Novel Treatment Approaches to Multiple Myeloma

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Multiple myeloma (MM) is a remarkable example of rapid bench-to-bedside translation in new drug development. The proteasome inhibitor bortezomib (V) and immunomodulatory drug lenalidomide (R) target MM cells in the bone marrow (BM) microenvironment to overcome conventional drug resistance in laboratory and animal models, and were rapidly translated to clinical trials demonstrating their efficacy earlier in the disease course, with doubling of median survival as a direct result. Combinations of targeted therapies such as RV with dexamethasone (D) achieve unprecedented extent and frequency of response, and the role of high dose therapy and stem cell transplantation is being re-evaluated in this context. Immune-based therapies underdevelopment include: elotuzumab (anti-CS1) and daratumumab (anti-CD38) MoAbs; anti-BAFF MoAb; CD138DM immunotoxin; MM cell-dendritic cell vaccines; and CD138, CS-1, and XBP-1 peptide vaccines. For example, genomic analyses showed CS-1 to be universally expressed at the gene and protein level in patient MM cells, and bedside back to bench studies validated its role in MM cell survival in our preclinical models. A derived clinical trial of elotuzomab in relapsed refractory MM achieved stable disease, but did not trigger clinical responses sufficient to warrant its further development as a single agent. However, our laboratory studies showed that lenalidomide augments antibody dependent cellular cytotoxicity, and a derived clinical trial of this combination now shows great promise. Next-generation agents targeting the MM cell in its microenvironment include: deubiquitinating enzyme inhibitors; chymotryptic (carfilzomib, Onyx 0912, MLN 9708) and more broad (NPI-0052) proteasome inhibitors; as well as next generation immunomodulatory drug pomalidamide. Carfilzomib has recently received, and pomalidomide is now under consideration for, accelerated approval to treat relapsed refractory MM, highlighting their ability to overcome resistance even to bortezomib and lenalidomide. MLN9708 is oral and achieves remarkable extent and frequency of response when combined with RD, suggesting an all oral regimen to treat MM in the future. Rationally-based combination therapies including bortezomib with Akt or HDAC inhibitors (HDAC1,2 inhibitors vorinostat or panabinostat, HDAC6 selective inhibitor ACY 1215) are active even in bortezomib refractory MM. Finally, genomics is used for development of personalized therapy and new target discovery. Gene profiling, microRNA profiling, and DNA-based single nucleotide polymorphism (SNP) array studies can predict prognosis, but no universal signature is established. Gene sequencing studies reveal mutated genes in processes consistent with MM biology including:

protein homeostasis, NF-kB signaling, interferon regulatory factor 4 and blimp, and histone methylating enzymes; as well as unexpected BRAF mutations. Oncogenomic studies have identified novel target and targeted therapies which have been validated in our models of MM in the BM milieu, including bromodomain inhibitors and Btk inhibitors. Importantly, personalized medicine must include profiling of patient samples not only at diagnosis but also over time, as early studies now show continued evolution of genetic changes with progressive MM. Myeloma therefore represents a paradigm of targeting the tumor in its microenvironment which has already markedly improved patient outcome in MM and has great potential in other hematologic malignancies and solid tumors as well.

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