My-DST Drug Assay to Optimize Therapy for Multiple Myeloma

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Background

- Multiple Myeloma is a malignancy of plasma cells accounting for ~10% of all hematologic cancers.[1]
- ~32,000 new cases of myeloma are diagnosed each year in the United States.[2]
- Therapy has evolved from traditional chemotherapy to monoclonal antibodies, proteasome inhibitors, and immunomodulatory agents, often in addition to autologous stem cell transplant. [3-5]
- Treatment outcomes have improved but these new treatments are also associated with potential toxicities and significant cost.
- Personalized treatment can be more efficacious and potentially avoid unnecessary side effects and costs.
- Multiple myeloma has broad genetic heterogeneity, many oncogenic drivers, and no targetable gene product making precision medicine challenging.
- Taking a phenotypic approach using *ex vivo* drug sensitivity profiling of tumor samples may lead to targeted personalized therapy, using only active agents, to minimize cost and toxicities.

My-DST

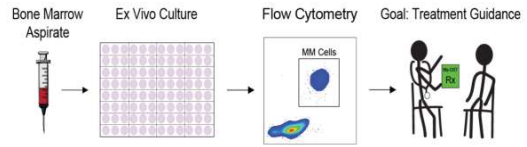

Figure 1: My-DST schematic

- My-DST is an ex-vivo drug sensitivity assay that tests agents used to treat multiple myeloma against patient's cells.
- First, a patient's bone marrow aspirate undergoes mononuclear cell selection.
- Cells are then treated with a panel of anti-myeloma drugs and screened for plasma cell survival using flow cytometry.
- Drugs with greater than 20% cell killing are estimated to be active agents.

Patient Case: 72 y.o. Male

- First developed back pain in sacrum radiating down both legs
- Lumbar x-ray suspicious for lytic bone lesion. Spine MRI with multi-level metastatic disease
- Biopsy of L5 lesion suggestive of plasma cell neoplasm
- Presented to AMC blood disorders clinic for eval and workup
- Diagnosed with IgA-lambda multiple myeloma with lytic bone disease
- ISS stage 1, R-ISS 1, SD 3a, normal karyotype, del13q (std risk)
- My-DST was performed on a sample donated by the patient which showed resistance to immunomodulatory drugs but sensitivity to proteasome inhibitors
- He was treated with four total lines of therapy (see table below)
- As predicted by My-DST, he had a minimal response (MR) to the immunomodulatory agent Lenalidomide, but quickly achieved a very good partial response (VGPR) using bortezomib (proteasome inhibitor) and dexamethasone.

Line of Therapy	Response
1. Lenalidomide + Dexamethasone (Rd)	MR
2. Bortezomib + Dexamethasone (Vd)	VGPR → PoD
3. Elotuzumab + Revlimid + Dexamethasone (EloRd)	PR → PoD
4. Elotuzumab + Pomalidomide + Dexamethasone (EloPd)	PR

Figure 2: Lines of therapy patient received and corresponding response. MR: minimal response, VGPR: very good partial response;, PR: partial response, PoD: progression of disease.

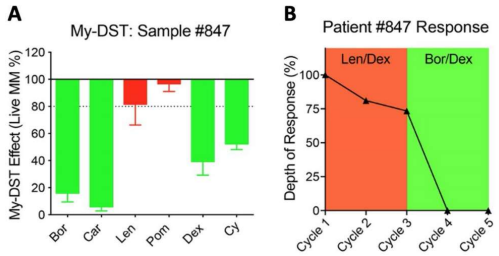

Figure 3: (A) My-DST results from patient sample at time of diagnosis. 81% viable myeloma cells after lenalidomide exposure and only 15% viable after bortezomib. (B) Patient response for line one and two of treatment based on serum free light chains.

Discussion

- Patients with multiple myeloma eventually relapse and become resistant to treatment.
- There are now many treatment choices, but response and side effects are often unpredictable.
- With multiple myeloma which affects primarily older patients with a median onset of 70 years, frailty and comorbidities are also important when discussing toxic treatments.[1]
- Elderly and frail patients are sometimes undertreated or overtreated leading to worse clinical outcomes. Personalized therapies and better drug selection may improve the response for this population.[6]
- This patient case demonstrates the potential benefit of personalized medicine in multiple myeloma treatment as the clinical course corresponded with ex vivo sensitivities.
- My-DST may be one method to improve outcomes for multiple myeloma though a more personalized approach.

Conclusions

- Multiple myeloma is a heterogenous hematologic malignancy with an expanding array of treatments.
- A more optimized/personalized therapy selection approach would reduce exposure to potentially harmful agents with side effects, eliminate wasted time from ineffective agents, and reduce costs.
- This patient case was consistent with the My-DST assay results as he had an inadequate response to lenalidomide/dexamethasone but achieved a very good partial response when switched to bortezomib/dexamethasone.
- Further studies with My-DST need o be done to further evaluate the success of phenotypic-based therapy.

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