Impact of dose ratio variation on the comparative effectiveness of daunorubicin- and idarubicin-based regimens in acute myeloid leukaemia: a meta-regression analysis

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BACKGROUND

- Intensive induction therapy for acute myeloid leukaemia (AML) combines **cytarabine with an anthracycline**, mostly either daunorubicin (DNR) or idarubicin (IDA).
- The anthracycline used in practice varies due to differences in drug availability, cost, and local guidelines.
- **DNR and IDA are structurally similar** - the only difference being the presence of a methoxy group[1,2] (Figure 1).
- Recommended induction doses are **DNR 60 mg/m^2 for 3 days and IDA 12 mg/m^2 for 3 days** (ratio 5:1)[3].
- Comparative efficacy of DNR vs IDA has been widely debated with previous meta-analyses (including a Cochrane review [4]) sometimes concluding that IDA is superior to DNR.
- **Most trials used less-than-recommended doses of DNR**, potentially biasing results. Consequently, variation in the DNR:IDA dose ratio may confound the results of meta-analyses.
- Most published meta-analyses **did not consider the impact of variation in DNR:IDA dose ratios** on outcomes and have concluded that DNR is less effective than IDA.
- Understanding the comparative efficacy between DNR and IDA at recommended doses is essential for clinicians, guideline committees, and health technology assessors globally.

OBJECTIVES

- To evaluate the **comparative effectiveness of DNR- and IDA-based induction regimens in AML**, accounting for dose ratio variation as a potential source of bias, and to determine whether these agents are therapeutically equivalent when used at recommended doses.

METHODS

- A **comprehensive search** of the PubMed, EMBASE and the Cochrane Central Register of Controlled Trials databases (up to February 2023) was conducted to locate **prospective, randomised clinical trials and meta-analyses** directly comparing intravenous DNR- and IDA-based regimens in patients with AML.
- Trials were **appraised for risk of bias**, with particular attention to variation in the DNR:IDA dose ratio.
- The **primary outcome of interest** for this analysis was **overall survival (OS)**. Thus, trials that reported, or allowed derivation of, hazard ratios (HRs) for OS were eligible for inclusion in a meta-regression.
- **Meta-regression** is a statistical tool that allows meta-analyses to adjust for imbalances across studies. In this case, it was used to examine the association between variation in the DNR:IDA dose ratio and OS outcomes.
- **OS HRs for DNR- vs IDA-based regimens were estimated through a hierarchy of approaches.** If the report of a trial included an estimated HR comparing OS in the trial arms directly together with its 95% CI, then the analysis incorporated these estimates. When the HR was not specified, patient-level data for OS were reconstructed from Kaplan-Meier analyses provided, using the technique originally described by Guyot 2012[5] and refined by Liu 2021[6]. The derived patient-level OS data were then used to derive the HRs and the 95% CIs around the HRs.
- A meta-regression was performed, using the Comprehensive Meta-Analysis software**, to evaluate comparative overall survival, with the DNR:IDA dose ratio included as an explanatory variable** to account for its potential confounding effect.

RESULTS

- Of **369 citations retrieved** by the search of the literature, **16 prospective, randomised trials** directly comparing intravenous DNR- and IDA-based regimens were identified.
- **Only four trials compared DNR and IDA at the recommended doses**. Among trials using recommended doses, no significant differences in complete remission rates were observed between DNR and IDA. Most trials (11/16) used lower-than-recommended DNR doses.
- **HRs for OS were reported or were able to be derived for 10 of the 16 trials.** One of the trials[13] reported a comparison of DNR and two regimens of IDA, so 11 comparisons were available (Table 1). Meta-regression was performed using these 11 comparisons.
- The results of the meta-regression (Figure 2) indicated that **DNR:IDA dose ratio was a statistically significant modifier of overall survival** (coefficient = 0.0668; 95% CI: 0.0095, 0.1241; p = 0.0222). There was no evidence of heterogeneity across trials (Q = 6.28, df = 9, p = 0.71; I^2 = 0.0%;τ^2 = 0.0000).
- The positive coefficient (0.0668) means that, as the DNR:IDA dose ratio increases (i.e., as DNR dosing relative to IDA dosing increases), the HR for OS increases. **There is no evidence of a significant difference in OS when regimens are compared at their recommended doses.**

LIMITATIONS

- There was **variation in patient populations, induction regimens, and co-administered therapies** across trials.
- **Only a small subset of trials compared DNR and IDA at the recommended, equipotent doses** (DNR 60 mg/m^2 for 3 days vs IDA 12 mg/m^2 for 3 days).
- **HRs were not reported for some trials** thus there was some reliance on reconstructed survival data from published Kaplan-Meier curves, which may introduce estimation error.
- There remains **potential for unmeasured confounding** due to differences in patient characteristics, supportive care, or consolidation therapies across trials, which may have influenced outcomes.
- There is a **potential for reporting bias as not all trials reported all relevant outcomes**. Furthermore, the potential for publication bias in the reporting of trials comparing DNR and IDA cannot be excluded.

Figure 1: Chemical structures of daunorubicin and idarubicin highlighting the difference between the molecules (i.e., the methoxy group)

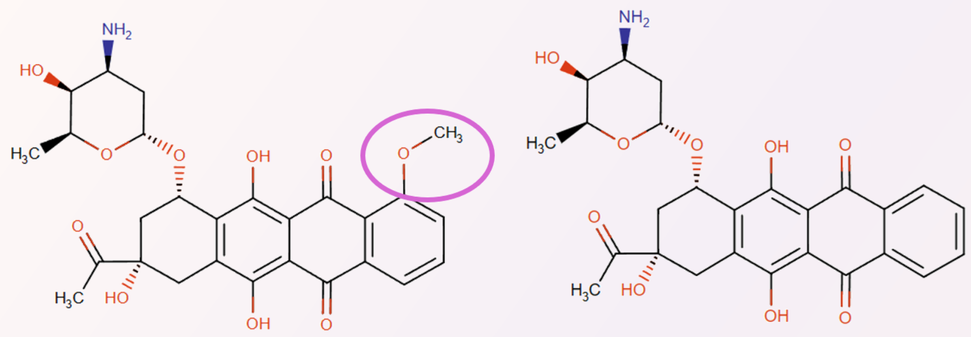
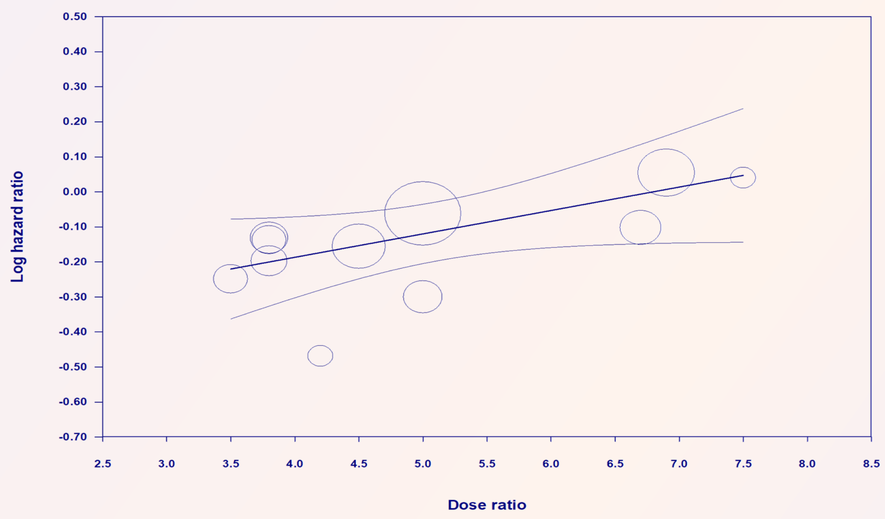


Table 1: Trials included in the meta-regression

Trial	N (DNR)	N (IDA)	DNR dose (mg/m^2 × days)	IDA dose (mg/m^2 × days	DNR:IDA ratio	HR IDA v DNR (95% CI)
Berman et al, 1991[7]	60	60	50 × 3	12 × 3	4.17	**0.626* (0.424 - 0.924)**
Wiernik et al, 1992[8]	113	101	45 × 3	13 × 3	3.46	0.780* (0.585 - 1.040)
Vogler et al, 1992[9]	60	49	45 × 3	12 × 3	3.75	0.821* (0.625 - 1.079)
Reiffers et al, 1996[10]	108	112	50 × 3	8 × 5	3.75	0.872* (0.653 - 1.163)
Rowe et al, 2004[11]	116	118	45 × 3	12 × 3	3.75	0.877* (0.675 - 1.140)
Mandelli et al, 2009[12]	721	717	50 × 3	10 × 3	5	0.94 (0.81 - 1.09)^
Pautas et al, 2010[13]	156	155	80 × 3	12 × 3	6.67	0.903* (0.675 - 1.140)
		157		12 × 4	5.0	**0.741* (0.575 - 0.956)**
Ohtake et al, 2011[14]	525	532	50 × 5	12 × 3	6.94	1.056* (0.888 - 1.257)
Récher et al, 2014[15]	411	412	60 × 3	8 × 5	4.5	0.856* (0.711 - 1.031)
Lee et al, 2017[16]	150	149	90 × 3	12 × 3	7.5	1.041 (0.685 - 1.488)

Abbreviations: CI = confidence interval; DNR = daunorubicin; HR = hazard ratio; IDA = idarubicin
Bolded text denotes a statistically significant HR
* HR was calculated based on reconstructed patient-level survival data from Kaplan-Meier analyses
^ 97.5% CI reported by the publication rather than the 95% CI

Figure 2: Regression of log HR for OS (IDA vs DNR) versus ratio of DNR dose : IDA dose*



* The size of each circle reflects the sample size of the corresponding trial, and the position of the centre of each circle represents the log of the HR point estimate from that trial. The bold line shows the fitted linear regression, and the lighter lines represent the upper and lower 95% confidence limits around the regression line.

CONCLUSIONS

After adjusting for DNR:IDA dose ratio, no significant difference in overall survival was observed between DNR- and IDA-based regimens at recommended doses.

Conclusions of apparent superiority of IDA in prior meta-analyses likely reflects failure to consider the impact of dosing on outcomes and, in particular, sub-optimal DNR dosing.

These findings support the use of either agent at recommended doses (in combination with cytarabine) for AML induction and highlight the importance of accounting for dose ratio in comparative trials.

Results from comparative trials of new regimens versus either agent at recommended doses (in combination with cytarabine) can reasonably be assumed to be applicable to both standard anthracyclines.

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References

1. Kim S, et al. National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 42890, Idarubicin.
2. Kim S, et al. National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 30323, Daunorubicin.
3. National Comprehensive Cancer Network. (2025). Acute Myeloid Leukemia (version 2.2026).
4. Li X, et al. *Cochrane Database Syst Rev. 2025;6:CD010432.*
5. Guyot P, et al. *BMC Med Res Methodol. 2012;*12:9.
6. Liu N, et al. *BMC Medical Res Methodol. 2021;*21(1):111.
7. Berman E, et al. *Blood. 1991;*77(8):1666–74.
8. Wiernik P, et al. *Blood.1992;*79(2):313–19.
9. Vogler WR, et al. *J Clin Oncol. 1992;*10(7):1103–11.
10. Reiffers J, et al. *Leukemia. 1996;*10(3):389–95.
11. Rowe JM, et al. *Blood. 2024;*103(2):479–85.
12. Mandelli F, et al. *J Clin Oncol. 2009;*27(32):5397–5403.
13. Pautas C, et al. *J Clin Oncol.* 2010;28(5):808–14.
14. Ohtake S, et al. *Blood.* 2011;117(8):2358–65.
15. Récher C, et al. *Leukemia. 2014;*28(2):440–43.
16. Lee J-H, et al. *J Clin Oncol. 2017;*35(24):2754–63.

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