Phase I Study of Escalating Doses of Carfilzomib with Hyper-CVAD in Patients with Newly Diagnosed Acute Lymphoblastic Leukemia/Lymphoma

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Introduction

- Hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper-CVAD) results in high complete remission (CR) rates, long-term survival in 30-40%[1], and measurable/minimal residual disease (MRD) negativity in 50% adults with acute lymphoblastic leukemia (ALL)[2].
- Proteasome inhibitors have synergistic activity with chemotherapy in relapsed ALL[3].
- Carfilzomib, a next-generation irreversible and selective inhibitor of the chymotrypsin-like activity of the proteasome, shows increased specificity, potency, and cellular apoptotic sensitivity compared to bortezomib in ALL[4].
- Carfilzomib shows preclinical activity in ALL *ex vivo* studies, and has promising synergism with dexamethasone[3-4].
- We hypothesized that adding carfilzomib to Hyper-CVAD would be safe and could better outcomes in adults with ALL.

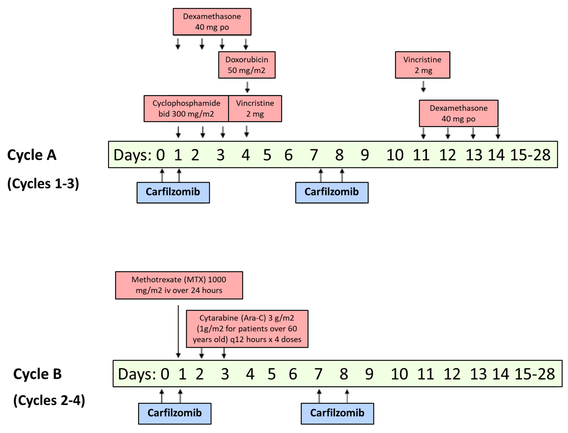
Objectives

- Primary objective: to determine safety, tolerability, and recommended phase two dose of carfilzomib added to Hyper-CVAD in patients with newly diagnosed, untreated Philadelphia chromosome negative ALL.
- Secondary objectives: to determine rate of CR and MRD negativity (NCT02293109)

Methods

- We conducted a Phase 1 study on newly diagnosed ALL patients aged 18-65 with adequate left ventricular, renal, and liver function.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 required.
- Patients received a total of four 28-day cycles of standard Hyper-CVAD (two courses each of cycle A and B), and were followed for up to 28 days after completion of therapy.
- For each of the four cycles, four doses of carfilzomib were added on days 0, 1, 7 and 8 (Figure 1).
- Rituximab was added for CD20 positive disease patients.
- Dose escalation of a standard 3+3 design with carfilzomib dose levels (DL) of 20mg/m^2 (DL1), 27mg/m^2 (DL2) and 36mg/m^2 (DL3).
- Dose-limiting toxicities (DTLs) were assessed through completion of one A and B cycle.
- Adverse events (AEs) were graded using NCI Common Terminology for Adverse Events version 4.03.
- MRD was tested by multiparameter flow cytometry (MFC) and <0.01% was considered negative.

Figure 1. Study treatments and doses.



Results

Table 1. Patient characteristics.

Baseline characteristics	n (%)/median [range]
	n = 10 (100)
Age, years	38 [23-61]
Gender	
Male	5 (50%)
Female	5 (50%)
ECOG	
0	4 (40%)
1	5 (50%)
2	1 (10%)
Diagnosis	
B-ALL	8 (80%)
T-ALL	2 (20%)
Cytogenetics	
Normal	3 (30%)
IgH Rearrangement	4 (40%)
Other	3 (30%)
CD20+	
Present	5 (50%)
Absent	5 (50%)
WBC	8.95 [1.5-201.5]
CNS Disease	
Present	1 (10%)
Absent	9 (90%)

Results

Patient disposition and treatment.

- 10 patients enrolled.
  - DL1 carfilzomib 20mg/m^2 (n = 3)
  - DL2 carfilzomib 27mg/m^2 (n = 3)
  - DL3 carfilzomib 36mg/m^2 (n = 4)
- One subject was replaced during cycle 1 for adverse events not meeting DLT criteria.
- No patient experienced a DLT.
- Median cycles completed = 4 [range 1-4].
- 20% of patients (n =2) had a dose modification (both related to AE), and 30% (n = 3) had a dose delay (two related to AE).

Table 2. Treatment-emergent adverse events (AEs) possibly, probably or definitely related to study therapy in ≥ 20% of participants with events ≥ grade 3.

n = 10	All grades	Grade ≥3
Any AE	10 (100%)	10 (100%)
Blood and Lymphatic System		
Anemia	10 (100%)	10 (100%)
Febrile Neutropenia	7 (70%)	7 (70%)
Thrombocytopenia	10 (100%)	10 (100%)
Leukopenia	10 (100%)	10 (100%)
Neutropenia	10 (100%)	10 (100%)
Lymphopenia	9 (90%)	9 (90%)
Metabolism and nutrition disorders		
Hyponatremia	7 (70%)	2 (20%)
Hypocalcemia	5 (50%)	2 (20%)
*No grade 5 events. No cardiac AEs apart from related grade 1 sinus tachycardia in one patient.		

Table 3. Treatment-emergent serious adverse events (SAEs) possibly, probably or definitely related to study therapy in ≥ 20% of participants with events ≥ grade 3.

n = 10	All grades	Grade ≥3
Any SAE	7 (70%)	7 (70%)
Blood and Lymphatic System		
Febrile Neutropenia	6 (60%)	6 (60%)
Thrombocytopenia	2 (20%)	2 (20%)
Leukopenia	2 (20%)	2 (20%)

Table 4. Rate of complete remission (CR).

CR (n = 10)	n (%)
After 2 cycles	9 (90%)
After 4 cycles	10 (100%)

Table 5. Minimal/measurable residual disease (MRD).

MRD negative	n (%)
After 4 cycles (n = 10)	7 (70%)
Overall (n = 10)	8 (80%)
B-ALL (n = 8)	7 (88%)
T-ALL (n = 2)	1 (50%)

Conclusions

- The addition of carfilzomib to Hyper-CVAD is safe and tolerable in patients with untreated ALL.
- No DLTs seen with carfilzomib doses up to 36mg/m^2.
- The combination shows promising preliminary efficacy with high rates of MRD negative CR compared to historical controls receiving standard Hyper-CVAD. The regimen may be more active in B-ALL.
- These results support further study of Hyper-CVAD plus carfilzomib in ALL.

References

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