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SWOG0919: A Phase 2 Study of Idarubicin and Cytarabine in Combination with Pravastatin for Relapsed Acute Myeloid Leukaemia

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Summary

Inhibition of cholesterol synthesis and uptake sensitizes acute myeloid leukaemia (AML) blasts to chemotherapy. A Phase 1 study demonstrated the safety of high dose pravastatin given with idarubicin and cytarabine in patients with AML and also demonstrated an encouraging response rate. The Southwestern Oncology Group (SWOG) trial, SWOG S0919, was a Phase 2 trial evaluating the complete remission (CR) rate in a larger number of patients with relapsed AML treated with idarubicin, cytarabine and pravastatin. This study closed to accrual after meeting the defined criterion for a positive study. Thirty-six patients with a median age of 59 years (range 23–78) were enrolled. The median time from diagnosis to registration was 18 months. Relapse status was first relapse, 17 patients (47%); second relapse, 15 patients (42%); third relapse, 2 patients (5.5%) and fourth relapse, 2 patients (5.5%). The response rate was 75% (95% confidence interval: 58–88%; 20 CRs, 7 CR with incomplete count recovery (CRi)), and the median overall survival was 12 months. The p-value comparing 75% to 30% (the null response rate based on prior

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Authorship Contributions

AA: performed the research, designed the research study, contributed patients, analysed the data and wrote the paper.
SM, MO: designed the research study, analysed the data and helped revise the final paper.
EC, DM, AL, MS: performed the research, contributed patients and helped revise the final paper.
CW: helped revise the final paper.
FA: helped design the research study, analyse the data and revised the final paper.

Disclosure/Conflicts of Interest

There are no conflicts of interest to disclose.

SWOG experience) was 3.356×10^{-4}. Given the encouraging CR/CRi rate, this regimen should be considered for testing in a prospective randomized trial against best conventional therapy.

Keywords

acute myeloid leukaemia; cholesterol; relapse; pravastatin; chemotherapy

Introduction

Acute myeloid leukaemia (AML) is difficult to cure. Although 65% of patients achieve a complete remission (CR) with chemotherapy, only 15–30% remain free of disease for 5 years because of a high incidence of relapse (Miller & Daoust, 2000). Another 20–25% of patients have refractory AML and never achieve CR with induction chemotherapy (Miller & Daoust, 2000).

Cholesterol homeostasis is abnormal in AML cells, with cholesterol synthesis and low-density lipoprotein (LDL) import being hyperactive in AML blasts compared to normal myeloid progenitor cells (Banker *et al*, 2004; Ho *et al*, 1978; Vitols *et al*, 1984; Vitols *et al*, 1990; Rudling *et al*, 1998). AML blasts frequently overexpress the genes for the LDL receptor and 3-hydroxy-3-methylglutaryl coenzyme reductase (HMG-CoAR), and therefore import and synthesize cholesterol at higher levels than normal myeloid progenitors (Kornblau *et al*, 2007). Patients with AML and high white blood cell counts sometimes have marked hypocholesteraemia at the time of diagnosis, suggesting increased cholesterol metabolism, and this typically resolves when patients achieve a CR (Banker *et al*, 2004; Kornblau *et al*, 2007). These observations suggest that AML cells may require high levels of cholesterol for their survival and that abnormalities in cholesterol homeostasis are necessary for AML cell survival (Banker *et al*, 2004). Therefore, the cholesterol pathway may be an effective target in the treatment of AML. *In vitro*, simvastatin, an HMG-CoA reductase inhibitor, inhibits myeloid leukaemia cell growth (Newman *et al*, 1994). Cholesterol turnover further increases in AML cells shortly after exposure to chemotherapy (Banker *et al*, 2004; Kornblau *et al*, 2007). The increased turnover is the result of both increased cholesterol uptake and increased cholesterol synthesis (Banker *et al*, 2004). Inhibiting cholesterol uptake and cholesterol synthesis sensitizes AML cells to cytotoxic therapy, and does so to a far greater degree than it sensitizes normal myeloid progenitors (Kornblau *et al*, 2007; Li *et al*, 2003; Stirewalt *et al*, 2003). These observations were the basis of a previously published Phase 1 study combining pravastatin with idarubicin and intermediate dose cytarabine (Kornblau *et al*, 2007). That study demonstrated the safety of combining pravastatin with intermediate dose cytarabine and idarubicin (Kornblau *et al*, 2007). Pravastatin was chosen because of its high bioavailability and because it is not substantially metabolized by the cytochrome p450 system (Kornblau *et al*, 2007). A maximum tolerated dose for pravastatin when combined with idarubicin and intermediate dose cytarabine was not reached but the dose escalation was stopped at 1280 mg when the number of pills became prohibitive. The CR rates were encouraging (54%), suggesting that Phase 2 evaluation of this approach is warranted. Here, we report the results of S0919: a Phase 2 trial of pravastatin/intermediate dose cytarabine/idarubicin in patients with relapsed AML.

Methods

Patients were treated at Southwestern Oncology Group (SWOG) member institutions between August 2009 and November 2012. Pravastatin was supplied by Bristol-Myers Squibb (New Brunswick, NJ, USA). The protocol (ClinicalTrials.gov Identifier: NCT00840177) was approved by each institution's review board and signed written informed consent was obtained from all registered patients. Eligibility included: age ≥ 18 years, relapsed AML, cardiac ejection fraction ≥ 45%, CR/CR with incomplete count recovery (CRi) following the most recent chemotherapy lasting ≥ 3 months, and no prior haematopoietic stem cell transplant (HSCT). Treatment consisted of oral pravastatin 1280 mg by mouth on days 1–8, idarubicin 12 mg/m^2/day intravenously (IV) days 4–6, and cytarabine 1.5 g/m^2/day continuous IV infusion days 4–7. Patients achieving a CR could receive 2 cycles of consolidation with oral pravastatin 1280 mg by mouth days 1–6, idarubicin 12 mg/m^2/day IV days 4–5 and cytarabine 1.5 g/m^2/day continuous IV infusion days 4–5. CR and CRi were defined by International Working Group (IWG) criteria (Cheson *et al*, 2003).

Statistics

Fifty eligible patients were to be accrued. If ≥ 21 patients achieved a CR or CRi, the regimen would be considered sufficiently effective with a critical level (probability of erroneously concluding the regimen warrants further study) of 4.8% if the true CR rate was 30% (null) and power (probability of correctly concluding the regimen warrants further study) of 90% if the true rate was 50%. These numbers are based on previous data demonstrating a CR rate of 40% in patients with AML in first relapse and CR duration of 12–24 months with cytarabine-based regimens (Estey *et al*, 1996).

Results

The study closed to accrual on 1 November, 2012 after meeting the pre-defined criterion for a positive study. Patient characteristics, including the World Health Organization (WHO) classification (Vardiman *et al* 2009), are listed in Table I. Thirty-six patients with a median age of 59 years (range 23–78) were enrolled. Seventeen patients (47%) were male and the median white blood cell count was 2.8 × 10^9/l (range 0.7–110.6). The median time from diagnosis to registration was 18 months (range 5–136). The median duration of last CR was 11 months (range 4 months–9 years). Cytogenetic risk according to SWOG classification (Slovak *et al* 2000) included: miscellaneous: 2 patients (6%), favourable: 7 patients (19%), intermediate: 13 patients (36%), unfavorable: 9 patients (25%) and no growth or not done: 5 patients (14%). Relapse status included: first relapse, 17 patients (47%); second relapse, 15 patients (42%); third relapse, 2 patients (5.5%); fourth relapse, 2 patients (5.5%). Clinical onset of AML included: *de novo* (28 patients: 78%); myelodysplasia-related (6 patients: 17%); treatment-related (1 patient: 3%) and unknown (1 patient: 3%). Twenty-four out of 32 patients (75%) had received high-dose cytarabine either as post-remission or salvage therapy. Other salvage therapies previously received included: mylotarg, FLAG (fludarabine, cytarabine, granulocyte colony-stimulating factor)/idarubicin, clofarabine,

cytarabine/anthracycline, CLAG (cladribine, cytarabine, granulocyte colony-stimulating factor) and 5-azacitidine.

The response rate was 75% (95% confidence interval [CI] 58–88%; 20 CR, 7 CRi) and median overall survival was 12 months (95% CI 9–14 months). All patients received 1 cycle of induction therapy. Among the subset of patients who achieved a CR/CRi, the median time to response was 40 days (range 25–66 days) and the median relapse-free survival was 12 months (95% CI 6–20 months). Of the 25% of patients not achieving remission, 4 died during induction and 5 had resistant AML. Three of the four deaths were related to infectious complications and were possibly related to treatment. The p–value comparing 75% to 30% (the null response rate) was 3.356×10^{-4}. Response to protocol therapy was not associated with duration of last CR or prior high dose cytarabine exposure. Table II outlines response rate according to salvage number and preceding response. Patients in second relapse or higher were combined to test the association between response rate and relapse status. The p-value for Fisher's exact test [CR/no CR by first relapse/≥ second relapse) was 0.70. There was no evidence of an association between response rate and relapse status. Table III outlines Grade 3–5 treatment-related toxicities. No myositis or unexpected toxicities were observed. Seven patients received consolidation chemotherapy on protocol; there was no treatment-related mortality associated with consolidation therapy on protocol. At least 14 patients (39%) were able to proceed to allogeneic HSCT.

Discussion

The CR/CRi rate in this relapsed population treated with the combination of pravastatin, idarubicin and cytarabine is encouraging and suggests that targeting the cholesterol pathway in combination with chemotherapy may improve efficacy without increasing toxicity. Further interpretations about this trial are limited by the trial's small size and uncontrolled structure. Ultimately, a randomized Phase 3 trial with chemotherapy versus chemotherapy plus pravastatin is needed to definitively address the benefit of statin therapy. Although the idarubicin/cytarabine-based backbone could have contributed to the improved response rate, this is unlikely given the historical response rates seen with cytarabine-based regimens in this population (see below). In addition, the CR rate with this particular backbone regimen was 77% in newly diagnosed AML patients (Estey *et al*, 2001); and one would expect the CR rate to be lower in the relapsed population, as is true of any regimen. The treatment was well-tolerated and the response rate was high compared to the null hypothesis ($p= 3.356 \times 10^{-4}$) which was based on historical data with cytarabine-based regimens in the relapsed AML population (response rate 40%) (Estey *et al*, 1996). The very high complete response rate led to early closure of the trial and outcomes compare favourably to other published data. Thomas et al. (2012) examined the outcome of younger adult AML patients relapsing after entry on the Acute Leukaemia French Association (ALFA)-9802 trial. Only 44% of patients achieved a second remission and the median overall survival was 8.9 months. Clofarabine as a single agent or in combination with cytarabine demonstrated CR rates of 42% in patients with relapsed and refractory AML (Burnett *et al*, 2010). Vignetti et al. (1996) demonstrated a second CR (CR2) rate of 68% with the MEC regimen (mitoxantrone, etoposide, cytarabine). However, this study was limited to AML patients in first relapse and the toxicities of this particular regimen were significant. In our current trial, more than half

of the patients were in at least second relapse; and the median age was 59 years. In addition to the high response rate in our trial, the median overall survival was 12 months, which compares favourably to other trials, such as that reported by Thomas *et al* (2012). This is probably related to the number of patients who were able to proceed to allogeneic HSCT (at least 14 out of 36); given that, ultimately, allogeneic transplant is the only curative treatment for these patients and transplant in CR2 is associated with improved outcome (Thomas *et al*, 2012). In addition to working on the cholesterol pathway in AML, it is also possible that pravastatin may have had a therapeutic advantage in patients with *FLT3* mutations in this trial. A recent publication (Williams *et al*, 2012) suggests that statins inhibit FLT3 glycosylation in human and murine cells and prolong survival of mice with *FLT3* mutated (internal tandem duplication, ITD) leukaemia. The *FLT3* status was not known in all of the patients on this trial. However, of the 17 patients with known *FLT3* status, 6 patients had the *FLT3*-ITD mutation. All of these patients achieved a CR/CRi, except for 1 patient who died during re-induction therapy; suggesting that further exploring this hypothesis in future trials would be worthwhile.

A previous Phase 1 trial suggested that the highest serum bioavailability of pravastatin is reached at doses > 1280 mg/day (Kornblau *et al*, 2007). Higher doses were not used in the current trial given the concern regarding tolerability; however, given the low toxicity profile, this could be further explored. Previous studies with lovastatin have suggested that the maximal effect of statin blockade is observed after 7 days of lovastatin administration (Thibault *et al*, 1996). This schema was not used in the Phase 1 or 2 trials, given the concerns about delaying chemotherapy in these patients. Future avenues of research include: (1) evaluating other cholesterol-lowering medications in combination; (2) evaluating the newer statins, which are more potent inhibitors; (3) loading with pravastatin for a longer time prior to chemotherapy in patients without a rapidly proliferative disease and (4) including maintenance therapy with pravastatin for certain intervals after the initial loading period. Integral laboratory correlates, included as part of any future trials, should also help give us better insight into the biology and pathways affecting response and outcome.

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Table I

Patient Characteristics (n=36)

Median age (years)	59 (range 23–78)
Median time from initial diagnosis to registration (months)	18 (range 5–136)
Relapse status (salvage number)	Number of patients (%)
1st	17 (47%)
2nd	15 (42%)
3rd	2 (5.8%)
4th	2 (5.8%)
Cytogenetic risk at the time of relapse(SWOG classification)	
Miscellaneous	2 (6%)
Favourable	7 (19%)
Intermediate	13 (36%)
Unfavourable	9 (25%)
No growth or not done	5 (14%)
WHO classification	
Acute erythroid leukaemia	1 (3%)
AML not otherwise categorized	7 (19%)
Acute myelomonocytic leukaemia	4 (11%)
AML with abnormal bone marrow eosinophils	3 (8%)
AML without maturation	6 (17%)
AML with maturation	2 (6%)
Acute monoblastic and monocytic leukaemia	5 (14%)
AML with multilineage dysplasia	2 (6%)
AML with t(8;21); (*RUNX1*/*RUNX1T1*)	3 (8%)
AML and MDS, therapy-related	2 (6%)

SWOG, Southwestern Oncology Group; WHO, World Health Organization; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome.

Table II

Response Rate According to Relapse Number and Duration of Preceding Response

Response rate by relapse number		
Relapse number	**Number of patients (%)**	**Response rate (CR/CRi)**
1	17 (47%)	71%
2	15 (42%)	87%
3	2 (5.5%)	100%
4	2 (5.5%)	0%

Response rate by duration of preceding response		
Duration of preceding response	**Number of patients in this group**	**Response rate (CR/CRi)**
< 12 months	17	76%
≥12 months	19	74%
≤ 6 months	6	67%
≥6 months	30	77%

CR, complete response; CRi, CR with incomplete count recovery.

Table III

Grade 3–5 Induction Therapy Toxicities (n=35)

	Adverse Event	Grade 3	Grade 4	Grade 5
Blood/bone marrow	Blood—other	2	0	0
	Bone marrow cellularity	1	0	0
	Haemoglobin	9	2	0
	Leucocytes	1	15	0
	Neutrophils	2	12	0
	Lymphocytes	0	6	0
	Platelets	2	15	0
Cardiac	Asystole	0	0	1
	Atrial fibrillation	0	1	0
	Atrial flutter	1	0	0
	Cardiac-other	0	1	0
	Hypertension	1	0	0
	LV dysfunction	2	0	0
	Pulmonary hypertension	1	0	0
	Hypotension	1	0	0
Constitutional symptoms	Fatigue	2	1	0
	Anorexia	1	0	0
Gastrointestinal	Diarrhoea	3	0	0
	Oesophagitis	1	0	0
	Ileus	1	0	0
	Mucositis	0	1	0
	Nausea	2	0	0
	Vomiting	2	0	0
Haemorrhage	Haemorrhage/bleeding (not CNS)	2	0	0
Infection	Febrile neutropenia	19	0	1
	GI infection	1	0	0
	Bacteraemia	3	2	0
	Infection-blood			
	Infection-other	1	0	0
	Pulmonary infection	6	0	2
Metabolic/laboratory	Bilirubin	2	0	0
	Hyperglycaemia	1	0	0
	Hypernatraemia	1	0	0
	Hypoalbuminaemia	1	0	0
Metabolic/laboratory	Hypocalcaemia	2	0	0

	Adverse Event	Grade 3	Grade 4	Grade 5
	Hypokalaemia	5	1	0
	Hyponatraemia	1	0	0
	Hypophosphataemia	2	0	0
	Lipase	1	0	0
Neurology	Confusion	1	0	0
	Syncope	1	0	0
Ocular	Ocular—other	1	0	0
Pain	Abdominal pain	1	0	0
Pulmonary	Dyspnea	1	0	1
	Hypoxia	0	0	1

LV, left ventricle; CNS, central nervous system; GI, gastrointestinal