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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Development of First in Class DNA-Zip Code Drug Conjugate (ZDC) in Multiple Myeloma

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Multiple myeloma is a heterogeneous malignant plasma cell disorder with complex molecular and genetic abnormalities. Significant advances have been made in the treatment of multiple myeloma; however, a large proportion of patients fail to attain a favorable response and relapse. Due to efficacy and toxicity, the development of drug conjugates for multiple myeloma has been limited. Our lab discovered that circulating tumor DNA (ctDNA) serves as a cell-specific mechanism for genetic transmission. Certain retrotransposon sequences within the ctDNA were identified as being crucial for the tropism of ctDNA to target tumor cells (Cinar et al bioRxiv.2022). We therefore query whether these transposons can be exploited for the targeted drug delivery. To do so, chemically synthetize and CY5-labeled multiple retrotransposons DNA sequences (a.k.a Zip Codes, ZC) to perform high through put screening assessing for cell targeting. Our findings showed that the AluSp and MER11c DNA sequences (MM-ZC1 and 2) with unique MM mutations were the most efficient and specific DNA sequences for targeting myeloma cells. Furthermore, Flow cytometry and CYTOF validated the specific MM cell targeting on full bone marrow samples from MM patients. Based on this analysis we used MMZC1 for further drug development. We design a drug conjugation approach for the MMZC and screen various drugs for their killing potential. Two potent MM ZC drug conjugates (ZDC) were identified by high throughput viability screening assay: ZC-DM4, a microtubule inhibitor, and ZC-Carfilzomib, an irreversible proteasome inhibitor. We move forward exploration with ZC-DM4 due to limited carfilzomib-linker drug availability. Experiments cancer cell lines in vitro demonstrated that MMZC-DM4 had a potent killing effect on MM cells (IC50: 3.25 nM) but not on other cancer cell lines. These results were the validated in vivo. Maximum tolerated dosing studies (MTD) demonstrated excellent tolerability in all doses (ranges from 1 to 20 mg of MMZC-DM4/Kg (equivalent to 0.007-0.149 mg of DM4/kg). To look for an efficacy signal of MMZC-DM4, MM xenograft mice were given MMZC-DM4 twice a week for three weeks. Due to limitations in production, we treated the animals biweekly with three distinct low doses of MMZC-DM4: 1.9, 3.75, and 7.5 mg/kg (equivalent to 0.014, 0.028, and 0.056 mg of DM4/kg) and compared their response to mice not treated with MMZC-DM4 and mice treated weekly with bortezomib. MMZC-DM4 at such small doses reduced the tumor by 30% without affecting body weight, WBC, HB, AST, or platelets. In contrast, Bortezomib was associated with 90% growth inhibition at the expense of significant weight loss that required treatment interruptions and thrombocytopenia. Currently, investigations are being conducted to examine the therapeutic efficacy of greater doses of MMZC-DM4. This study described the first-in-class MM targeted medicine delivery employing an MM zic code drug conjugate. Our findings suggest new method for targeted delivery therapeutic cargo material directly to cancer cells that could revolutionize cancer treatment.

Disclosures No relevant conflicts of interest to declare.

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