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Potential for improved survival with intensification of daunorubicin based induction chemotherapy in acute myeloid leukemia patients who do not receive transplant: A multicenter retrospective study

John L. Reagan[a,*], Matthew R. Sullivan[b], Eric S. Winer[a], Frederick Lansigan[b], Michael S. Cardin[c], Jorge J. Castillo[d]

[a] Division of Hematology and Oncology, Rhode Island Hospital, The Warren Alpert Medical School of Brown University, Providence, RI, USA
[b] Division of Hematology and Oncology, Dartmouth Hitchcock Medical Center, Geisel School of Medicine, Lebanon, NH, USA
[c] Division of Pharmacy, Rhode Island Hospital Comprehensive Cancer Center, Providence, RI, USA
[d] Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Introduction: During induction daunorubicin intensification from 45 mg/m^2/day to 90 mg/m^2/day has shown improved response and survival rates in AML patients. We retrospectively reviewed outcomes of daunorubicin 60 mg/m^2/day (DNR60) versus daunorubicin 90 mg/m^2/day (DNR90) in adult AML patients.
Material and methods: Newly diagnosed AML patients ≥18 years who received 7 + 3 with or without etoposide as frontline therapy from 1/1/2006 to 5/1/2013 were identified. Chi-square and Wilcoxon rank sum tests were used to compare characteristics. Kaplan–Meier curves were estimated for overall survival (OS). Univariate and multivariate Cox proportional hazard regression models were developed to determine independent predictors for survival.
Results: A total of 128 patients were included (DNR90 = 48 patients, DNR60 = 80 patients). The estimated 3-year OS rate in the DNR90 group was 56% (95% CI 38–70%), while in the DNR60 group was 34% (95% CI 23–44%). Multivariate analysis (MVA) in non-allotransplanted patients showed that unfavorable cytogenetics and worse performance status were associated with decreased OS while DNR intensification, etoposide use and site were associated with improved OS. In MVA of allotransplanted patients re-induction based on day-14 marrow was associated with worse OS.
Conclusions: Based on our retrospective study, initial DNR based induction chemotherapy intensification improved OS in non-allotransplanted patients. Prospective studies are needed to confirm this preliminary finding.

1. Introduction

The standard therapy for acute myelogenous leukemia (AML) over the past 30 years has been centered on the traditional "7 + 3" regimen consisting of daunorubicin (DNR), an anthracycline, administer over three days alongside cytarabine, a nucleoside analog, administered over 7 days [1]. With 7 + 3 induction, complete remission (CR) rates of 40–80% have been reported [1,2]. One explanation for this variation is that leukemic resistance to upfront therapy is centered on many individual patient characteristics such as older age as well as poor performance status, which portends one of the most adverse prognostic features [3].

Recent randomized studies have reported significant improvements in CR and overall survival (OS) rates with intensification of DNR dose in patients with AML who are younger than 60, and in a subgroup of patients aged 60–65 years [2,4,5]. The standard-dose DNR used in these reports was 45 mg/m^2/day (DNR45), which was compared to a higher dose of 90 mg/m^2/day (DNR90). Thus far, there have been three studies showing improved efficacy of DNR90 compared to the DNR45. Each study was run by a large cooperative group; one based in the United States [4], another based in Western Europe [5], and the third based in South Korea [2]. Prior to the data supporting DNR90, the standard dose of DNR at many institutions, including our own, was 60 mg/m^2/day (DNR60), based on previous studies showing improved response rates compared to DNR45 with similar reported toxicity profiles [1,6–10].

* Corresponding author at: Rhode Island Hospital, George 3, Providence, RI 02903, USA. Tel.: +1 401 444 5391; fax: +1 401 444 4184.
E-mail address: jreagan@lifespan.org (J.L. Reagan).

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To date, there has been no prospective study evaluating the efficacy and toxicity profiles of DNR60 in comparison with DNR90 as part of the 7 + 3 regimen for single planned induction treatment of AML. Of particular importance to this question is that as age increases, especially for those patients over 50, the benefit of high-dose DNR decreases when compared to standard-dose DNR while the toxicity also appears to increase [4,5]. We conducted a multicenter retrospective chart review to determine differences in clinical outcomes between DNR60 and DNR90.

2. Materials and methods

Consecutive newly diagnosed AML patients 18 years or older who received induction therapy with DNR and cytarabine from January 1st, 2006 to May 1st, 2013 were identified through the Rhode Island Hospital (RIH), The Miriam Hospital (TMH), and Dartmouth Hitchcock Medical Center (DHMC) cancer center medical records. Acute promyelocytic leukemia patients were excluded. Patients received either DNR60 or DNR90 on days 1–3 as an IV bolus along with concurrent cytarabine 100–200 mg/m^2/day administered as a 24-hour infusion on days 1–7. A subset of patients in each DNR cohort also received etoposide 100 mg/m^2/day on days 1–3 over 2 h. Inclusion of etoposide to DNR-based induction chemotherapy had become a frequent practice at our sites during the study time period based on involvement in a recent cooperative group trial [11]. The study was approved by the Institutional Review Boards of all participating sites.

Demographic data (age, sex, ECOG performance status, site of treatment de-identified as site 1, 2, or 3) as well as AML specific data (initial white blood cell count [WBC], initial bone marrow [BM] blast count, cytogenetic risk stratification, CR rate, and OS) were recorded. Cytogenetic risk was categorized as favorable, intermediate and unfavorable based on the National Comprehensive Cancer Network (NCCN) guidelines [12]. CR was defined by International Working Group (IWG) in AML criteria [13]. Day-14 BM biopsies were obtained per attending physician discretion, as was the clinical decision regarding re-induction based on day-14 BM biopsy results. Patients were determined to be in CR from initial chemotherapy if they attained IWG AML CR criteria after either first or second induction with DNR-based chemotherapy. OS was defined as the time in months elapsed from diagnosis until death or end of follow-up.

Clinical characteristics of the patients are presented using descriptive statistics. Chi-square and Wilcoxon rank-sum tests were used to determine differences in categorical and continuous variables, respectively, between the standard and high-dose DNR groups. Logistic regression models were fitted to investigate the relation between clinical variables and attainment of CR. The outcome of interest for the logistic regression analyses was odds ratio (OR) of attaining CR with 95% confidence interval (CI). OS curves were estimated using the Kaplan–Meier method [14], and compared using the log-rank test [15]. Univariate and multivariate Cox proportional-hazard regression models were fitted to evaluate the relation between clinical variables and OS [16]. The outcome of interest for the Cox regression analyses was hazard ratio (HR) of death from any cause with 95% CI. For OS analysis patients were divided into two groups, those that did not receive allogeneic stem cell transplantation (allo-SCT) and those that did receive allo-SCT. In the multivariable models, p-values <0.05 were considered statistically significant. All calculations and graphs were obtained using Stata/SE 13.1 (StataCorp LP, College Station, TX, USA).

3. Results

Our study included 128 patients with newly diagnosed AML, 80 (62.5%) received DNR60 and 48 (37.5%) received DNR90 as part of induction therapy. Selected characteristics of the patients are shown in Table 1. The DNR90 cohort was younger than the DNR60 cohort. Also, patients in the DNR90 cohort, had better ECOG performance status and were more likely to have received etoposide than their DNR60 counterparts. Overall, 31 patients (27%) required a second course of induction chemotherapy based on residual disease on day-14 bone marrow biopsy. DNR60 patients were more likely to have required a second course of induction than DNR90 patients. There was no difference in median white blood cell (WBC) or WBC counts over 50,000/μL, although there was a trend toward hyperleukocytosis in the DNR60 group. There were no differences in sex, initial median bone marrow blast percent and cytogenetic risk categorical distribution between the DNR90 and DNR60 cohorts. Inter-site comparison between sites 1 and 3 revealed greater use of etoposide (42% at site 1, 19% at site 3, $p = 0.01$) and older patients (site 1 median age = 61, site 3 median age = 57, $p = 0.02$) at site 1 while patients at site 3 were more likely to receive DNR90 (site 1 = 24%, site 3 = 52%, $p = 0.004$). Furthermore, although not statistically significant there were fewer patients with favorable risk cytogenetics at site 1 compared to site 3 (site 1 = 6%, site 3 = 21%, $p = 0.07$).

At the end of induction, 87 patients (68%) obtained pathological CR, 29 (23%) did not obtain CR, and 12 (9%) were not evaluable.

Table 1
Select patient characteristics of the DNR60 and DNR90 cohorts.

Variable	All patients		DNR60 ($n = 80$)		DNR90 ($n = 48$)		p-Value
	Median or *N*	Range or %	Median or *N*	Range or %	Median or *N*	Range or %	
Median age (years)	58	18–78	61.5	18–78	53.5	26–75	<0.001
Sex							
Women	64	50%	39	49%	25	52%	0.72
Men	64	50%	41	51%	23	48%	
ECOG							
0	72	56%	37	46%	35	73%	0.01
1	49	38%	37	46%	12	25%	
2	7	5%	6	8%	1	12%	
Median BM blasts	53.5%	16–98	56%	20–98	50%	16–93	0.29
Median WBC at diagnosis (cells/μL)	7.25	0.3–279	7.85	0.3–210	6.3	1.1–279	0.82
Risk category							
Favorable	15	12	9	12	6	13	0.54
Intermediate	70	56	41	53	29	62	
Unfavorable	39	31	27	35	12	26	
Etoposide							
No	94	73	64	80	30	63	0.03
Yes	34	27	16	20	18	38	
Re-induction							
No	97	76	55	69	25	87	0.02
Yes	31	24	25	31	6	13	
Site							
Site 1	50	39	38	48	12	25	0.01
Site 2	26	20	17	22	9	19	
Site 3	52	41	25	31	27	56	

ECOG: Eastern Cooperative Oncology Group; BM: bone marrow; WBC: white blood cells; DNR60: daunorubicin 60 mg/m^2/day; DNR90: daunorubicin 90 mg/m^2/day.