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2672 Pre-Clinical Evaluation of a Camsirubicin Analog Mnpr-202 in Diffuse Large B Cell Lymphoma

Oral and Poster Abstracts
Session: 605. Molecular Pharmacology and Drug Resistance: Lymphoid Neoplasms: Poster II

Sunday, December 11, 2022, 6:00 PM-8:00 PM
Hall D (Ernest N. Morial Convention Center)

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Diffuse large B cell lymphoma (DLBCL) is the most common subtype of aggressive lymphoma, for which the standard-of-care treatment is rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). Although the majority of patients respond to R-CHOP, around 40% relapse after first line treatment. Inability to tolerate or maintain dose-intensity of the anthracycline doxorubicin increases relapse risk after R-CHOP treatment. A key side effect of doxorubicin that contributes to its poor tolerance especially in the elderly is its cardiotoxicity. Thus, the development of anthracycline derivatives which retain anti-cancer properties but show reduced cardiotoxicity could have an impact in the treatment of DLBCL. Camsirubicin (MNPR-201; GPX-150; 5-imino-13-deoxydoxorubicin) is a novel analog of doxorubicin, which shows reduced cardiotoxicity in pre-clinical studies, and to-date across two Phase 1 trials and a Phase 2 trial has not shown any of the signs of irreversible heart damage seen with doxorobucin. Here we report on early pre-clinical studies in DLBCL cell lines with MNPR-202, a camsirubicin analog which retains the non-cardiotoxic backbone but is modified at other sites, which may enable it to evade doxorubicin drug resistance mechanisms.

We performed a comparative *in vitro* study between doxorubicin and MNPR-202 to evaluate the feasibility of substituting doxorubicin with this novel compound. By treating 8 DLBCL cell lines (SC-1, SU-DHL-2, SU-DHL-4, SU-DHL-6, OCI-Ly3, OCI-Ly8, HT, and DOHH2) with either doxorubicin or MNPR-202, we compared broad phenotypes such as cell proliferation, extent of apoptosis, and DNA damage. We determined through Cell Titer Blue assays that doxorubicin and MNPR-202 had similar effects on cell proliferation and comparable IC50s. Interestingly, with 24-48 hours of drug exposure, MNPR-202 appeared to be more potent in inducing apoptosis as indicated by Annexin-PI staining. Western blot analysis for y-H2AX, a marker of DNA damage, also demonstrated increased DNA damage after MNPR-202 treatment relative to doxorubicin.

Next, we compared activation of immunomodulatory innate immune response genes of the cGAS/STING and RIG-I pathways by doxorubicin and MNPR-202, using qPCR of interferon stimulated genes after drug treatment in lymphoma cells. In contrast to the experiments on DNA damage and apoptosis, doxorubicin treatment consistently induced the expression of these genes while MNPR-202 did not.

Finally, in an effort to determine potential synergistic compounds MNPR-202 could be combined with to enhance efficacy, we performed a drug screen with a library of approximately 200 compounds. This screen revealed distinct differences in the synergy profile between doxorubicin and MNPR-202. For example, a clear antagonistic effect on cell killing was seen between PLK1 inhibitor, volasertib, and doxorubicin, but between volasertib and MNPR-202, this antagonism was seen to a significantly lesser extent.

Taken together, these findings indicate that doxorubicin and MNPR-202 overall have a similar cytotoxic potency, but likely work through distinct cellular pathways. MNPR-202 appears to induce more DNA damage and apoptosis, but less ancillary innate immune activation. These intracellular differences also influence drug synergies observed with the two chemotherapeutics, implying that in the context of certain combinatorial regimens, MNPR-202 may be superior to doxorubicin. Overall these findings suggest promise for further *in vivo* and clinical evaluation of MNPR-202 as a potentially effective yet non-cardiotoxic anthracycline derivative in lymphoma.

Disclosures: Nair: *Monopar Therapeutics:* Current Employment. **Chng:** *Amgen:* Honoraria; *J&J:* Honoraria, Research Funding; *Celgene:* Honoraria, Research Funding; *BMS:* Honoraria; *Abbvie:* Honoraria; *Novartis:* Honoraria; *Takeda:* Honoraria; *Hummingbird:* Research Funding. **Robinson:** *Monopar Therapeutics:* Current Employment, Other: CDR is the Co-Founder, Chief Executive Officer and Board Member of Monopar Therapeutics. **Jeyasekharan:** *Turbine Ltd:* Consultancy; *Perkin Elmer:* Other: Travel funding; *IQVIA:* Consultancy; *MSD:* Consultancy; *Janssen:* Consultancy, Research Funding; *Antengene:* Consultancy; *AstraZeneca:* Consultancy, Research Funding.

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