Unsatisfactory efficacy in randomized study of reduced-dose CPX-351 for medically less fit adults with newly diagnosed acute myeloid leukemia or other high-grade myeloid neoplasm

The need for new therapies for medically less fit adults with acute myeloid leukemia (AML) is unquestioned.[1] CPX-351, a liposomal formulation of cytarabine and daunorubicin,[2] may be an attractive option. In patients with relapsed/refractory leukemia, in whom CPX-351 was administered on days 1, 3, and 5 of a treatment cycle, a maximum tolerated dose (MTD) of 101 units/m^2 was identified, but responses were seen with doses as low as 32 units/m^2.[3] In a subsequent study in fit adults age 60-75 years with newly diagnosed AML who were randomized 2:1 between CPX-351 (100 units/m^2) and 7+3, 60-day mortality was lower with CPX-351 (4.7% *vs.* 14.6%, *P*=0.053) while response rates were higher (66.7% *vs.* 51.2%, *P*=0.07).[4] Pre-planned subset analyses indicated improved survival in patients with secondary leukemias.[4]

These observations prompted us to conduct a randomized phase 2 trial (clinicaltrials.gov identifier 01804101) testing attenuated doses of CPX-351 (32 or 64 units/m^2 per dose *vs.* the more usual 101 units/m^2) in less fit adults aged ≥18 years with untreated AML (acute promyelocytic leukemia excepted) or other myeloid neoplasms with ≥10% blasts in peripheral blood and/or bone marrow and a treatment-related mortality (TRM) score of >13.1. This score, composed of weighted information from 8 covariates (age, performance status, white blood cell [WBC] count, peripheral blood blast percentage, type of AML [*de novo vs.* secondary], platelet count, albumin, and serum creatinine), has corresponded to a >13.1% probability of death within 28 days ("TRM") of receiving intensive chemotherapy for newly diagnosed AML.[5] Patients were also required to have a left ventricular ejection fraction ≥40% and, because of the hepatic metabolism of CPX-351, a bilirubin ≤2.0 mg/dL and AST/ALT ≤4 times the upper limit of normal, unless elevations were felt to be due to hepatic leukemia infiltration. An expected survival of <1 year from another illness, uncontrolled infection, or treatment with other investigational agents were exclusions. Prior low-intensity treatment, including use of DNA methyltransferase inhibitors, lenalidomide, and growth factors for low-grade myelodysplastic syndrome (<10% blasts) was permitted. Cytogenetic risk was assessed according to the modified United Kingdom Medical Research Council/National Cancer Research Institute (MRC/NCRI) criteria.[6] Secondary disease was defined as either therapy-related myeloid neoplasm or a prior hematologic disorder before diagnosis of AML/high-grade myeloid neoplasm. Treatment responses were defined according to standard criteria.[7,8] Measurable ("minimal") residual disease (MRD) was assessed by multiparametric flow cytometry, with any level of MRD considered positive (MRDpos).[9,10] Relapse after study treatment was defined by standard morphologic criteria[7,8] or emergence of MRD after MRD negativity was achieved if this finding led to therapeutic intervention. The protocol was approved by the Fred Hutchinson Cancer Research Center and Stanford University Institutional Review Boards, and patients gave written informed consent in accordance with the Declaration of Helsinki.

Patients were randomized 1:1 to receive CPX-351 at either 32 or 64 units/m^2 per dose intravenously over 90 min on days 1, 3, and 5 for up to 4 identical induction/re-induction courses. Administration of CPX-351 in the outpatient clinic was permitted, as was outpatient care following inpatient drug administration. Patients achieving either complete remission (CR) or CR with incomplete platelet count recovery (CRp) could receive up to 4 courses of post-remission treatment with CPX-351 using the same dose on days 1 and 3 only. Patients were taken off study for lack of CR/CRp achievement after 4 cycles of therapy, consolidation with HCT, excess toxicity, or relapse.

Because of the small sample size, randomization was stratified using a dynamic allocation scheme[11] based on: 1) TRM score (13.1-22.8 *vs.* >22.8); 2) cytogenetic risk (monosomal karyotype *vs.* other unfavorable *vs.* intermediate/favorable); and 3) presence/absence of secondary disease. For each dose, we used a Bayesian design that adaptively monitored response (CR achievement) and toxicity (death by day 28, excluding deaths due to progressive disease and no treatment-related toxicity).[12] Prior probabilities of response and toxicity for standard (historical) treatment and the experimental (CPX-351) treatment were defined using a beta distribution. For standard, we used β(30, 70) for response and toxicity, corresponding to CR and TRM rates of 30% in 100 patients. For CPX-351, we used β(0.6, 1.4) for response and toxicity, corresponding to CR and TRM rates of 30% in 2 patients. This non-informative distribution allows the current ("posterior") probability distributions to be dominated by the trial data. In each arm of this trial, patients

Table 1. Operating characteristics of the statistical design under various clinical scenarios.

Scenario	True Probability				Probability Stop After (#Pts)					Average #Pts
	CR/ TRM	CR/ no TRM	No CR/ TRM	No CR/ No TRM	20	25	30	35	40	
1	0.01	0.29	0.14	0.56	35	40	43	45	0.48	35
2	0.01	0.39	0.09	0.51	0.09	10	0.11	0.11	0.12	42
3	0.01	0.29	0.29	0.41	0.79	0.86	0.90	0.92	0.94	23
4	0.01	0.19	0.29	0.51	0.88	0.92	0.95	0.96	0.98	22

Scenario 1: the TRM and CR rates are 15% and 30%, respectively, the minimum desirable outcome. Under these circumstances, there is a 52% chance an arm will accrue the maximum of 45 patients; the average number of patients is 35. *Scenario 2*: outcomes are better with a TRM rate of only 10% and a CR rate of 40%. Here, there is an 88% chance an arm will run to completion (45 patients), and the average number of patients treated is 42. *Scenario 3*: represents the "null": both the TRM rate and the CR rate are the same as historical (each 30%). Here the average number of patients treated is only 23 and there is 90% probability an arm would stop after accruing 30 patients. *Scenario 4*: the TRM rate remains at 30% but the CR rate is only 20%, and the trial is somewhat more likely to stop early. The trial was designed using the program Multc Lean that is freely available at the MD Anderson Cancer Center, Department of Statistics, website: (*http://biostatistics.mdanderson.org/softwaredownload/*).

were treated in cohorts of size 5. A minimum number of 20 patients were randomized before an arm was considered for early closure. If an arm was not closed prematurely, a maximum of 45 patients were planned to be treated, for a maximum sample size of 90. An arm was to close if after 20, 25, 30, or 35 treated patients the posterior probability was <0.90 that the true TRM rate was <15% (the targeted TRM rate *vs.* 30% historical) or if the posterior probability was <0.10 that the true CR rate with CPX-351 was >30% (the minimally acceptable CR rate). These criteria led to the following stopping rules: 1) for response – stop if the number of CRs was ≤4/20, 5/25, 6/30, 7/35, or 9/40 (10/45); for toxicity – stop if the number of patients dying by day 28 was ≥3/10, 4/15, 5/20, 6/25, 7/30, 8/35, or 9/40 (10/45). If an arm closed subsequent patients were planned to be treated on the remain-

Table 2. Characteristics of study cohort.

Parameter	32 units/m² cohort, n=38	64 units/m² cohort, n=10	Entire cohort, n=48
Median age (range), years	70.6 (39.1-88.5)	70.6 (53.1-91.1)	70.5 (39.1-91.1)
Male gender, n (%)	24 (63.2%)	7 (70.0%)	31 (64.6%)
Disease-type			
AML			
With recurrent genetic abnormalities	11 (28.9%)	–	11 (22.9%)
With myelodysplasia-related changes	12 (31.6%)	6 (60.0%)	18 (37.5%)
Therapy-related AML	5 (13.2%)	1 (10.0%)	6 (12.5%)
AML, not otherwise specified	6 (15.8%)	1 (10.0%)	7 (14.6%)
MDS/MPN			
CMML-2	–	1 (10.0%)	1 (2.1%)
MDS-EB2	3 (7.9%)	1 (10.0%)	4 (8.3%)
Therapy-related MDS	1 (2.6%)	–	1 (2.1%)
Secondary disease*	21 (55.3%)	8 (80.0%)	29 (60.4%)
Median TRM score (range)	25.2 (13.2-90.0)	31.3 (14.7-58.1)	25.7 (13.2-90.0)
Performance status, n (%)			
1	3 (7.9%)	2 (20.0%)	5 (10.4%)
2	19 (50.0%)	4 (40.0%)	23 (47.9%)
3	13 (34.2%)	4 (40.0%)	17 (35.4%)
4	3 (7.9%)	–	3 (6.3%)
Cytogenetic risk, n (%)			
Favorable	3 (7.9%)	–	3 (6.3%)
Intermediate	18 (47.4%)	2 (20.0%)	20 (41.7%)
Adverse	16 (42.1%)	7 (70.0%)	23 (47.9%)
Monosomal karyotype	11 (28.9%)	7 (70.0%)	18 (37.5%)
Unknown (insufficient growth)	1 (2.6%)	1 (10.0%)	2 (4.2%)
Mutational status, n (%)			
FLT3-ITD			
No	30 (78.9%)	5 (50.0%)	35 (72.9%)
Yes	1 (2.6%)	1 (10.0%)	2 (4.2%)
Unknown	7 (18.4%)	4 (40.0%)	11 (22.9%)
NPM1			
No	19 (50.0%)	5 (50.0%)	24 (50.0%)
Yes	8 (21.1%)	–	8 (16.7%)
Unknown	11 (28.9%)	5 (50.0%)	16 (33.3%)
Laboratory findings at baseline, median (range)			
WBC (x 10^9L)	12.1 (0.8-341.2)	4.2 (0.8-41.7)	10.2 (0.8-341.2)
Peripheral blood blasts (%)	25.5 (0-94)	10.5 (0-44)	13.5 (0-94)
Hemoglobin (g/dL)	8.6 (5.1-14.1)	8.6 (6.6-10.8)	8.6 (5.1-14.1)
Platelets (x 10^9L)	30.3 (1-143)	19 (6-84)	29.5 (1-143)
Creatinine (mg/dL)	1.09 (0.51-6.91)	0.98 (0.63-2.58)	1.08 (0.51-6.91)
Total bilirubin (mg/dL)	0.9 (0.2-2.1)	1.3 (0.3-1.8)	0.95 (0.2-2.1)
AST (U/L)	28 (0-182)	24 (7-41)	28 (0-182)
ALT (U/L)	21 (5-373)	19 (9-37)	20.5 (5-373)

*AML transformed from antecedent hematologic disorder or AML/MPN/MDS after prior cytotoxic therapy. ALT: alanine aminotransferase; AML: acute myeloid leukemia; AST: aspartate aminotransferase; CMML-2: chronic myelomonocytic leukemia-2; MDS-EB-2: myelodysplastic syndrome with excess blasts-2; TRM: treatment-related mortality; WBC: white blood cell count.

Table 3. Best response to study therapy and survival estimates of study cohort.

Response	32 units/m² cohort, n=38	64 units/m² cohort, n=10	Entire cohort, n=48
CR, n (%)			
MRD^{neg}	8 (21.1%)	–	8 (16.7%)
MRD^{pos}	2 (5.3%)	1 (10.0%)	3 (6.3%)
CRp, n (%)			
MRD^{neg}	–	–	–
MRD^{pos}	–	–	–
Overall remission rate (CR+CRp), n (%)	10 (26.3%)	1 (10.0%)	11 (22.9%)
CRi, n (%)			
MRD^{neg}	–	1 (10.0%)	1 (2.1%)
MRD^{pos}	1 (2.6%)	–	1 (2.1%)
Resistant disease, n (%)	21 (55.3%)	6 (60.0%)	27 (56.3%)
Death from indeterminate cause, n (%)	6 (15.8%)	2 (20.0%)	8 (16.7%)
Early death*, n (%)	11 (28.9%)	4 (40.0%)	15 (31.2%)
Median overall survival, months	3	6	3
6-month survival, %	39%	50%	42%
12-month survival, %	17%	20%	18%
Median relapse-free survival, months	7	1 month, 9 months**	7
6-month relapse-free survival, %	55%		54%
12-month relapse-free survival, %	9%		8%

*Death within 28 days of initiation of study therapy; **observed values. CR: complete remission; CRi: complete remission with incomplete blood count recovery; CRp: complete remission with incomplete platelet recovery; MRD: measurable residual disease.

ing arm. The operating characteristics of this design under various clinical scenarios are summarized in Table 1. The trial was designed using Multc Lean (*http://biostatistics.mdanderson.org/softwaredownload/*). Data cut-off date for analysis was July 10, 2017.

Between May 2013 and November 2016, 48 eligible adults (median age 70.5 [range: 39.1-91.1] years) with a median TRM score of 25.7 (range: 13.2-90.0) and a median ECOG performance status of 2 (range: 1-4) on the day of consent, were enrolled (Table 2). Forty-two of these patients (88%) had AML. Cytogenetic risk was favorable in 3, intermediate in 20, and adverse in 23, and unknown (insufficient growth) in 2; eighteen patients had a monosomal karyotype. 29 patients had secondary disease. Patients received a median of 2 (range, 1-6) cycles of CPX-351 therapy. The first 20 patients were randomly allocated. Among the 10 patients randomized to the higher CPX-351 dose, 1 patient each obtained a CR and CR with incomplete blood count recovery (CRi), respectively; both received CPX-351 post-remission therapy (1 and 4 cycles). Four patients (40%) died by day 28 (Table 3). All early deaths were infection-related and occurred in patients presenting with TRM scores of 14.7, 24.1, 33.4, and 58.1. Median survival of the 10 patients treated at the 64 units/m²/dose was 6 months, with 20% 12-month survival. Both responders relapsed (after 27 and 251 days) and died on day 320 and 364 after treatment initiation. Because of the 4 early deaths (3 of whom received care partially as outpatients) in these first 10 patients, accrual to the 64 units/m²/dose arm stopped, and the remaining 28 patients were enrolled in the lower-dose (32 units/m² per dose) arm.

Among 38 patients given 32 unit/m² per dose of CPX-351, there were 10 CRs (26%; 8 without flow cytometric evidence of MRD), 1 CRi, 21 with resistant disease, and 6 deaths from indeterminate cause (Table 3). Among the 6 patients who achieved an MRD-negative CR with the first cycle of therapy, median time to platelet count of 100,000/μL and ANC of 1,000/μL was 24.5 (range: 20-47) and 29.5 (range: 26-33) days. Eleven of these 39 patients (29%) died before day 28. In three, no drug toxicity was noted, but early disease progression led to treatment discontinuation and transition to hospice care. In at least two additional patients, disease progression was a major contributor to early death. Two of the 8 patients who experienced early death but no disease progression received care partially as outpatients. Median survival of the 38 patients treated with 32 unit/m² was 3 months, with 17% 12-month survival. Among the 11 responders, who all received post-remission therapy with CPX-351 (1-4 [median: 2] cycles), relapse-free survival was 7 months. Grade 3-5 treatment-emergent adverse events during cycle #1 for both patient cohorts are summarized in the *Online Supplementary Table.*

The optimal treatment intensity for less fit adults with AML remains unknown. Within the constraints of historical controls and the design which afforded more protection against a false-positive than a false-negative result, our data suggest that CPX-351 at either 32 or 64 units/m² is relatively unlikely to decrease TRM to 15% (from ~30% historically) while maintaining CR rate of 30% in patients at high risk of TRM. Further adjustments in eligibility and CPX-351 dosing to maximize efficacy and reduce early leukemia-related deaths are needed. In the absence of randomization, it is difficult to compare reduced-dose CPX-351 with low-dose cytarabine, DNA methyltransferase inhibitors, or investigational drugs pursued for less fit adults with AML, noting clinical trials testing such agents commonly use stringent eligibility criteria despite their intent for the unfit. While our study illustrates the difficulty of balancing therapeutic resistance and disease/treatment-related complications in this

challenging patient subset, it demonstrates, similar to a report by Montalban-Bravo *et al.*,[13] that such patients can, and must, be studied as part of a clinical trial.

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