Biochemical and Symptomatic Relapse Disease 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 Relapsed Myeloma

- 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)

What are the tools we use to treat relapse?

FISH=fluorescence in situ hybridization

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

Salvage Therapy: NCCN v1.2014 Guidelines

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 •Bortezomib, cyclophosphamide, dexamethasone •Carfilzomib* •Cyclophosphamide, lenalidomide, dexamethasone •Dexamethasone, cyclophosphamide, etoposide, cisplatin (DCEP) •Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide (DT-PACE) ± bortezomib (VDT-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 other therapies including bortezomib and an IMiD and have demonstrated disease progression on or within 60 days of completion of the last therapy

National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: multiple myeloma. v1.2014 (release date 9/6/2013).

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 >3 years; DOR was good; no progression from CR up to 1 year after discontinuing maintenance; no high-risk features by FISH/cytogenetics	•Bortezomib/ cyclophosphamide/ dexamethasone (CyBorD), HDT-ASCT primary therapy followed by 2 years lenalidomide maintenance discontinued due to fatigue	•Presenting now with biochemical and symptomatic relapse: IgG spike and renal insufficiency, respectively; no other comorbidities; good performance status, age 65 (still transplant eligible)

DOR=duration of response; SCT=stem cell transplant

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

Management Plan

- Given the good duration and depth of response, it would be reasonable to repeat the primary induction therapy and monitor for response
- Technically, the patient has been through two lines of therapy, first primary induction therapy with CyBorD/HDT-ASCT followed by lenalidomide maintenance
  - Maintenance was discontinued due to fatigue (intolerance) and not due to loss of response
- Patient has renal insufficiency so bortezomib-based therapy is preferable
  - If CyBorD is used, check creatinine clearance rate
  - Cyclophosphamide in renal impairment: CrCl <10 mL/min, give 75% of normal dose; CrCl >10 mL/min, give full dose; this patient would receive full dose
- Provide hydration if needed; bisphosphonate if patient has hypercalcemia

Cyclophosphamide and bortezomib Prescribing Inserts.; Mateos MV, San Miguel JF. *Ther Adv Hematol*. 2012;3(2):117-124.; Moreau P, et al. *Clin Pharmacokinet*. 2012;51(12):823-829.; Chanan-Khan AA, et al. *Clin Cancer Res*. 2012;18(8):2145-2163.

Management Plan

- Some experts would begin with IV administration of bortezomib first cycle with the option to switch to SQ subsequently to reduce risk of peripheral neuropathy once renal impairment improves
  - Rationale (pharmacokinetic): maximum (peak) plasma drug concentration (C(max)) is lower with SQ administration than IV and time to C(max) (t(max)) is longer which normally does not have any consequence for efficacy but achieving high (C(max)) in shortest duration in renal impaired patients may be desirable as bortezomib has been shown to have the potential to rapidly reverse renal impairment due to multiple myeloma; note that the majority of these studies were performed using IV administration
  - Provide required support for bortezomib-based regimens including herpes zoster prophylaxis, monitor for peripheral neuropathy, monitor for hematologic side effects including cytopenia
- Goal: deepest possible response for longest duration
- Should failure to achieve depth of response obtained previously, (≥VGPR); the option to switch out cyclophosphamide for lenalidomide is reasonable
- Explore possible next step option of salvage transplant
- Always consider referral to clinical trial

Cyclophosphamide and bortezomib Prescribing Inserts; Mateos MV, San Miguel JF. *Ther Adv Hematol*. 2012;3(2):117-124.; Moreau P, et al. *Clin Pharmacokinet*. 2012;51(12):823-829.; Chanan-Khan AA, et al. *Clin Cancer Res*. 2012;18(8):2145-2163.