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Idarubicin appears equivalent to dose-intense daunorubicin for remission induction in patients with acute myeloid leukemia

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ABSTRACT

Daunorubicin has historically been considered the anthracycline of choice at many cancer centers for the treatment of acute myeloid leukemia (AML). Drug shortages have required the substitution of daunorubicin with idarubicin. Randomized studies have shown idarubicin (10–12 mg/m^2) to be comparable or superior to standard dose daunorubicin (45–60 mg/m^2) for achieving complete remission (CR). Whether these results can be extrapolated to dose-intense daunorubicin (90 mg/m^2), recently shown to improve CR rates when compared to standard daunorubicin doses remains uncertain. This observational study was conducted at Northwestern Memorial Hospital (NMH) to compare CR rates. The results suggest idarubicin is equivalent to daunorubicin, and for some subsets of patients, idarubicin may have superior CR rates.

1. Introduction

The United States health system has been coping with ongoing cancer drug shortages. In 2011, more than 200 drugs were on the shortage list kept on the American Society of Health-System Pharmacists website, including dozens of generic cancer drugs [1]. Critical cancer drug shortages cause delays in treatment, or treatment with suboptimal alternate therapies, which can impact survival. Daunorubicin, a standard component in the "7 plus 3" regimen (daunorubicin/cytarabine) used for the treatment of patients with newly diagnosed acute myeloid leukemia(AML) for more than 40 years, became commercially unavailable in 2011, which necessitated replacement with an alternate anthracycline. Previously published studies have shown idarubicin 12 mg/m^2 (IDA-12) to be equal to, or possibly superior to standard dose daunorubicin (45–60 mg/m^2) for achieving CR [2–9]. Dose-intense daunorubicin 90 mg/m^2 (DAU-90) has now been shown to improve CR compared to standard dose daunorubucin 45 mg/m^2 in older and younger patients [10,11]. However, DAU-90 has not been directly compared to IDA-12 for achieving CR in AML. Thus, an observational study was conducted at Northwestern Memorial Hospital to compare CR rates in consecutive patients receiving either DAU-90 or IDA-12 remission induction therapy in AML.

2. Methods

Medical records were used to identify consecutive newly diagnosed patients with AML who received daunorubicin 90 mg/m^2(DAU-90) or idarubicin 12 mg/m^2(IDA-12) as part of the standard induction "7 plus 3" induction regimen. DAU-90 patients were treated from 7/11/2007-10/20/10 and IDA-12 treated from7/01/2011-6/12/2012. Patients with acute promyelocytic leukemia (APL) were excluded. Patients with a prior diagnosis of myelodysplastic syndrome which subsequently evolved into AML were included. AML was diagnosed according to WHO criteria [12]. Cytogenetic risk (good, intermediate, unfavorable) was defined according to published guidelines [13]. Combined risk was calculated using both cytogenetic risk and FLT-3 ITD mutation status. Patients who were FLT-3 ITD positive, regardless of karyotpe, were categorized as high risk [14]. Patients received daunorubin 90 mg/m^2 IV bolus or idarubicin 12 mg/m^2 IV bolus on days 1–3. Cytarabine 100 mg/m^2 by continuous infusion was given concomitantly on days 1–7 to both groups. All patients underwent bone marrow biopsy on day 14 after initiation of therapy. If residual disease was found, patients were considered induction treatment failure. Patients without residual disease were re-biopsied at the time of count recovery to assess whether CR was achieved. Patients who did not achieve CR after a single IDA-12 course did not receive another course of IDA-12, but underwent re-induction with one of several regimens according to physician discretion.

Chi-square, *t*-test and Wilcoxon rank sum test were used for univariate analysis, and adjusted multiple logistic regression model was used for multivariate analysis. Cumulative rates of CR were estimated according to the Kaplan–Meier method and were evaluated with the log-rank test. This study was approved by the Northwestern University Institutional Review Board.

3. Results

Twenty-eight IDA-12 and 37 DAU-90 patients were enrolled in the study. Tables 1 and 2 show patient demographics and outcome respectively. The 2 groups did not differ with respect to

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Table 1
Patient characteristics.

Patient characteristics	Idarubicin 12 mg/m^2 28	Daunorubin 90 mg/m^2 37	*p*-Value
Male	13	18	0.8592
Age/median (range)	56 (24–73)	48 (21–72)	0.1508
Age > 60	10	6	0.0708
Age > 55	14	12	0.31
Weight/kg (range)	84.8 (51–124)	82.8 (48–130)	0.6831
BSA	1.92 (1.45–2.30)	1.93 (1.47–2.43)	0.9233
Percent blasts prior to therapy	63.8 (15–100)	50.3 (20–95)	0.0575
Maximum WBC prior to therapy	25.7 (0.2–137)	35.3 (0–252)	0.4365
NPM positive (%)	7/22 (32)	6/25(25)	0.5499
FLT-3 ITD(%)	6/23 (26)	4/32 (12.5)	0.2902
-5/5q-,7/7q-	6/27(22)	7/33(21)	0.99
Karyotype (*cytogenetics*)			
Good (%)	3/28 (11)	8/35 (23)	0.3187
Intermediate	8/28 (29)	12/35 (34)	0.7864
Unfavorable	17/28 (61)	15/35 (43)	0.2074
Unknown	0/28(0)	2/37(5)	0.5019
Combined risk factors (*cyto + molecular*)			
Good (%)	3/28 (11)	8/36 (22)	0.3217
Intermediate	8/28 (29)	9/36 (25)	0.7818
Unfavorable	17/28 (61)	19/36 (53)	0.6149

gender, age, weight, baseline maximum WBC count, cytogenetic risk, number of patients with cytogenetics suggestive of pre-existing MDS(-5/5q-, -7/7q-)or percent of patients with FLT-3 ITD mutation. Patients treated with IDA-12 had higher baseline marrow blasts counts prior to therapy ($p < 0.0575$). Most patients (IDA-12-70% and DAU-90-56%) subsequently underwent stem cell transplantation. Overall, CR was similar between IDA-12 and DAU-90 treated patients ($p < 0.1072$). Subset analysis shows CR rates were significantly higher in IDA-12 treated patients who had an

Table 2
Idarubicin and daunorubicin rates of complete remission.

Characteristic	Idarubicin 12 mg/m^2	Daunorubin 90 mg/m^2	*p*-Value
Complete remission after first induction with IDA-12 or DAU-90 (*n*%)	17/28 (61)	15/37 (41)	0.1072
Overall complete remission (second induction)	22/28 (78)	30/37 (80)	0.99
Karyotype (*cytogenetics*)	17/28 (61)	13/35 (37)	0.2937
Good	2/3 (67)	5/8(63)	0.99
Intermediate	5/8 (63)	5/12(41)	0.649
Unfavorable	10/17 (60)	3/15(20)	0.0359
Combined risk factors (*cyto + molecular*)	17/28 (61)	14/36	0.1072
Good	2/3 (67)	5/8 (63)	0.99
Intermediate	5/8 (63)	5/9 (55)	0.99
Unfavorable	10/17 (60)	4/19 (31)	0.0388
Age > 60	8/10 (80)	1/6 (17)	0.035
Age < 60	9/18 (50)	14/31 (45)	0.7746
Age > 55	7/14 (50)	2/13 (16)	0.0063
Age < 55	10/14 (71)	13/24 (54)	0.99
Subsequent stem cell transplantation (*n*)	14/20 (70)	20/37 (54)	0.2727
Early (day 60) post transplant mortality	1/14 (7)	1/20 (5)	0.99
CTCL grade 3–4 toxicity (excluding blood)	7/27 (26)	5/37 (14)	0.3311
Non-relapse mortality (day 30)	5/27 (19)	2/37 (5)	0.1222

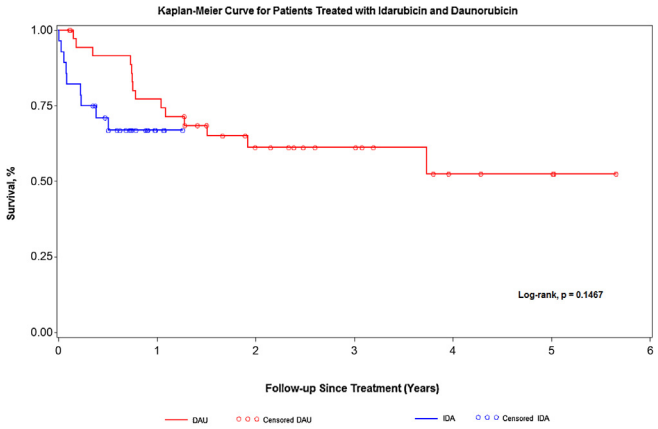

Fig. 1. Kaplan–Meier curve for patients treated with idarubicin and daunorubicin.

unfavorable karyotype ($p < 0.0359$) or unfavorable combined cytogenetic risk ($p < 0.0388$) or for age > 55 ($p < .0063$). Of the six IDA-12 patients who received a second induction course, which included HIDAC ($n = 5$) or dose-intense cyclophosphamide and etoposide ($n = 1$), five achieved CR. Of the fifteen DAU-90 patients who received a second induction course, which included HIDAC ($n = 8$), lower dose "7 plus 3" ($n = 6$) or mitoxanthrone, etoposide and intermediate-dose cytarabine (MEC = 1), thirteen patients achieved CR. Overall CR after two inductions regimens was the same for IDA-12 and DAU-90 treated patients ($p < 0.99$). Kaplan–Meier curve (Fig. 1) shows no difference in overall survival (log rank, $p = 0.1467$).

Grade 3–4 toxicity was similar between treatment groups. Microbiologically confirmed infections, predominantly from the bloodstream, occurred frequently in both cohorts groups without a significant difference. No cardiac toxicities were observed in IDA-12 treated patients. Sustained sinus tachycardia and sinus bradycardia, which resolved spontaneously were observed in 2 DAU-12 patients. Five patients in the IDA-12 treatment group died during treatment, including two from acute bleeding episodes, two from infectious causes(bacteremia and mucomycosis) and one from disease progression. Two patients in the DAU-90 group died, both from sepsis. All cause mortality within 30 days of treatment was not significantly different ($p < 0.122$). For those patients who subsequently went to stem cell transplantation, early post-HSCT mortality (day 60) was observed in 1 IDA-12 patient and 1 DAU-90 patient.

4. Discussion

Critical drug shortages continue to impact on the health care system. This dilemma is especially concerning in cancer treatment, where the equivalence of alternate therapies is frequently unknown. The present observational study shows that a single course of "7 plus 3"with IDA-12 results in a similar CR rate compared to a single course of 7 + 3 with DAU-90 as induction therapy for AML. A subset analysis shows that older adults (>60) have a higher CR rate with IDA-12 compared to DAU-90 ($p < 0.035$). In addition, patients with poor cytogenetic risk category achieved CR significantly more often with IDA-12 compared to DAU-90 ($p < 0.0359$). Overall morbidity and mortality within 30days of treatment were similar between the 2 study groups. Overall survival as shown in the Kaplan–Meier survival curve appears slightly worse in the IDA-12 cohort compared to DAU-90, yet statistically non-significant.

Some caution is required in the interpretation of these results. The comparison is not concurrent as idarubicin was used during daunorubicin shortage, and the two cohorts had minimal actual overlapping follow-up time. Additionally, the idarubicin cohort