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Short Commentary

Past, Present and Future of Uproleselan-A New Anti-Leukemia Drug

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DECRIPTION

Acute Myeloid Leukemia (AML) therapy has improved over decades, yet patients continue to die from persistent or recurrent disease, as well as complications of therapy. 2024 estimated new cases and deaths in the United States (US) were 20,800 and 11,220, respectively [1]. Five-year survival from 2014-2020 was 31.9% [2]. Over time, survival has improved due to better supportive care, new anti-leukemia drugs, and advances in management of chemotherapy toxicity. Yet cytotoxic therapies induce remissions and prolong survival at the cost of potentially fatal organ damage, immune dysfunction, and marrow suppression. Hence, new conventional therapy agents have not significantly improved outcomes, except for all-trans retinoic acid and arsenic trioxide in acute promyelocytic leukemia [3]. Importantly, increasing numbers of patients are receiving allogeneic Hematopoietic Cell Transplantation (HCT), the treatment with highest probability of cure, partly due to emergence of haploidentical HCT [4,5]. The E-selectin antagonist uproleselan introduces a promising new mechanism with potential for AML therapy. E-selectin is an endothelial cell surface mediator of cellular adhesion. Selectin glycoproteins mediate binding to cell surface carbohydrates on leukocytes [6], such as the E-selectin binding ligand, sialyl Lewis^x [7]. Three homologous selectins are distinguished by their cells of origin: E-selectin in endothelial cells, P-selectin in platelets, and L-selectin in lymphocytes [8].

E-selectin is expressed on vascular endothelium where it supports both normal hematopoiesis and innate inflammatory cell migration to local sites of inflammation. Winkler and associates showed in mice that bone marrow endothelial cells express E-selectin in the vascular Hematopoietic Stem Cell (HSC) niche [9]. Both HSC quiescence and self-renewal potential were increased in E-selectin knockout (Sele (-/-)) mice, or alternatively after administration of an E-selectin antagonist (GMI-1070, rivipansel). Given that bone marrow suppression follows cytotoxic chemotherapy, transient E-selectin blockade potentially represents a promising treatment for HSC protection during chemotherapy or irradiation. Correspondingly, AML cells bind to E-selectin in bone marrow and display chemotherapy resistance [10]. Thus, E-selectin inhibition may disrupt cell adhesion, mobilize leukemic cells into the blood, and increase their susceptibility to cytotoxic chemotherapy. *In vitro* studies show that E-selectin mediates AML chemotherapy resistance and thus presents a promising therapeutic target [10, 11]. AML blasts with highest E-selectin binding potential possess a 12-fold greater probability to survive after cytotoxic chemotherapy in mice and are primary contributors to disease relapse [12]. Thus, therapeutic blockade of E-selectin by uproleselan is hypothesized to inhibit pro-survival signaling, impair blast regeneration, and reduce resistance to cytotoxic chemotherapy [12]. Additionally, chemotherapy-induced mucositis and neutropenia associate preclinically with E-selectin upregulation, suggesting that uproleselan might protect the gastrointestinal tract and reduce mucositis risk following intensive chemotherapy. Winkler et al., [9,13] showed that E-selectin inhibition accelerated neutrophil recovery and reduced intestinal mucositis and death in mice after chemotherapy or total body irradiation.

Uproleselan, a small molecule inhibitor of E-selectin now in clinical trials, interferes with leukemia cell adhesion and increases cytotoxic chemotherapy efficacy, despite lacking single-agent anti-leukemia efficacy [8]. The agent exhibits less than 10% plasma protein binding, is not metabolized by liver, and does not induce or inhibit CYP enzymes or P-glycoprotein Uy et al., Appendix A. Supplementary Data, Pre-Clinical Pharmacology Supplement) [8]. Uproleselan is renally excreted and has a half-life of 3.4 hours. Clinical studies show that uproleselan has unremarkable toxicity with no relationships observed among systemic uproleselan pharmacokinetics (AUC or Cmax) *versus* anemia, neutropenia, thrombocytopenia, febrile neutropenia, infection, mucositis, sepsis, hypoxemia, renal adverse events, or changes in bleeding time or coagulation factors [8,14,15].

Clinicians are interested in both increased anti-leukemia efficacy and protection against mucositis for their patients. A phase 1-2 trial in older adults with relapsed/refractory or newly diagnosed AML assessed uproleselan's safety, tolerability, and efficacy when administered in combination with conventional cytotoxic

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chemotherapy. The Recommended Phase 2 Dose (RP2D) was established in 19 patients with relapsed/refractory AML who received uproleselan with Mitoxantrone Etoposide Cytarabine (MEC) induction chemotherapy. The uproleselan RP2D was established to be 10 mg/kg IV. The initial cohort was expanded to 66 patients, and separately a cohort of 25 newly diagnosed AML patients were given uproleselan plus conventional 7+3 induction therapy. Adverse event rates resembled those using MEC or 7+3 regimens alone. Notably, severe oral mucositis was reported in only 2% of patients treated with uproleselan. In relapsed/refractory AML, the complete remission (CR)/CR incomplete (CRi) rate was reported to be 39%, and 69% of responders were negative for Measurable Residual Disease (MRD). For newly diagnosed AML, CR/CRi was 72% [14]. Uproleselan subsequently was studied in two large, randomized trials. The first (NCT03616470 at www.clinicaltrials.gov) combines uproleselan or placebo with intensive chemotherapy in 388 adults with relapsed or refractory AML. Enrollment completed in November 2021, and results are pending. A second, adaptive phase 2-3 trial (NCT03701308 at www.clinicaltrials.gov) studies 7+3 induction with or without uproleselan AML patients >60 years old with previously untreated AML. The phase 2 portion has completed enrollment of 267 patients, and results are pending [8].

Given unremarkable toxicity of uproleselan and its apparent lack of drug-drug interactions, uproleselan is also being studied in combination with other AML chemotherapy regimens. Jonas and co-workers are studying uproleselan with azacytidine and venetoclax for frontline treatment of older or unfit patients in a phase 1b open label trial (NCT04964505 at www.clinicaltrials.gov). No dose-limiting toxicities were noted in six of eight patients who completed treatment; five CRs and one CRi were observed, of whom 4 (67%) were MRD negative. Huante and colleagues combined uproleselan with cladribine and low-dose cytarabine in 20 patients with secondary AML, all of whom had adverse cytogenetics and prior hypomethylating agent therapy (NCT04848974 at www.clinicaltrials.gov) [15-17].

CONCLUSION

This combination reduced marrow blasts in 72% of recipients and appears to be a low-risk approach to marrow blast reduction in preparation for HCT in this difficult to treat population. Future study of uproleselan may include investigations with molecular targeted agents, for prevention of diarrhea/mucositis, in addition to HCT, and as part of treatments for other hematologic malignancies, such as multiple myeloma. Data thus far suggest uproleselan may be a valuable addition to anti-AML therapy.

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