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Review Article

High-dose versus Standard-dose Daunorubicin in Induction Chemotherapy for Acute Myeloid Leukemia: A Meta-Analysis

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Abstract

Objective: This systematic review and meta-analysis aimed to compare the efficacy and safety of high-dose versus standard-dose daunorubicin in induction therapy for adult acute myeloid leukemia (AML), focusing on complete remission (CR), overall survival (OS), and event-free survival (EFS).

Methodology: PubMed (Medline), Scopus, Science Direct, and Google Scholar were comprehensively and systematically explored for literature published in English, published from inception till January 30, 2025. Eligible studies included RCTs and retrospective cohorts comparing high-dose (>60 mg/m²/day) versus standard-dose (45–60 mg/m²/day) daunorubicin in adult AML patients, reporting at least one of the following outcomes: CR, OS, or EFS. Ten studies met eligibility criteria. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using random-effects models. Subgroup analyses were performed based on standard-dose levels (45 vs. 60 mg/m²). Heterogeneity and sensitivity analyses were also conducted.

Results: CR rates were numerically higher in the high-dose group but did not reach statistical significance (RR = 1.07; 95% CI: 0.94–1.22; P = 0.32). High-dose daunorubicin significantly improved 1-year OS (RR = 1.14; 95% CI: 1.06–1.23; P = 0.0002) and 5-year OS (RR = 1.32; 95% CI: 1.07–1.63; P = 0.01), especially when compared to the 45 mg/m² dose. While 1-year EFS showed no significant difference, pooled long-term EFS favored the high-dose group (RR = 1.26; 95% CI: 1.01–1.57; P = 0.04). Toxicity profiles were comparable between groups.

Conclusion: High-dose daunorubicin improves OS and long-term EFS in adult AML patients, particularly when compared to a standard dose of 45 mg/m², without increasing serious toxicity. It may be preferred in induction regimens where survival benefit is prioritized.

Keywords: Acute Myeloid Leukemia, Daunorubicin, Induction Chemotherapy, Meta-analysis, Overall Survival, Event-Free Survival, Complete Remission.

Introduction

Acute myeloid leukemia (AML) is a cancer of the blood and bone marrow characterized by the uncontrolled proliferation of immature myeloid precursor cells.[1] Despite advancements in understanding its pathophysiology, treatment regimens have largely remained unchanged over the past four decades.[1,2] The standard induction chemotherapy protocol commonly known as the "3+7" regimen that combines pyrimidine analogue cytarabine 100–200 mg/m²/day for 7 days with an anthracycline dose of 45–60 mg/m²/day for 3 days of (daunorubicin or idarubicin). This is followed by a consolidation phase with high-dose cytarabine in most cases.[3] One exception to this approach is acute promyelocytic leukemia (APML), which requires alternate agents such as all-trans retinoic acid (ATRA) or arsenic trioxide.[4,5]

However, even with standard treatment, clinical outcomes in AML remain suboptimal, with complete remission (CR) rates ranging from 50% to 80% in non-APML cases.[6, 7] and 5-year overall survival (OS) ranging between 13% and 40%.[8,9] Though the addition of targeted therapies and dose adjustments have shown some improvements, the prognosis for many AML subtypes remains poor.[10,11]

While intensified cytarabine dosing has demonstrated improvements in disease-free survival (DFS) in some trials, it has also been associated with increased toxicity.[12] Recently, interest has shifted toward evaluating the potential benefit of intensifying daunorubicin dosage. Several randomized controlled trials (RCTs) and observational studies have evaluated the effects of escalated daunorubicin dose of 90 mg/m²/day during induction therapy. But findings are inconsistent, and no definitive consensus has been established about the benefits of higher doses regarding remission or survival.[13, 14]

In light of this uncertainty, we carried out a meta-analysis of existing literature to analyze the clinical outcomes of high-dose (90 mg/m²) versus standard-dose (45 or 60 mg/m²) daunorubicin in

induction chemotherapy for AML. We aimed to evaluate differences in CR rates, OS, and event free survival (EFS) to inform clinical practice and contribute to treatment optimization strategies.

Methodology

This meta-analysis was performed to evaluate whether high-dose daunorubicin (>60 mg/m²/day) improves treatment outcomes compared to standard-dose (45 or 60 mg/m²/day) in induction phase in adults diagnosed with AML. The study was registered with PROSPERO (Registration No: CRD42019137595).

Literature Search Strategy

Four electronic databases, including PubMed (Medline), Scopus, Science Direct, and Google Scholar were comprehensively and systematically explored for literature published in English from inception till January 30, 2025. The search terms were combined using Boolean operators and included the following: "high-dose daunorubicin AND AML", "anthracycline dose intensification AND acute myeloid leukemia", "90 mg daunorubicin in AML", and "high-dose anthracycline in AML". To ensure sensitivity, manual search for relevant articles was also carried out. Two independent authors scrutinized all titles and abstracts for eligibility and evaluated the full text of potentially relevant articles. Disagreements were resolved by a third author. Study selection adhered to the PRISMA guidelines,[15] and a flow diagram was generated to illustrate the inclusion process (Figure 1).

Eligibility Criteria

Studies were included if they (1) were published in English; (2) included adult patients (≥18 years) confirmed as AML patients (excluding acute promyelocytic leukemia); (3) compared high dose daunorubicin (>60 mg/m²/day, typically 90 mg/m²/day) with standard dose daunorubicin (45 or 60 mg/m²/day) as part of the 3+7 induction regimen; (4) were full-text articles with original data, and (5) reported at least one of the following outcomes: CR, OS, or EFS. The types of study designs included were randomized controlled trials as well as and retrospective cohorts. The studies excluded were reviews, meta-analyses, editorials, conference abstracts, book chapters, non-comparative studies, or studies lacking the outcomes of interest.

Data Extraction and Outcomes

Data extraction was independently carried out by two authors using a standardized data collection form. Extracted data included: study title, first author, publication year, study design and setting, sample size, patient demographics, daunorubicin dosing schedule in high- and standard-dose arms, chemotherapy details, and outcome data. The primary outcome was CR, including CR with incomplete hematologic recovery (CRi). Secondary outcomes included OS at 1 year and 5 years, and EFS at 1 year and 2/5 years. Discrepancies during data extraction were resolved by discussion or arbitration by a third author.

Definitions were based on the International Working Group criteria for AML. Complete remission (CR) was defined as <5% blasts in the bone marrow, neutrophils >1.0×10⁹/L, and platelets >100×10⁹/L in peripheral blood, with no extramedullary disease. CRi referred to CR with incomplete recovery of peripheral counts. OS was defined as the time from diagnosis to death from any cause. EFS was considered a surrogate for disease-free survival (DFS) or relapse-free survival (RFS) and defined as the time from CR to relapse, progression, or death. CR rates used in the meta-analysis included both CR and CRi, given that some studies grouped them together in reporting. Toxicity data were not uniformly reported across studies and therefore were not included in the meta-analysis outcomes.[3]

Quality Assessment

Risk of bias in the included studies was assessed using the Cochrane Risk of Bias 2.0 tool, which assesses bias across several aspects that includes: randomization process, divergence from planned interventions, missing outcome data, measurement of outcomes, and selection of the reported results. Risk of bias was rated three ways that is low, high or some concerns. Two authors conducted the assessment independently, and any disagreements were decided through consensus. Heterogeneity was assessed using the Chi-square (χ^2) test and quantified with the I^2 statistic. Heterogeneity was interpreted as low (<25%), moderate (25–50%), or substantial (>50%). Sensitivity analyses were performed by removing one study at a time to assess the robustness of the pooled results.

Data Synthesis and Statistical Analysis

Statistical analyses were performed using Review Manager (RevMan) version 5.3. Risk ratios (RR) with 95% confidence intervals (CI) were used for dichotomous outcomes. A random-effects model was employed due to the anticipated clinical and methodological heterogeneity among studies. A p-value <0.05 was considered statistically significant.

Subgroup analyses were conducted based on standard-dose daunorubicin (45 mg/m² vs. 60 mg/m²) to determine whether outcome differences were influenced by the comparator dose. Forest plots were generated for all primary and secondary outcomes. Funnel plots to assess publication bias were not constructed due to the limited number of studies per outcome, consistent with Cochrane guidelines.[16]

Results

Study Selection

The initial database and manual searches yielded 2,036 records. After removing 188 duplicates, 1,848 records remained. Title and abstract screening excluded 1,710 irrelevant records (non-comparative, non-English, or review-type publications). Full-text assessment of 137 articles resulted in 128 exclusions due to failure to meet eligibility criteria. Ultimately, ten studies (published between 2009 and 2023) were analyzed in this meta-analysis (Figure 1).

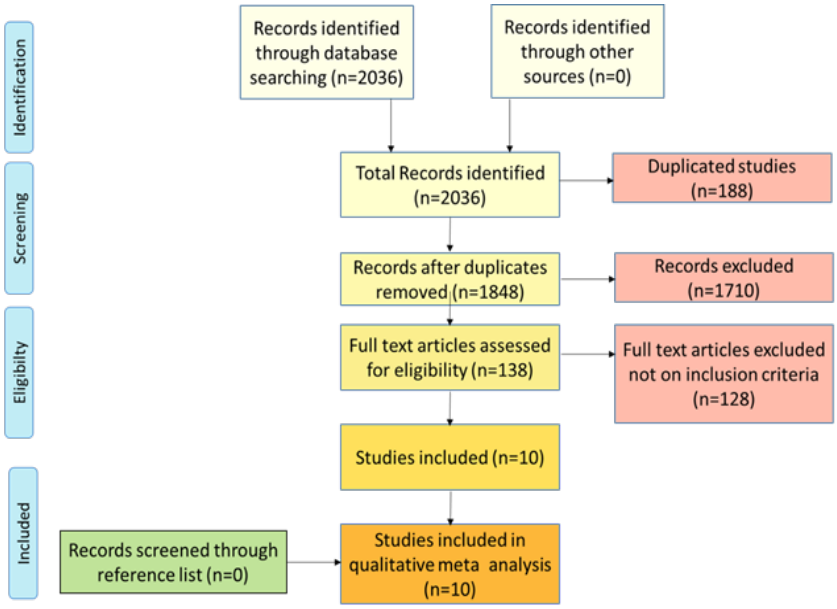

Figure 1: Characteristics of Included Studies

A total of 3,433 adult AML patients were enrolled across the nine studies, with 1,681 receiving high-dose daunorubicin and 1,752 receiving standard doses. Five studies were randomized controlled trials and four were retrospective cohorts. The high-dose regimen typically included 90 mg/m²/day of daunorubicin for three days, except in one study where 80 mg/m² was used (included only in sensitivity analysis). Standard-dose regimens used either 45 mg/m² (in four studies), 60 mg/m² (in four studies), or both (in one study).

CR data were available from eight studies (one was excluded from CR comparison due to universal CR in both groups). OS at 1 and 5 years was reported in seven studies; EFS was variably reported at 1, 2, or 5 years.

Meta-analysis showed that although the CR rate was numerically higher with high-dose daunorubicin, but could not reach statistical significance. Notably, 1-year and 5-year OS were significantly improved with escalated dose, particularly patients previously treated with the 45

Table 1: Summary of Studies Comparing High- vs. Standard-Dose Daunorubicin in AML

Study	Study Design	Sample Size (n)	Group Size (High vs. Standard, n)	Daunorubicin (High vs. Standard, mg/m²/day)	CR Rate (High vs. Standard, %)	5-Year OS (High vs. Standard, %)
Fernandez et al. (2009)[13]	Randomized	582	289 / 293	90 / 45	70.6 vs 57.3	38 vs 23
Prebet et al. (2014)[17]	Retrospective	86	29 / 57	90 / 60	100.0 vs 100.0	92 vs 82
Burnett et al. (2015)[18]	Randomized	1206	604 / 602	90 / 60	81.0 vs 84.0	59 vs 60
Löwenberg et al. (2009)[19]	Randomized	813	402 / 411	90 / 45	51.7 vs 34.8	13 vs 13.5
Lee et al. (2011)[20]	Randomized	383	194 / 189	90 / 45	82.5 vs 72.0	47 vs 36
Reagan et al. (2015)[21]	Retrospective	128	48 / 80	90 / 60	79.2 vs 61.3	NR
Choi et al. (2018)[28]	Retrospective	95	44 / 51	90 / 45	77.3 vs 56.9	50 vs 25
Portugal et al. (2017)[23]	Retrospective	26	12 / 14	90 / 45–60	66.7 vs 64.3	56 vs 34
Vaezi et al. (2017)[24]	Randomized	114	59 / 55	80 / 60	66.7 vs 75.9	58 vs 56
Röllig et al. (2025)[25]	Randomized	864	432 / 432	90 / 60	44 vs 48	65 vs 58 (3 years OS)

Note: CR: Complete Remission. OS: Overall Survival, defined as the time from diagnosis or treatment initiation to death from any cause. NR: Not Reported.

mg/m² standard dose. EFS at 1 year showed no significant difference, while long-term EFS (2–5 years) demonstrated a modest but statistically significant benefit favoring high-dose daunorubicin.

Heterogeneity across studies varied. CR rate analysis showed high heterogeneity (I^2 = 81%), with greater inconsistency in the 45 mg subgroup. In contrast, 1-year OS showed moderate overall heterogeneity (I^2 = 55%) but none within the 45 mg subgroup. Substantial heterogeneity was observed for 5-year OS and mixed patterns were found across EFS outcomes.

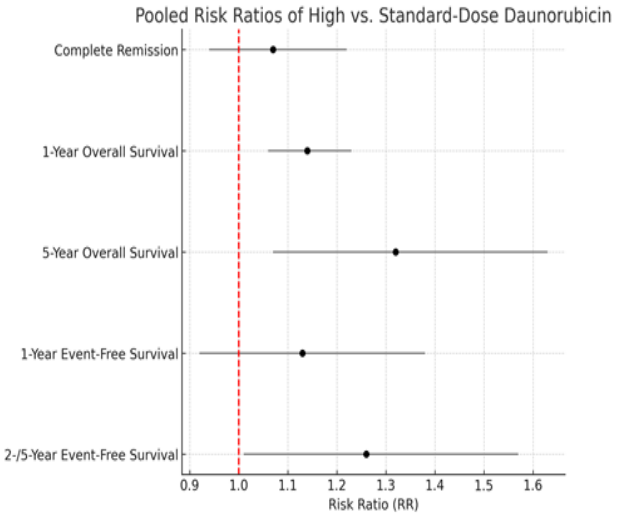

Figure 2: Pooled Risk Ratios with 95% CIs comparing High- vs. Standard-Dose Daunorubicin across major outcomes (CR, OS, EFS).

Discussion

This meta-analysis synthesized data from ten studies comparing high dose with standard dose daunorubicin in adult AML patients. There was no significant difference in CR rates on pooled analysis, although a numerically higher proportion of patients achieved CR in the high dose group (Table-1). In contrast, high dose daunorubicin significantly improved 1-year OS, with the survival benefit being more pronounced in the subgroup receiving a standard dose of 45 mg than in the 60 mg group (Figure 2). This advantage persisted at 5 years, particularly in the 45 mg subgroup (Figure-2). EFS, a composite measure of time to relapse, progression, or death, showed no significant difference at 1 year (Figure-2). However, high-dose daunorubicin demonstrated a modest long-term benefit in pooled 2-/5-year EFS, although subgroup analysis did not reach significance (Figure 2).

Ara-C combined with an anthracycline most commonly daunorubicin or idarubicin has formed the backbone of AML induction therapy for nearly four decades.[25,26] The classic "7 + 3" regimen delivers complete remission rates of about 60-80 % in younger adults, yet long-term overall survival rarely surpasses 40-45%, and results are even poorer in older or adverse-risk patients.[26] These limitations have fuelled investigations into dose-intensification strategies. Over the past two decades, multiple trials have escalated cytarabine exposure, demonstrating meaningful event-free-survival gains increased toxicity.[27,28] Thereafter the idea of high dose anthracycline intensification gained attention.[25] Several studies comparing high-dose daunorubicin (90 mg m^{-2}) with standard doses (45-60 mg m^{-2}) report deeper early blast clearance and improved overall survival,[13,17] providing the mechanistic and clinical rationale for the present meta-analysis of high- versus standard-dose daunorubicin.

We carried out a meta-analysis that included both randomized controlled trials and retrospective studies comparing 90 mg/m² daunorubicin to standard-dose regimens (45 mg or 60 mg). Subgroup analysis was conducted for both standard doses in our study. All studies reported CR, OS, and EFS or its surrogates (RFS, DFS). Although high-dose daunorubicin yielded higher CR numerically, it was not statistically significant. However, high dose daunorubicin showed a clear survival advantage in both short- and long-term OS, particularly when compared to the 45 mg standard-dose subgroup in the studies included. The 1-year OS was better for the high dose group in both combined and subgroup analyses, with a stronger effect in the 45 mg group. This benefit persisted at 5 years in the overall analysis and in the 45 mg subgroup, but was not significant in the 60 mg subgroup. EFS, while not improved at 1 year (Figure 2), showed a significant advantage at 2/5 years in the overall analysis (Figure 2), though subgroup comparisons were non-significant. Comparisons with meta-analyses of high-dose cytarabine suggest that while it may not significantly improve CR or OS, it does improve EFS.[27]

Heterogeneity in our analysis varied across outcomes and subgroups, with zero heterogeneity in the 45 mg subgroup for 1-year OS and moderate to substantial heterogeneity in others. This variation may affect the interpretability of pooled estimates. More robust and elaborative clinical trials are required to define the optimal dose and regimen for AML induction therapy.Several included studies reported better CR rates with high-dose daunorubicin, particularly in those receiving 45 mg as the comparator. Löwenberg et al. (2019) observed improved CR even in patients over 60,[19] while Fernandez et al. (2009) did not find such benefit in those above 50.[13] Cytogenetic profiles also influenced outcomes. Escalated daunorubicin dose provided no benefit in patients with unfavorable cytogenetic markers such as FLT3-ITD or MLL-PTD mutations and MDR1 gene overexpression. Patients with the FLT3-ITD mutation were also found to have a lower median survival.[13] Burnett et al. (2015) found benefit only in patients with favorable cytogenetics.[18]

AML mostly (75%) present in age range of 60 years of or above. But even intensive chemotherapy high dose daunorubicin administration treatment, CR rates fall between 40-55% only but an improved median DFS 6-12 months in these patients older than 60 yesrs.[29] Two large scale studies has documented that dose intensification can improve survival and reduce mortality in elderly patients of AML.[30, 31]

Toxicity profiles were generally comparable between high- and standard-dose groups across most studies. However, Löwenberg et al. and Portugal et al. reported higher infection rates and gastrointestinal toxicity in the high-dose group.[19,23] Burnett et al. also reported more severe gastrointestinal side effects during the first induction cycle in the high-dose group.[18]

Overall, this meta-analysis supports the use of high-dose daunorubicin in selected patient populations, especially

where improved OS is a priority, although the associated toxicities and patient-specific factors such as age and cytogenetic profile must be carefully considered.

Limitations

Variations in study design, outcome definitions, and patient characteristics may influence the consistency of pooled results. The inclusion of retrospective studies introduces a risk of bias. Additionally, limited reporting on toxicity outcomes prevents a comprehensive safety assessment.

Conclusion

By administering high dose daunorubicin in induction therapy, a greater number of patients achieved complete remission although statistical significance level was not achieved. High dose daunorubicin improves event free survival and overall survival, both at 1 and 5 years especially when compared to 45 mg dose. This improvement shows a low toxicity of high dose daunorubicin and must be recommended for maintaining quality of life and long term survival of AML patients.

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