severe RF and significant BJP were associated with a lower probability of RF reversal
- Patients who responded to treatment achieved RF reversal more often than in those who did not (85% versus 56%, *P*=.046)

BJP=Bence-Jones protein

Kastritis E, et al. *Haematologica*. 2007;92:546-549.

Impact of Renal Insufficiency on Time to Progression and Overall Survival*

	None (Cl_{Cr} > 80 mL/min)		Mild (50 ≤ Cl_{Cr} ≤ 80 mL/min)		Moderate (30 ≤ Cl_{Cr} < 50 mL/min)		Severe (Cl_{Cr} < 30 mL/min)	
	Len+ Dex[1]	Bort[2]	Len + Dex[1]	Bort[2]	Len + Dex[1]	Bort[2]	Len + Dex[1]	Bort[2]
Patients, n	158	118	125	137	42	43	16	15
TTP median, months	11.3	6.3	12.1	6.2	11.4	5.6	7.9	4.2
OS median, months	NR	NR	34.7	30.0	30.4	22.8	18.6	22.0

Patients with relapsed MM with varying degrees of renal impairment

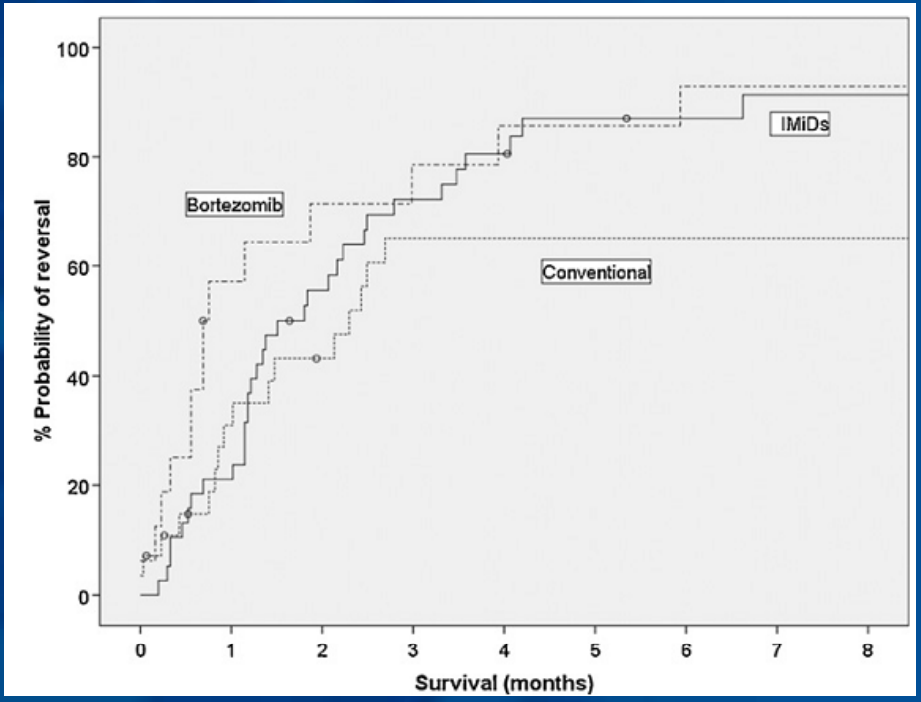
*Not a head-to-head trial comparison

TTP=time to progression; OS=overall survival; Len=lenalidomide; Bort=bortezomib; Dex=dexamethasone; MM=multiple myeloma

[1]Weber D, et al. *J Clin Oncol*. 2008;26:Abstract 8542. [2]San Miguel JF, et al. *Haematologica*. 2007; Abstract PO-114.

Reversing Renal Insufficiency in Newly Diagnosed MM With Novel Agents

- Single center, 96 consecutive, newly diagnosed, patients with MM and RI, over 10 years, were evaluated
- RI was defined as a sustained estimated creatinine clearance (CrCl) <50 mL/min, calculated by the Cockroft-Gault formula, despite volume replacement and reversal of hypercalcemia



- Group A (n= 32) conventional chemo plus dexamethasone (VAD, VAD-like regimens, melphalan plus dexamethasone)
- -Group B (n=47) received IMiD-based regimens (Thal or Len with high-dose dexamethasone and/or cyclophosphamide or melphalan)
- Group C (n=17) received bortezomib- and dexamethasone-containing regimens
- High-dose dexamethasone was given at the standard dosage in all regimens and no low-dose dexamethasone was used in the study population
- Besides antimyeloma treatment, all patients received supportive care: rigorous intravenous hydration, alkalization of urine, correction of hypercalcemia and discontinuation of all nephrotoxic agents. Renal dialysis was offered to all patients with an appropriate indication

Thal=thalidomide

Roussou M, et al. *Leuk Res*. 2010;(10)1395-1397.

Lenalidomide Starting Dose Adjustment for Renal Impairment

Lenalidomide requires dose adjustments according to the severity of impairment

Starting Dose Adjustment for Renal Impairment

Category	Renal Function (Cockcroft-Gault CLcr)	Disease	
		Multiple Myeloma	Myelodysplastic Syndromes
Moderate Renal Impairment	30 ≤ CLcr < 60 mL/min	10 mg Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours	5 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days the dose should be administered following dialysis	5 mg 3 times a week following each dialysis

Lenalidomide FDA Label.