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616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Fludarabine, Cytarabine (ARA-C) and Pegylated Erwinase (PEGCRISANTASPASE) in Patients with Relapsed or Refractory Leukemia

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Background:
Asparaginase, which depletes serum asparagine by breaking it down into asparagine, is part of the standard of care along with chemotherapy, in adolescent and young adult patients with acute lymphoblastic leukemia (ALL). Leukemic blasts require asparagine for survival, therefore serving as an important therapeutic target; among the mechanisms of resistance includes the upregulation of expression of asparagine synthetase (AS) (gene located in chromosome 7). Depletion of asparagine and more recently glutamine may also have an important role in the treatment of acute myelogenous leukemia, either alone or in combination with chemotherapy. Pegcristaspase (PegC) is a long-acting pegylated asparaginase derived from Erwinia that also has a glutaminase activity. We hypothesize that the combination of chemotherapy and PegC might overcome resistance and provide therapeutic benefit pts with relapsed and/or refractory leukemias.

Methods:
This is a phase Ib study of fludarabine, cytarabine (ara-c), and PegC in patients with relapsed or refractory leukemia (NCT 04526795).
Pts received induction cycle (C) (defined as 5 weeks) with PegC on day (D) 1 and 15 as single agent. Fludarabine (30mg/m ^{2}/D) and 4 hours later Cytarabine (1.5g/m ^{2}/D) are given D 8 to D 11. A 3+3 dose-escalation approach was implemented to evaluate 3 different dose levels for pegcrisantaspase (level -2: 350 IU/m ^{2}; level -1: 500 IU/m ^{2}; and level 1: 750UI/m ^{2}). Once the MTD is established, an expansion cohort to further evaluate safety and efficacy was opened. Endpoints included safety, overall response rate (complete remission [CR], CR with incomplete count recovery [CRi], partial remission [PR], or morphologic leukemia free state [MLFS]) of fludarabine, araC, and pegcrisantaspase in patients with relapsed and refractory leukemias. Response was denoted as per the ELN 2017 criteria.

Results:
From April 2021, 15 pts have been treated on the trial, 12 (80%) pts with AML, 2 pts (13%) with ALL (one patient was Ph+ ALL), and 1 patient with isolated myeloid sarcoma. The median age was 46 years (range, 22-61), median bone marrow blasts were 37% (1-90) . 9/15 (60%) patients had complex karyotype. Patient characteristics are summarized in Table 1. The median lines of prior therapy was 4 (range, 1-9). Six pts were treated at dose level -1 and then at dose level 1. There were no dose limiting toxicities to proceed to the expansion cohort. From the 15 treated pts, 2 patients from the dose level -1 died from sepsis related to disease progression within the first 4 weeks. Overall, 3 pts (20%) responded to treatment (2CRp and 1 CRi). The patient with Ph+ B-ALL achieved CRp, proceeded to SCT, and remains alive in remission. The 2 other patients (both with AML) relapsed after 6 weeks and 4 months, respectively. The median overall survival was 2.6 months. (Figure 1)
A total of 29 adverse events (AE) were noted in 13/15 patients. The most common AEs was grade ≥ grade 3 neutropenic fever (10 pts, 67%; including 2 grade 5 events). The only possibly related AE was tumor lysis syndrome in one patient, grade 3, and was successfully managed per institutional guidelines.

Conclusion:
In this high-risk, heavily treated population, the combination of fludarabine, cytarabine, and PegC is feasible. Responding patients included 2 AML and 1 ALL. Further exploratory analysis about the relation between response and asparagine depletion as well as specific sensitive subsets could clarify which patients might benefit the most from this combination.

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Table 1. Baseline Characteristics		N (%), median [range] (N=32)
Age (yrs)		64 (22-81)
Gender	Males	6 (40)
ECOG PS	0	3 (20)
	1	9 (60)
	2	3 (20)
Diagnosis	AML	12 (80)
	B-ALL	2 (13)
	MS	1 (7)
BM Blasts (%)		37 [1-90]
Cytogenetics	Diploid	3 (20)
	Complex	9 (60)
	Ph	1 (7)
	MECOM	3 (20)
	Del(7)	3 (20)
	Del(17p)	1 (7)
	KMT2A	4 (27)
	Del(5)	4 (27)
Mutations	RAS (N/K)	6 (40)
	DNMT3A	2 (13)
	ASXL1	2 (13)
	NPM1	5 (33)
	TP53	2 (6)
Prior therapy details	Prior lines	4 [1-9]
	Venetoclax exposed	14 (93)
	SCT	8 (62)

Treatment outcomes		N (%), median [range]
Cycles on therapy		1 [1-3]
ORR		3 (23)
	CRp	2 (15)
	CRi	1 (8)
Non- responders		12 (80)
	NR	10 (67)
	Died in aplasia	2 (13)
Time to count recovery (in responders; C1) (days)	ANC ≥ 0.5 x 10^9/L	36 [11-43]
	Platelet ≥ 50 x 10^9/L	37 [25-63]

Figure 1. Swimmer's plot on each patient outcome.
*Patient 9 was not evaluable for response due to early death.
CR Complete response. Cri Complete response with incomplete hematological recovery. NR No response. HSCT Hematopoietic stem cell transplant

Figure 1