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Phase I study of cladribine, cytarabine (Ara-C), granulocyte colony stimulating factor (G-CSF) (CLAG Regimen) and simultaneous escalating doses of imatinib mesylate (Gleevec) in relapsed/refractory AML☆

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Abstract

Receptor activated tyrosine kinases such as c-kit, c-fms and PDGFR are known targets of inhibition by imatinib mesylate (Gleevec) and are expressed on AML blasts. Marrow stromal cells and monocytes express KIT ligand, M-CSF and PDGF and are therefore capable of activating survival pathways in these leukemic cells. Given the synergy in vitro between Ara-C and imatinib mesylate on AML cell growth inhibition, we initiated a Phase I study combining CLAG + imatinib mesylate in AML patients.

Patients with relapsed, refractory AML or CML myeloid blast crisis were eligible to receive Cladribine 5 mg/m^2 days 3–7, Cytarabine 2 gm/m^2 days 3–7, G-CSF 300 mcg days 2–7, and escalating doses of imatinib mesylate given on days 1–15. The level 1 Gleevec dose was 400 mg, while level 2 was 600 mg and the level 3 dose 800 mg. A total of 16 patients were enrolled, 15 AML and 1 CML myeloid blast crisis. The dose escalation occurred as planned and there was no clear evidence of added toxicity due to imatinib mesylate. One patient with an extensive cardiac history died of cardiac causes on day 1 of therapy however no other deaths occurred within 30 days of starting therapy. One patient had a Grade 3 skin rash at dose level 2. The most common toxicities encountered during induction therapy were nausea, vomiting, rash and diarrhea that were transient and/or reversible. At the 800 mg dose 1 patient developed a decline in cardiac ejection fraction on day 20 who later died of sepsis, so this was considered a dose limiting toxicity.

Of 16 evaluable patients 11 achieved a hypocellular marrow after initial induction with 1 additional patient achieving a hypocellular marrow following a second course of the same regimen. Four patients (25%) achieved a complete morphologic response with normal cytogenetics, 2 patients (12.5%) achieved a complete morphologic response only and 1 patient had a complete response in the bone marrow but incomplete blood count recovery. The overall response rate was 43.8%. The median overall survival was 175 days (95% CI 16.24–333.76) and the median relapse free survival was 76 days.

The addition of imatinib mesylate to CLAG was well tolerated with acceptable toxicities and response rates comparable to other salvage regimens. To assess the efficacy of imatinib mesylate in combination with CLAG, a larger phase II trial is now planned.

Keywords: Relapsed leukemia; Refractory leukemia; Acute myeloid leukemia; Imatinib mesylate; Cladribine; Cytarabine; Filgrastim

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1. Introduction

Outcome of relapsed acute myeloid leukemia (AML) in adults remains poor. Standard induction chemotherapy regimens using daunorubicin and cytarabine or their analogs induce complete remission rates between 60 and 80% in adult patients; however, most later relapse, with 5-year disease-free survival rates estimated to be approximately 30% [1–3]. Various chemotherapeutic agents have been used for salvage therapy after first relapse, with most current clinical trials incorporating monoclonal antibodies and novel targeted agents. It is clear that a multi-targeted strategy is likely needed to improve the outcome in relapsed or refractory disease.

The CLAG combination regimen, consisting of cladribine (2-chlorodeoxyadenosine), cytarabine and granulocyte-colony stimulating factor (G-CSF), was developed as a re-induction therapy in patients with relapsed or refractory AML. Cladribine has been shown to increase intracellular levels of Ara-CTP within the leukemic cell, thus having an apparent synergistic effect in vitro with cytarabine, the backbone of many induction as well as salvage regimens [4,5]. Ten of the 20 patients (50%) enrolled in the initial study evaluating the CLAG regimen in patients with relapsed or refractory disease achieved a CR with a median duration of 22.5 weeks. In a separate multicenter study where 58 patients with refractory or relapsed AML were treated with CLAG, the CR rate was 50% [4,6].

c-Kit is a class III receptor tyrosine kinase that is expressed not only in human malignancies such as gastrointestinal stromal tumors (GISTs), small cell lung cancer and breast cancer, but also on mast cells and normal hematopoietic progenitor cells. Together with its ligand stem cell factor (SCF), c-kit is involved in maintaining normal hematopoiesis, growth and differentiation [7]. It is also expressed in 65–90% of de novo AML cases and c-kit mutations are described in cases of mastocytosis associated with AML [7–9]. Additionally, point mutations as well as c-kit deletion–insertion abnormalities have also been described in patients with AML and may play a role in disease pathogenesis [10,11].

Imatinib mesylate (ST1571, Gleevec®) is first line treatment for patients with chronic myelogenous leukemia. There is evidence to support its use in AML as well as follows. First, it has been shown to inhibit SCF-dependent c-kit phosphorylation in the MO7e AML cell line in vitro [12]. A phase II trial of imatinib mesylate 600 mg as a single agent in patients with c-kit positive relapsed or refractory AML showed that 4 out of 12 patients achieved a hematologic response with 2 partial responses and 2 complete hematologic remissions [13]. Also, imatinib mesylate has been shown to demonstrate synergy in vitro with cytotoxic chemotherapeutic agents such as fludarabine and idarubicin and a phase II trial of imatinib mesylate and low dose cytarabine in older patients not eligible for myelosuppressive chemotherapy revealed that although the objective hematologic response rate was low, 2 patients showed hematologic improvement, 1 had a partial response, and 1 had a complete response [7,14].

Table 1
Study schema

	Day							
	1	2	3	4	5	6	7	8–15
Imatinib mesylate	X	X	X	X	X	X	X	X
Cladribine			X	X	X	X	X	
Ara-C			X	X	X	X	X	
G-CSF		X	X	X	X	X	X	

On the basis of these observations, we initiated a phase I study combining CLAG with imatinib mesylate (CLAG/Gleevec®) in patients with relapsed AML.

2. Patients, materials, and methods

2.1. Study group

Previously treated adults 18 years or older with relapsed or refractory non-FAB M3 AML or CML in myeloid blast crisis were eligible after informed consent was obtained according to institutional guidelines. Refractory AML was defined as a failure to achieve a complete remission (CR) after 2 cycles of induction chemotherapy or the persistence of greater than 40% bone marrow blasts after one cycle of chemotherapy induction. Relapsed AML was defined as any evidence of disease recurrence after achieving CR. If relapse occurred in less than 3 months, the AML was considered refractory and these patients were also eligible for the study. Additional eligibility criteria included the following: (1) ECOG performance status 2 or below (Eastern Cooperative Oncology Group [ECOG]); (2) adequate liver function (serum bilirubin 2 mg/dl or below, AST less than 2.5× institutional upper limits of normal) and renal function with a creatinine less than 2.5 mg/dl. If the creatinine was greater than or equal to 2.0, the patient would have the GFR measured and the dose of cytarabine adjusted accordingly; (3) cardiac ejection fraction (EF) of greater than 30% and New York Heart Association Criteria Grade I/II heart failure only; (4) absence of any other active or uncontrolled infection or any other severe concurrent disease; (5) absence of any history of allergic reactions attributed to compounds of similar chemical or biologic composition to imatinib or any component of the CLAG regimen. Approval for the study was granted by the Institutional Review Board (IRB) of the University of Rochester and was conducted in accordance with the basic principles of the Declaration of Helsinki.

2.2. Treatment schedule

Imatinib mesylate was given on days 1–15 once daily in a phase I dose escalation design. G-CSF was administered subcutaneously at 300 mcg daily for 6 days beginning 24 h before the first dose of cladribine starting on day 2 for 6 days. On days 3–7, cladribine was administered as a 2-h intravenous infusion at a dose of 5 mg/m^2 daily for 5 consecutive days followed 2 h later by cytarabine at a dose of 2 gm/m^2 as a 4-h intravenous infusion (Table 1). A second cycle of the same regimen could be applied if a complete remission was not achieved. An additional cycle of the same regimen as consolidation could be used at the discretion of the treating physician; however, no patient did. If the patient developed a