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POSTER ABSTRACTS

614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

The Topoisomerase-I Inhibitor Gimatecan Exhibits Potent and Selective Activities Against B-Cell Precursor Acute Lymphoblastic Leukemia with a Favorable Cardiotoxicity Profile

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Topoisomerase-II inhibitors such as daunorubicin have long been the standard chemotherapeutic agents for managing acute leukemias. Yet, severe complications could be resulted from their myelosuppressive and cardiotoxic nature. Here, we report preclinical evidence showing the exceptional activities of gimatecan, an orally available topoisomerase-I inhibitor currently being investigated in Phase II trials for solid cancers, on hematologic malignancies.

Activity screening on leukemia cell lines revealed a substantially higher potency of gimatecan than frontline chemotherapeutics against B-cell precursor acute lymphoblastic leukemia (BCP-ALL) driven by on-target depletion of topoisomerase-I. Gimatecan had a median IC50 of 0.9 nM against BCP-ALL with profound selectivity over acute myeloid leukemia (AML, 3.6-fold, $P< 0.01$) or hematopoietic stem/progenitor cells (HSPCs, 75-fold, $P< 0.001$). In contrast, the four standard chemotherapeutics (cytarabine, daunorubicin, dexamethasone and vincristine) exhibited much higher median IC50s against BCP-ALL (18-2,201 nM). Following single-agent gimatecan treatment, complete dissolution of medullary and extramedullary leukemia (CNS and testis) by >95% inhibition concomitant with markedly extended survival (1.2 to 3.3-fold, $P< 0.01$) were demonstrated in animals grafted with cytogenetically distinct lymphoid leukemia cell lines (Reh, *ETV6-RUNX1+*; 697, *TCF3-PBX1+*; RS4;11, *KMT2A-AFF1+*; HAL-01, *TCF3-HLF+*) and in patient-derived xenografts from three cases of highly resistant BCP-ALL failing salvage chemotherapy or upfront immunotherapies. Splenocytes isolated from NSG mice relapsed from gimatecan treatment demonstrated recurrent drug sensitivity *ex vivo* comparing with vehicle controls and that gimatecan reinduction offered additional survival benefits in the xenograft model ($P< 0.05$). The therapeutic efficacy was also observed at varied initial tumor load, together suggesting its potential for reinduction and flexibility on the administration schedule.

In NSG mice reconstituted with cord blood HSPCs, gimatecan displayed a mild but transient suppression on normal hematopoiesis without bias on lineage output (63% reduction at 6 weeks, $P=0.002$; not statistically significant at 14 weeks). Importantly, gimatecan did not affect the viability of human iPSC-derived cardiomyocytes (hiPSC-CM) even at the highest tested dose (1,000 nM) as opposed to daunorubicin (IC50: 130 nM). Concordantly, no noticeable signs of DNA damage (by γ-H2AX staining) or apoptotic events (by enumeration of condensed nuclei) on hiPSC-CMs were observed after gimatecan exposure at doses at or above its Cmax (~130 nM). The gross structure of heart tissues harvested from gimatecan-treated mice was also intact without signs of cardiotoxicity at the dose effective to suppress leukemia (0.2 mg/kg). When compared with malignant B-lymphoblasts, there was a declined expression of topoisomerase-I in HSPCs (0.63-fold, $P=0.025$) and cardiomyocytes (0.24-fold, $P<0.001$), potentially explaining its selectivity against BCP-ALL.

Mechanistically, gimatecan induced time- and dose-dependent cell death via intrinsic apoptosis coupled with G2/M cell cycle arrest. RNA-seq analysis of gimatecan-treated BCP-ALL cells showed activation of the tumor suppressive p53 pathway and

suppression of the MYC pathway. Phosphorylation of p53 and appearance of DNA damage markers, including CHK1/2, PARP and H2AX, were robustly detected upon gimatecan treatment.
In short, gimatecan possesses remarkable anti-leukemia activities and tolerable toxicity profiles compared to counterpart topoisomerase-II inhibitor. This study, therefore, puts forward a new agent for BCP-ALL and points towards randomized clinical trials to realize its potential on acute leukemias.

Disclosures No relevant conflicts of interest to declare.

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