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Idarubicin, Cytarabine and Pravastatin as Induction Therapy for Untreated Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

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Abstract

Background—Previous studies suggest that idarubicin/cytarabine(ara-C)/pravastatin (IAP) is an active salvage regimen for patients with AML. We therefore investigated this regimen in patients with newly-diagnosed AML or MDS (≥10% blasts).

Methods—Patients were eligible if the anticipated treatment-related mortality (TRM) was <10%. Patients received pravastatin (1,280 mg/day po; days 1-8), cytarabine (1.5 g/m^2/day; days 4-7) and idarubicin (12 mg/m^2/day, days 4-6). Up to 3 cycles of consolidation with a shortened course was permitted. The primary endpoints were “good CR” rate (CR on day 35 without minimal residual disease) and TRM in the first 28 days. The study was to stop if after each cohort of 5 patients (a) the Bayesian posterior probability was < 5% that the true “good CR rate” was ≥ 70% or (b) the posterior probability was >25% that the TRM rate was ≥5%.

Results—Twenty-four patients were included. Conventional CR was achieved in 15 (63%) patients but only 12 (50%) achieved “good CR”. 4 of 12 (33%) patients with “good CR” relapsed at median of 16 weeks (10.5-19). Five (21%) patients had refractory disease. Survival probability at 1 year was 72% (48.7-64). Two (8.3%) patients died within 28 days from multi organ failure. The most common grade 3-4 adverse effects were febrile neutropenia (75%) and diarrhea (25%). Based on the stopping rules accrual ceased after entry of these 24 patients.

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Conclusion—IAP did not meet the pre-defined efficacy criteria for success. Therefore, we would not recommend this regimen for phase 3 testing in this patient subset.

Background

Although achieving a complete remission (CR) appears necessary for long-term survival in AML at least after receipt of 3+7 or congeners (1), CR per se is not generally sufficient to prolong survival. (1-3) One plausible explanation is that conventionally defined CRs vary widely in their quality, with only high quality CRs translating into a survival advantage. In particular, presence of minimal residual disease (MRD) at the time of CR or slow count recovery are independent risk factors for relapse and thus indicate a poor quality CR. (4, 5) Therefore, implementation of more stringent criteria for CR that account for MRD and time to count recovery seems logical.

In-vitro studies have suggested that high intracellular cholesterol levels in AML cells may be part of an adaptive chemoresistance mechanism and blockade of cholesterol synthesis with HMG-CoA reductase inhibitors (statins) restored chemosensitivity. (6, 7) Addition of statins to standard chemotherapy for AML has been explored in an attempt to improve outcomes. In a phase-I study, pravastatin was added to the standard induction regimen of idarubicin and high-dose cytarabine (Ara-C) and was associated with acceptable toxicity and resulted in clinical responses (CR and CRp) in both the frontline (11 of 15) and salvage (9 of 22) settings. (8, 9) In their 0919 trial, the SWOG noted that IAP produced a CR rate of 55% in 36 patients relapsing after a minimum CR/CRi duration of 3 months following last chemotherapy, thus meeting the pre-defined efficacy criterion. (10) The SWOG results prompted us to examine whether IAP would increase the CR rates without MRD and with rapid count recovery (“good CRs”) without increasing treatment related mortality (TRM) in adults with newly-diagnosed AML.

Patients and Methods

Eligibility

Patients age 18 to 74 with diagnoses of AML (except acute promyelocytic leukemia), refractory anemia with excess blast type 2 (RAEB-II) or myeloproliferative neoplasm (MPN) with ≥ 10% blasts in the bone marrow or peripheral blood according to the 2008 WHO classification were eligible. (11) Eligibility required an expected risk of TRM (death in the first 4 weeks after beginning induction therapy) less than 10%, as determined by an algorithm based on historical data from SWOG and MD Anderson. (12) Conventional eligibility criteria (performance status, creatinine, age) are subsumed in the TRM score. Bilirubin is not included in the TRM score but needed to be < 2.0 mg/ml due to hepatic excretion and metabolism of idarubicin. The study was approved by our institutional review board and all patients provided written informed consent.

Primary and secondary endpoints

The study had 2 primary endpoints, defined as those adaptively monitored during the study. The first was rate of “good CR”. Good CR includes conventional criteria for CR (absolute neutrophil count > 1,000/μl, platelet count > 100,000/μl, marrow with <5% morphologic

blasts) and additionally the requirements that marrow MRD (detected by 10-color flow cytometry or conventional cytogenetic evaluation) be absent and that the above blood counts be attained. The details of the ten-color multiparametric flow cytometry are previously described by our group.(13) The second primary endpoint was rate of death within 28 days of starting induction therapy (TRM). Secondary endpoints were morphologic CR rate, relapse-free survival (RFS) and the overall survival (OS).

Treatment

Pravastatin 1,280 mg was administered orally daily from day 1 through day 8 of induction. This was given in 4 divided doses in the first 4 patients but, for ease of administration, was subsequently given once daily in line with previous trials. Idarubicin 12mg/m^2 was administered intravenously daily on days 4 through 6 while ara-C 1.5g/m^2/day was administered continuous IV infusion on days 4 through 7. Patients were taken off study if bone marrow examination between days 17-20 showed more than 60% morphologic blasts or if good CR was not observed, with bone marrow examination examined around day 35 to assess for flow cytometric or cytogenetic evidence of MRD.

Patient who achieved a “good CR” were allowed to receive up to three cycles of post-remission therapy with the same agents given as a shortened course: Pravastatin 1,280 mg orally daily from day 1 through 6. Idarubicin 12mg/m^2 intravenously daily on days 4 through 5 and cytarabine 1.5 g/m^2/day intravenously by continuous infusion on days 4 through 5.

To prevent/ameliorate fever and rash due to ara-C, prednisone 100mg daily could be administered on days 4 through 8 of induction and 4 through 7 of post CR remission therapy at the discretion of the treating physician. Prednisolone 1% eye drops were used to prevent ara-C-induced conjunctivitis and all patients received quinolones for antibacterial prophylaxis in addition to antiviral and antifungal prophylaxis.

Study design and statistical considerations

We used a Bayesian design to simultaneously monitor efficacy (good CR) and toxicity (TRM).(14, 15) Our institutional historical data indicated a “good CR” rate of 50% and a TRM rate of ≤5% and these numbers determined the study's prior probabilities. We aimed for 20% improvement in the good CR rate (50% to 70%) and a TRM ≤ 5. Outcomes were evaluated after each cohort of 5 patients, with the minimum sample size set at 20 and the maximum at 50.The study was to stop early if after evaluation of each cohort of 5 patients from numbers 21 through 45 either (a) the posterior probability was < 5% that the true “good CR rate” was ≥ 70% or (b) the posterior probability was >25% that the TRM rate was ≥ 5%. The operating characteristics of the design thus parameterized were such that if the true good CR and TRM rates were the same as historical the probability was 89% that accrual would stop before entry of 50 patients; this is analogous a false positive rate of 11%. If, on the other hand, the true good CR rate was > 70% and the true TRM rate < 5% the probability that 50 patients would be accrued was 68%, analogous to a power of 68%. As discussed below, the study stopped after accrual of 24 patients because the efficacy criteria

were not met. The likelihood that stopping would have occurred at this time if the efficacy and TRM goals were likely to be met is discussed below.

Results

Patient characteristics (table 1)

Between May 2013 and April 2014, 24 patients with median age 57 (35-72) were treated. 21 had AML, two RAEB-2, and one CMML with > 10 blasts. 86% of the AML patients had de novo disease. Only 4 patients (19%) had favorable cytogenetics per European leukemia network (ELN) criteria.(16) The two MDS patients had IPSS-R scores of 6 and 3.5 (17).

Good CR and CR (table 2)

Twelve patients (50%; 95% confidence interval 29-71%) achieved “good CR”. 3 others had a CR by conventional criteria but were not considered a good CR because of MRD; thus the conventional CR rate was 15/24 (63%; 95% CI 31-78%). 2 patients met criteria for CRi, and 5 had persistent AML.

TRM and other induction toxicity (tables 2-3)

TRM occurred in 2 patients (8%; 95% CI 1-27%). Both patients died of multiple organ failure secondary to sepsis on days 13 and 19 with neutropenic enterocolitis predisposing in 1 of the 2. The incidence of grade 3-4 toxicity was similar to that observed with IA without pravastatin. (18)

Subsequent Outcomes

9 of the 12 patients (75%) who achieved good CR received further IAP; 4 (33%) received 1, 3 (25%) received 2, and 2 (16%) had 3 further courses. The principal reason for no post-remission IAP was suspected toxicity: GI side effects (nausea, vomiting and diarrhea) in 1 and rhabdomyolysis though related to pravastatin in 1. Five of the 12 good CR patients (42%) and 2 of the 3 non-good CR patients (67%) received HCT.

Four of the 12 good CR patients (33%) have relapsed at a median of 16 weeks (range : 10.5 – 19) from initial CR; median follow-up time in the remaining 41 weeks (range: 17-67) Comparable figures for the 3 patients with conventional CR but with evidence of MRD are relapse in 1 patient (33%) after 24 weeks while the median follow-up for other 2 patients is 28 weeks. 6 patients have died (median time to death = 26 weeks (range: 1- 42 weeks)) and 18 are alive at a median follow-up of 48 weeks (range 13-64). The Kaplan-Meier survival probability at 1 year was 72% (95% CI: 48.7-86.9%).

There was no difference in the level of serum cholesterol reduction between patients who achieved CR vs. ones who did not (7.8 vs. 0.5 mg/dL; p=0.4).

Discussion

IAP did not meet our criterion for efficacy (good CR rate of 70%), leading to suspension of the trial after accrual of 24 patients. Several questions arise: (1) what was the probability of a false negative result, (2) is “good CR” a valid endpoint, (3) was the sought after

improvement unrealistic, and (4) why were the SWOG results in relapsed AML encouraging and our results in newly diagnosed patients not?

Beginning with the first question, the probability that early stopping would occur if the true good CR rate and TRM rates were the specified 70% and 5% respectively was 17% after entry of 25 patients. Hence it seems unlikely that our results are falsely negative at least with regard to these specifications. Of course this ignores the possibility that IAP might only be useful in certain subgroups. However, sample size calculations in AML are usually based on a similar view of the disease as a single entity. This is acknowledged to be unrealistic, begging the question how to design trials for small subgroups while retaining conventional power of 80-90% and p-value of 0.05 without requiring extraordinarily long times to complete accrual.

The most widely accepted endpoint in AML is survival. However occurrence of a sufficient number of deaths to comment realistically on survival can require 1-2 years. Hence using endpoints that can serve as surrogates for survival are desirable. Recent observations that improvements in CR rate do not necessarily translate into improvements in survival argue against use of CR as such a surrogate.(2, 3) Here we proceeded on the assumption that “good CR” might be a better surrogate than CR; while deriving from data showing that longer time to count recovery and presence of MRD at CR diminish the survival value of CR, this assumption remains to be tested. One attractive feature of using good CR as endpoint is that because good CR rates are lower than CR rates improvements in the former may be more plausible.

The degree of improvement that should be sought is also of interest. Certainly if we had specified a desired absolute improvement of 10% in good CR rate rather than 20% the study would not have stopped after accruing 24 patients. However, based on the results of our study, there is only an 18% probability that IAP is 10% better than historical regimens and an even lower chance (8%) that it is 15% better. Some would contend that improvements in AML occur in small increments and basing stopping treatment on larger increments is unrealistic and counterproductive. Others would counter that the number of patients and amount time of time needed to detect small improvements is far from desirable. This issue is likely to demand further discussion as the recognition that AML is several diseases each to be treated differently inevitably will mean fewer patients available for the various trials. It would seem that at least logistically the specified degree of improvement will have to be higher than currently, perhaps justified by the increased specificity of new therapies.

These issues aside it seems quite likely that our results in newly-diagnosed patients are not comparably satisfactory as those of Advani et al. in relapsed patients in the SWOG 0919 study. These authors reported a CR rate of 55% (20/36) vs. a CR rate of 63% (15/24) in our newly-diagnosed patients (95% CI for the difference in rates [-0.2 - 0.32], with “expected historical' rates of 30% and 70 -80% in the 2 groups respectively. A possible biologic explanation is that high intracellular cholesterol may figure more prominently as an adaptive mechanism leading to chemoresistance in relapsed AML and therefore the value of statin addition may be less in newly-diagnosed patients. Obviously, it is also possible that patient and disease characteristics may affect the outcome in AML more than treatment, here IAP.

Although age and cytogenetics were similar in our patients and Advani et al.'s, attempts to develop prognostics models to predict treatment failure based on individual patient characteristics have not been successful. For example, in a recent analysis of more than 4500 patients using data from MRC/NCRI, HOVON/SAKK, SWOG and MD Anderson Cancer Center, failure to achieve a CR despite surviving the first 28 days of therapy ("resistance") was as expected independently associated with age, performance status, white blood cell count, secondary disease, cytogenetic risk and FLT3-ITD/NPM1 mutation status at $p < 0.001$ for each. However, a model incorporating all these covariates had an area under the receiver operating curve (AUC) of only 0.79 essentially intermediate between certainties (AUC 1.0) and a coin flip (AUC 0.5).(19) Given this uncertainty it is possible that Advani et al's patients were "more favorable" than our in ways that remain difficult to define. As a corollary it is possible that our 24 patients were "more unfavorable" than our historical population, stressing the need for development of observed/expected ratios applicable to individual patients in a trial, although this would still suffer from the above-discussed limitations in our ability to derive expectations applicable to single arm trials.

With these constraints in mind our results suggest that despite its seeming success in relapsed patients IAP is not likely to produce a substantial increase in high quality remissions (good CRs) in newly diagnosed AML. Given various alternatives (for example volasertib)(20) we would not recommend the regimen for inclusion in a phase 3 trial in this population.

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Table 1

Patients Characteristics

	Total (n=24)
Median Age (range); years	57; (35-72)
Female Gender - n ;(%)	15; (62%)
Median WBC (range) at diagnosis × $10^3/\mu L$	6.7 (0.4-111)
Diagnosis:	
AML, n (%)	21 (87.5%)
De novo	18 (86%)
Secondary AML - Prior therapy	1 (4.5%)
Antecedent Hematologic Disorder	2 (9.5%)
MDS, n (%)	2 (8.5%)
CMML, n (%)	1 (4%)
ELN CG risk group, n (%) in AML patients (n=21)	
Favorable	4 (19%)
Intermediate-I	4 (19%)
Intermediate-II	6 (28.5%)
Adverse	7 (33.5%)
Molecular markers in AML patients (n=21)	
FLT3-ITD positive	2 (8%)
NPM1 positive	3 (14%)
CEBPA	1 (4%)
IPSS-R score, n(%) in MDS patients (n=2)	
Intermediate	1 (50%)
High	1 (50%)

TRM: treatment-related mortality, ELN: European leukemia network, IPSS-R: Revised International Prognostic Scoring System

Table II

Outcomes

Diagnosis	Good CR*†	CR	CRi	Refractory	TRM*	Relapse	HCT
All patients (24)	**12 (50%)**	**15 (63%)**	**2 (8%)**	**5 (21%)**	**2 (8%)**	**5 (21%)**	**11 (46%)**
AML (21); n (%)	**10 (48%)**	**13 (62%)**	**1 (5%)**	**5 (24%)**	**2 (9%)**	**4 (19%)**	**9 (43%)**
Risk groups‡							
Favorable (4)	3	0	0	0	1	0	0
Intermediate-I (4)	3	1	0	0	0	1	3
Intermediate-II (6)	2	1	1	1	1	2	2
Adverse (7)	2	1	0	4	0	3	4
MDS (2)	**2 (100%)**	**2(100%)**		**0**	**0**	**1 (50%)**	**1 (50%)**
CMML (1)	**0**	**0**	**1 (100%)**	**0**	**0**	**0**	**1 (100%)**

*Primary study endpoints ;

†CR without evidence of MRD ;

‡per ELN criteria ; MRD: minimal residual disease, TRM: treatment-related mortality, HCT: hematopoietic stem cell transplantation

Table III

Grade 3 and 4 adverse events

Adverse Event	Number of patient (%)	
	Grade 3	Grade 4
ID		
Febrile Neutropenia	17 (71%)	1 (4%)
Rash	3 (12.5%)	0
Hand-foot syndrome	2 (8.5%)	0
Septic Shock	0	1(4%)
GI		
Diarrhea	6 (25%)	0
Nausea/Vomiting	4 (17%)	0
Mucositis	3 (12.5%)	0
Transaminitis	2 (8.5%)	0
Colon pneumatosis	1 (4%)	0
GI bleeding	1 (4%)	0
Renal		
Tumor lysis syndrome	1 (4%)	0