1. BIOLOGY AND PRECLINICAL

FROM BENCH TO BEDSIDE: DRUG SENSITIVITY PROFILING TO OPTIMIZE THERAPY IN RELAPSED MULTIPLE MYELOMA

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Introduction. Relapsed multiple myeloma (MM) is a genetically heterogeneous malignancy characterized by variable responses to therapy in later lines of treatment. Despite the availability of highly effective agents, most patients eventually relapse and require additional therapeutic options. Precision medicine is increasingly important in this setting; however, the lack of robust predictive biomarkers limits individualized treatment selection. We evaluated a novel high-throughput drug sensitivity assay (clinicaltrials.gov NCT03389347) to predict treatment responses in relapsed/refractory MM.

Methods. Eligible patients had MM or plasma cell leukemia with relapsed/refractory disease, ≥3 prior lines of therapy (LOT) including an IMiD and a proteasome inhibitor (PI), <VGPR to initial therapy, or early relapse (<12 months) after autologous stem cell transplantation or first-line therapy. The primary objective was to successfully perform drug sensitivity testing and generate an actionable result. CD138+ plasma cells were isolated from bone marrow, blood (if circulating plasma cells were present), or plasmacytoma biopsies using magnetic bead separation. Samples were analyzed at the CLIA-approved Quellos HTS Core (University of Washington). Tumor cells were tested against 170 drugs (Oncopanel2 v1, n=30) or a refined 46-drug panel (Oncopanel2 v2, n=10). Drug response was assessed using IC50, area under the curve (AUC), and drug sensitivity scores (DSS) calculated with Breeze 2.0 software. Treatment recommendations were guided by assay results. Receiver operating characteristic (ROC) analysis and Youden's J index were used to evaluate DSS performance for selected drugs.

Results. Between March 2018 and December 2024, 40 patients were enrolled, with a mean of 5 prior LOT (range 2–15). Prior exposures included lenalidomide (100%), bortezomib (97.5%), carfilzomib (85%), daratumumab (82%), pomalidomide (77.5%), and BCMA CAR-T therapy (12.5%). Thirty patients received Oncopanel2 v1 and ten Oncopanel2 v2. The highest DSS scores in v1 were observed for bortezomib (median 47.7), carfilzomib (47.3), panobinostat (47), and romidepsin (45.4). In v2, the top agents were marizomib (46.1), carfilzomib (40.2), ixazomib (37.2), and oprozomib (31.6). Thirty-eight patients received a subsequent LOT, achieving an overall response rate of 51.4% (29.7% PR, 13.5% VGPR, 5.4% CR). Median progression-free survival was 5.7 months (95% CI 2.5–13). ROC analysis for bortezomib (n=12) and selinexor (n=8) showed AUCs of 0.471 and 0.462, respectively. Selinexor responders tended to have higher DSS values (27–35) compared with most non-responders (20–30), although this was not statistically significant (p=0.1).

Conclusions. High-throughput drug sensitivity testing is feasible in relapsed/refractory MM and can provide actionable results DSS performance varied by agent, underscoring the need for drug-specific threshold optimization. A trend toward higher DSS in selinexor responders suggests potential predictive value, but larger validation cohorts focusing on a limited drug set are required to establish clinical utility.

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