Leukemia Research 39 (2015) 812–817

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

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

ARTICLE INFO

Article history:
Received 23 December 2014
Received in revised form 2 April 2015
Accepted 19 April 2015
Available online 2 May 2015

Keywords:
Acute myeloid leukemia
Acute myeloid leukemia therapy
Chemotherapy
Leukemia

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).

http://dx.doi.org/10.1016/j.leukres.2015.04.015
0145-2126/

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.

Table 2
Univariate and multivariate regression analyses results for overall CR.

Variable	Univariate OR (95% CI)	*p*-Value	Multivariate OR (95% CI)	*p*-Value
Age	0.99 (0.96–1.02)	0.46	1.00 (0.96–1.04)	0.94
ECOG				
0	1.00 (Ref)		1.00 (Ref)	
1	0.97 (0.45–2.10)	0.94	1.00 (0.38–2.62)	1.00
2	1.17 (0.21–6.51)	0.86	1.30 (0.11–15.83)	0.84
Risk category				
Favorable	1.00 (Ref)		1.00 (Ref)	
Intermediate	0.58 (0.15–2.28)	0.44	0.79 (0.15–4.04)	0.78
Unfavorable	0.32 (0.08–1.33)	0.12	0.48 (0.09–2.55)	0.39
Etoposide				
No	1.00 (Ref)		1.00 (Ref)	
Yes	0.98 (0.42–2.27)	0.96	1.02 (0.37–2.83)	0.97
Re-induction at day 14				
No	1.00 (Ref)		1.00 (Ref)	
Yes	0.65 (0.28–1.52)	0.32	0.67 (0.23–1.91)	0.45
Site				
Site 1	1.00 (Ref)		1.00 (Ref)	
Site 2	0.99 (0.38–2.58)	0.98	0.97 (0.33–2.83)	0.96
Site 3	3.46 (1.39–8.61)	0.008	3.94 (1.25–12.40)	0.02
Dose				
DNR60	1.00 (Ref)		1.00 (Ref)	
DNR90	2.40 (1.05–5.51)	0.04	1.74 (0.63–4.84)	0.29

OR: odds ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; DNR60: daunorubicin 60 mg/m^2/day; DNR90: daunorubicin 90 mg/m^2/day.

Since most of the non-evaluable patients died before CR could be assessed, they were considered as not having achieved a CR for the regression analysis (worse-case scenario). The CR rate in the DNR90 and DNR60 groups were 79% and 61%, respectively. Neither initial WBC count nor BM blast count were associated with CR attainment. Logistic regression analysis showed DNR dose and treatment at site 3 to be associated with improved CR in univariate analysis. However, in the multivariate analysis, DNR dose did not retain significance although it was associated with an almost 2-fold increased likelihood of attaining CR. Only treatment site 3 was associated with higher rates of CR. Detailed results are shown in Table 2.

With a median follow-up of 47 months, the median OS for the entire cohort was 18 months with estimated 3-year OS rate of 42% (95% CI 32–51%). Kaplan–Meier OS curves are shown in Fig. 1. The median follow-up times for the DNR90 and DNR60 groups were 37 months and 52 months, respectively. 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%).

Out of 87 patients who achieved CR, 42 (48%) went on to receive allo-SCT. Five patients went on to allo-SCT without attaining CR. In order to determine the effects of initial induction chemotherapy on OS, patients were stratified into those who did not receive allo-SCT (Table 3) and those that did receive allo-SCT (Table 4). The univariate analysis (UVA) in patients who did not receive allo-SCT showed that age as well as intermediate and unfavorable risk cytogenetics was associated with decreased OS while treatment at site 3 and DNR90 dose was associated with increased OS. In multivariate analysis (MVA), ECOG PS of 2 and unfavorable cytogenetics were associated with decreased OS while treatment at site 3 and use of DNR90 retained their association with increased OS. Etoposide use also correlated with better OS ($p = 0.02$). In the UVA of patients who underwent allo-SCT, no patient characteristic was associated with OS. However, in MVA of transplanted patients the need for re-induction based on disease persistence on day-14 bone marrow conferred decreased OS.

In terms of 30-day mortality, 11/80 DNR60 patients had died by day 30 while 5/48 DNR90 patients had died by day 30. The Odds Ratio (OR) of 30-day mortality for DNR90 versus DNR60 is 0.73 (95% CI 0.19–2.48; $p = 0.58$). For 90-day mortality, 17/80 DNR60 had died by day 90 while 6/48 DNR90 had died. The OR of 90-day mortality for DNR90 versus DNR60 is 0.53 (95% CI 0.16–1.56; $p = 0.21$).

4. Discussion

In this retrospective study, we show a statistically significant improvement in OS for adults with newly diagnosed AML treated with an intensified daunorubicin based induction chemotherapy regimen (DNR90) who do not proceed to allo-SCT. Within our study, the estimated 3-year OS rate in the DNR90 group was 56%, while in the DNR60 group was 34%. In univariate analysis of patients who did not undergo allo-SCT, DNR90 was associated with a 68% reduction in the risk of death from any cause (HR 0.32) when compared with DNR60. This benefit retained its significance in MVA after adjusting for important prognostic factors such as age, performance status, cytogenetic risk, etoposide use, re-induction chemotherapy and site of treatment (HR 0.42). Etoposide use showed a 59% reduction in risk of death from any cause (HR 0.41) in non-transplant patients within this MVA. In patients who received allo-SCT, only re-induction based on day-14 BM biopsy influenced OS.

Interestingly, within our study there was a difference in CR and non-allo SCT OS within MVA between the sites 1 and 3. The improved outcomes associated with site 3 may be attributed to greater use of DNR90, younger patients and more cases of favorable risk cytogenetics at site 3 compared to site 1.

To the best of our knowledge, the only other retrospective studies to directly compare DNR60 to DNR90 in adult AML patients have shown a mixed response to DNR dose intensification based on whether the leukemia was classified as core binding factor (CBF) AML or not. Initially, in non-CBF AML patients $\leq$60 years Devillier and colleagues reported no improvement in overall response or relapse-free survival (RFS) with DNR90 versus DNR60 [17]. In this study, 300 consecutive AML patients were reviewed; 225 patients received DNR60 while 75 patients received DNR90. Of note, the median follow up in the DNR90 group was 31 months while the DNR60 group had a median follow up of 58 months. This same

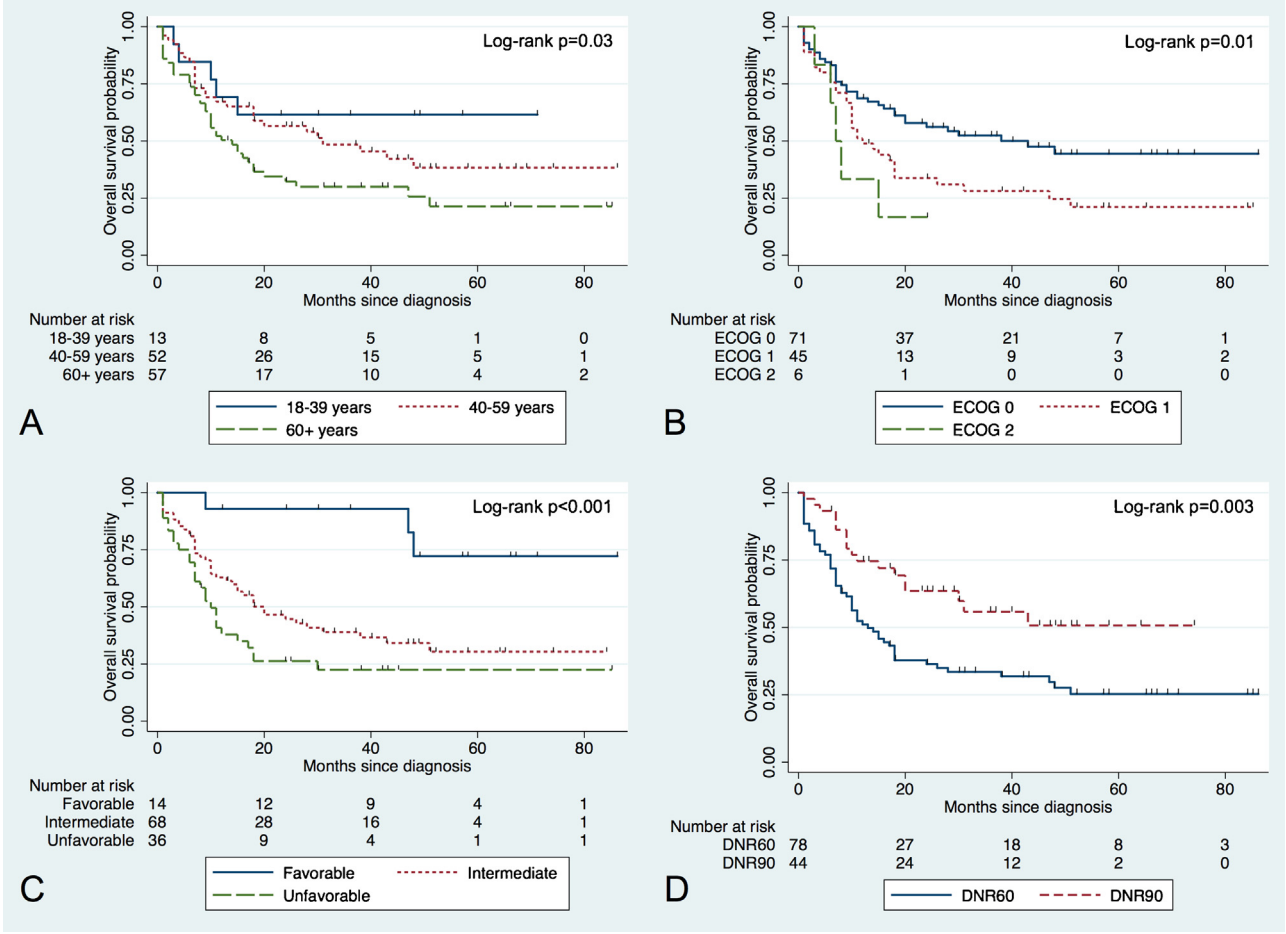

Fig. 1. Patient Kaplan Meier overall survival curves stratified based on age (A), ECOG PS (B), cytogenetic risk (C), and daunorubicin dose (D).

Table 3
Cox proportional-hazard regression analyses results for overall survival in patients who did not proceed to allogeneic transplant.

Variable	Univariate HR (95% CI)	*p*-Value	Multivariate HR (95% CI)	*p*-Value
Age	1.03 (1.00–1.06)	0.02	0.98 (0.94–1.02)	0.28
ECOG				
0	1.00 (Ref)		1.00 (Ref)	
1	1.61 (0.92–2.83)	0.10	1.83 (0.81–4.12)	0.15
2	1.69 (0.64–4.46)	0.29	4.77 (1.21–18.9)	0.03
Risk category				
Favorable	1.00 (Ref)		1.00 (Ref)	
Intermediate	3.36 (1.02–11.1)	0.05	2.29 (0.62–8.39)	0.21
Unfavorable	7.05 (2.03–24.5)	0.002	5.27 (1.39–20.0)	0.02
Etoposide				
No	1.00 (Ref)		1.00 (Ref)	
Yes	0.70 (0.37–1.33)	0.27	0.41 (0.19–0.86)	0.02
Re-induction on day 14				
No	1.00 (Ref)		1.00 (Ref)	
Yes	1.06 (0.58–1.95)	0.84	0.73 (0.32–1.66)	0.45
Site				
Site 1	1.00 (Ref)		1.00 (Ref)	
Site 2	0.88 (0.45–1.70)	0.70	0.63 (0.29–1.40)	0.73
Site 3	0.36 (0.19–0.68)	0.002	0.20 (0.08–0.51)	0.001
Dose				
DNR60	1.00 (Ref)		1.00 (Ref)	
DNR90	0.32 (0.16–0.65)	0.002	0.42 (0.19–0.92)	0.03

HR: hazard ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; DNR60: daunorubicin 60 mg/m^2/day; DNR90: daunorubicin 90 mg/m^2/day.

Table 4
Cox proportional-hazard regression analyses results for overall survival in patients who proceeded to allogeneic transplant.

Variable	Univariate HR (95% CI)	*p*-Value	Multivariate HR (95% CI)	*p*-Value
Age	0.99 (0.96–1.03)	0.71	0.97 (0.92–1.02)	0.22
ECOG[*]				
0	1.00 (Ref)		1.00 (Ref)	
1	1.70 (0.66–4.33)	0.27	1.36 (0.39–4.77)	0.64
Risk category[**]				
Intermediate	1.00 (Ref)		1.00 (Ref)	
Unfavorable	1.89 (0.72–4.93)	0.19	0.82 (0.22–3.11)	0.78
Etoposide				
No	1.00 (Ref)		1.00 (Ref)	
Yes	1.93 (0.76–4.86)	0.17	0.83 (0.20–3.45)	0.80
Re-induction on day 14				
No	1.00 (Ref)		1.00 (Ref)	
Yes	1.57 (0.61–4.08)	0.35	4.36 (1.12–17.0)	0.03
Site				
Site 1	1.00 (Ref)		1.00 (Ref)	
Site 2	0.57 (0.11–2.96)	0.51	0.22 (0.03–1.67)	0.14
Site 3	2.22 (0.77–6.50)	0.14	3.13 (0.68–14.4)	0.14
Dose				
DNR60	1.00 (Ref)		1.00 (Ref)	
DNR90	1.37 (0.54–3.47)	0.51	0.37 (0.08–1.71)	0.20

HR: hazard ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; DNR60: daunorubicin 60 mg/m^2/day; DNR90: daunorubicin 90 mg/m^2/day.
[*] There were no observations on the ECOG 2 category.
[**] There were no observations on the low-risk cytogenetics category.

group has reviewed outcomes following anthracycline intensification in previously untreated CBF AML patients ages 16–65 [18]. Eighty-six patients are included; 57 were treated with DRN60 and 29 with DNR90. Interestingly, all patients attained a CR while there was a trend toward improved OS and a statistically significant improvement in RFS for the DNR90 group compared to the DNR60 group. DNR90 retained its superiority over DNR60 for RFS in multivariate analysis.

In comparison, in our study the most pronounced effect of chemotherapy intensification was seen in those patients with intermediate risk cytogenetics with no improvement seen in the survival of favorable risk patients, i.e. CBF AML. A possible rationale for the lack of improvement in CBF AML is the relatively small sample size of our study as only 15 patients had favorable risk AML. In terms of intermediate risk cytogenetic AML, our study results differed from that reported by Devillier and colleagues in two main respects. First, our CR rate of 61% with DNR60 was less than the CR rate of 72% Devillier reported, although both are in line with reported CR rates in historical controls of 52–68% [19,20]. Meanwhile, our CR rate with DNR90 was 79% compared to their CR rate of 69%, which also compare favorably to the historical control CR rate of 64–83% [2,4,5]. The other possible rationale for this discrepancy is that in our study the median follow up time of the DNR90 cohort was longer than that reported by Devillier et al. (37 months vs. 31 months), and did not statistically differ between the DNR60 and DNR90 groups in our study ($p = 0.21$) as it did in their study ($p < 0.001$).

A recent prospective study has shown no difference in response rates or survival for DNR90 compared to DNR60 [21]. The main difference, however, between this prospective study and our own is how DNR was administered. In our series, patients underwent initial induction therapy with either DNR60 or DNR90 and then only received additional DNR if the day-14 bone marrow biopsy did not show CR, which occurred in 31 patients (27%). In Burnett et al.'s prospective study, a double induction was planned in which patients were randomized to either DNR60 or DNR90 then received a second induction course with daunorubicin 50 mg/m^2/day for 3 days. This additional DNR dosing likely mitigated any response and survival benefit seen with DNR intensification as evident by their CR rate of 84% with DNR60, which far exceeds that reported by historical controls [19,20].

The primary limitation of our study is that it is retrospective in nature and, by virtue of its design, prone to confounding bias. We attempted to deal with this bias by performing multivariate analysis with clinically relevant variables such as age, performance status, cytogenetic risk, etoposide use, need for re-induction and site of treatment in addition to daunorubicin dose. Classification bias was minimized in our study as all patients were diagnosed with AML by an expert hematopathologist at each center. Selection bias was limited in this study as all consecutive patients induced with 7 + 3 at each institution were included. The small sample size of our study limits conclusions from subgroup analyses. In addition, the lack of molecular studies that are now routinely available in the care of AML limits this dataset, particularly in terms of risk stratification of those patients with intermediate risk cytogenetics.

5. Conclusion

Our results suggest a role for upfront daunorubicin-based induction chemotherapy dose intensification in patients with AML. Standard clinical practice often calls for induction chemotherapy to be administered prior to the decision of whether or not to proceed to a consolidative allo-SCT. Therefore, our results support the continued use of daunorubicin 90 mg/m^2/day for 3 days in newly diagnosed AML patients provided a single initial induction strategy is planned. Confirmation of these findings in a randomized, prospective study is required.

Conflict of interest statement

JLR is supported by a Leukemia & Lymphoma Society Special Fellow in Clinical Research Grant Number CDA 4298-14. The authors report no other conflicts of interest.

Acknowledgement

The authors would like to thank Ms. Deana Landry for her administrative assistance in the preparation of this manuscript.

References

[1] Yates J, Glidewell O, Wiernik P, Cooper M, Steinberg D, Dosik H, et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. Blood 1982;60:454–62.
[2] Lee J-H, Joo Y-D, Kim H, Bae SH, Kim MK, Zang DY, et al. A randomized trial comparing standard versus high-dose daunorubicin induction in patients with acute myeloid leukemia. Blood 2011;118:3832–41.
[3] Estey E, Smith TL, Keating MJ, McCredie KB, Gehan EA, Freireich EJ. Prediction of survival during induction therapy in patients with newly diagnosed acute myeloblastic leukemia. Leukemia 1989;3:257–63.
[4] Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, Paietta EM, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 2009;361:1249–59.
[5] Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 2009;361:1235–48.
[6] Petersdorf SH, Kopecky KJ, Slovak M, Willman C, Nevill T, Brandwein J, et al. A phase III study of gemtuzumab ozogamicin during induction and post-consolidation therapy in younger patients with acute myeloid leukemia. Blood 2013;121:4854–60.
[7] Schiller G, Gajewski J, Territo M, Nimer S, Lee M, Belin T, et al. Long-term outcome of high-dose cytarabine-based consolidation chemotherapy for adults with acute myelogenous leukemia. Blood 1992;80:2977–82.
[8] Büchner T, Schlenk RF, Schaich M, Döhner K, Krahl R, Krauter J, et al. Acute MYELOID LEUKEMIA (AML): different treatment strategies versus a common standard arm—combined prospective analysis by the German AML Intergroup. J Clin Oncol 2012;30:3604–10.
[9] Weick J, Kopecky K, Appelbaum F, Head D, Kingsbury L, Balcerzak S, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. Blood 1996;88:2841–51.
[10] Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 1994;331:896–903.
[11] Kolitz JE, George SL, Marcucci G, Vij R, Powell BL, Allen SL, et al. P-glycoprotein inhibition using valspodar (PSC-833) does not improve outcomes for patients younger than age 60 years with newly diagnosed acute myeloid leukemia: Cancer and Leukemia Group B study 198082010. Blood 2010;116:1413–21.
[12] O'Donnell MR, Abboud CN, Altman J, Appelbaum FR, Arber DA, Attar E, et al. Acute myeloid leukemia. J Natl Comprehensive Cancer Network 2012;10:984–1021.
[13] Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21:4642–9.
[14] Kaplan ELMP. Nonparametric estimation from incomplete observations. J Am Statistical Assoc 1958;53:457–81.
[15] Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1 1966;50:163.
[16] Cox D. Regression models and life tables (with discussion). J Roy Statist Soc B 1972;34:187–220.
[17] Devillier R, Bertoli S, Prébet T, Huguet F, Etienne A, Charbonnier A, et al. Comparison of 60 or 90 mg/m^2 of daunorubicin in induction therapy for acute myeloid leukemia with intermediate or unfavorable cytogenetics. Am J Hematol 2014:E29–30.
[18] Prebet T, Bertoli S, Delaunay J, Pigneux A, Delabesse E, Mozziconacci MJ, et al. Anthracycline dose intensification improves molecular response and outcome of patients treated for core binding factor acute myeloid leukemia. Haematologica 2014;99:e185–7.
[19] Cassileth P, Lynch E, Hines J, Oken M, Mazza J, Bennett J, et al. Varying intensity of postremission therapy in acute myeloid leukemia. Blood 1992;79:1924–30.
[20] Rowe J, Andersen J, Mazza J, Bennett J, Paietta E, Hayes F, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (>55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood 1995;86:457–62.
[21] Burnett AK, Russell N, Hills RK, Kell J, Cavenagh J, Kjeldsen L, et al. A Randomised comparison of daunorubicin 90 mg/m^2 vs 60 mg/m^2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. ASH Annual Meeting Abstract 2014.