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ORIGINAL ARTICLE

Equipotent doses of daunorubicin and idarubicin for AML: a meta-analysis of clinical trials versus in vitro estimation

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Abstract

In the treatment of acute myeloid leukemia (AML), the "7 + 3"-based strategy, combining cytarabine 100–200 mg/m^2 for 7 days with an anthracycline for 3 days, remains the standard of care for younger and medically fit patients. Daunorubicin (DNR) and idarubicin (IDA) are the two anthracyclines most commonly used. DNR and IDA are used interchangeably with different conversion factors, as there is no high-level evidence on the equipotency of these two agents for AML treatment. To determine the equipotent doses of DNR and IDA, we first systematically reviewed studies directly comparing the clinical outcomes of AML induction therapy utilizing DNR and IDA. We found 15 articles that met our inclusion criteria and compared time-to-event survival end points as well as complete remission rates post-induction. The DNR:IDA equipotency ratio was estimated at 5.90 with 95% confidence interval (CI) 1.7–20.7. To validate the estimate from our meta-analysis biologically, we conducted in vitro tests comparing anti-AML activity of DNR and IDA against six AML cell lines and two primary AML cells from patients with different cytogenetic and molecular characteristics. Based on these in vitro data, the equipotency dose ratio between DNR and IDA was 4.06 with 95% CI 3.64–4.49. Combining the estimates from the meta-analysis and the in vitro data using inverse-variance weighting, the current best estimate of the DNR:IDA equipotent ratio is 4.1 with 95% CI 3.9–4.3. This estimate, however, is largely driven by the in vitro chemo-sensitivity data. Given clinical studies demonstrating the safety of IDA at higher doses, our work implies that dose intensification of IDA could be investigated in future clinical trials in AML.

Keywords Acute myeloid leukemia (AML) · Anthracycline · Daunorubicin · Idarubicin · Chemotherapy equipotency · Meta-analysis

Introduction

Anthracyclines, including daunorubicin (DNR) and idarubicin (IDA), are indispensable components of chemotherapy regimens used for the treatment of young and medically fit patients with acute myeloid leukemia (AML) [1]. Additionally, since 2017, the US Food and Drug Administration (FDA) approved eight new agents for the treatment of AML [2], and three of these approvals incorporate DNR, either in the drug formulation itself (i.e., liposomal formulation that combines DNR with cytarabine) or in the chemotherapy backbone that is used in combination with the new agent [3–5]. However, intermittent DNR drug shortages over the last decade have rendered use of IDA inevitable as an anthracycline substitute [6]. Additionally, early literature suggested that IDA may be preferable to DNR [7], perhaps by virtue of being less susceptible to cellular efflux by multidrug

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resistance proteins [8, 9] as well as by an increased duration of drug exposure related to the active metabolite of IDA [10]. Despite the often interchangeable use of IDA and DNR, there is an absence of high-level evidence to support an accurate DNR:IDA conversion. Anecdotally, a 5:1 dose ratio (e.g., 60 mg/m^2 DNR to 12 mg/m^2 IDA) is often used. However, this 5:1 conversion is extrapolated from Children's Oncology Group guidelines [11] addressing the cardiac isotoxic equivalency, and not anti-leukemic equipotency, of different anthracyclines. This conversion may not be applicable to adult patients, nor is this conversion consistently applied across clinical practice and clinical trials. There are several reported instances of 12 mg/m^2 of IDA used instead of 90 mg/m^2 of DNR without evidence for clinical equivalence [12].

In addition, the optimal dose of DNR required for induction therapy in patients with AML remains unclear [13], further contributing to the confusion regarding the appropriate DNR:IDA dose conversion [14]. Large randomized controlled clinical trials demonstrated the efficacy and safety of high doses of DNR (90 mg/m^2 daily on days 1–3 or 50 mg/m^2 daily on days 1–5) in induction regimens for AML [15–18]. However, this challenges the practice of using a flat dose and predetermined IDA dose of 12 mg/m^2 if indeed the appropriate dose conversion factor of DNR:IDA is 5:1.

To better elucidate the optimal conversion between DNR and IDA, we have conducted a two-part study, combining the results from a literature-based meta-analysis with estimates from in vitro cell survival testing in a panel of six AML cell lines and two primary AML cells from patients, to estimate the equipotency dose ratio between DNR and IDA in AML treatment.

Methods

Literature review

Our systemic review adhered to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement. To compare dose ratios of DNR with IDA, a literature search was conducted using PubMed, including studies published through January 17, 2017. The search terms included 'IDARUBICIN' and 'DAUNORUBICIN' and 'LEUKEMIA' and 'DOSE' (Fig. 1) and results were limited to peer-reviewed publications in English. Titles and abstracts were screened based on relevance to the clinical question. After abstract and title screening, full-text articles were assessed for eligibility inclusion. Risk of bias was assessed by considering the study rigor and the type of data analysis that was used. Data extraction included the following variables: authors, article title, journal title, year published, type of study, population, and outcomes identified in study. A narrative synthesis of the findings was structured around the target patient characteristics, chemotherapy received, and type of outcome. The variables which we specifically analyzed in our meta-analysis are listed in Supplementary Table 1.

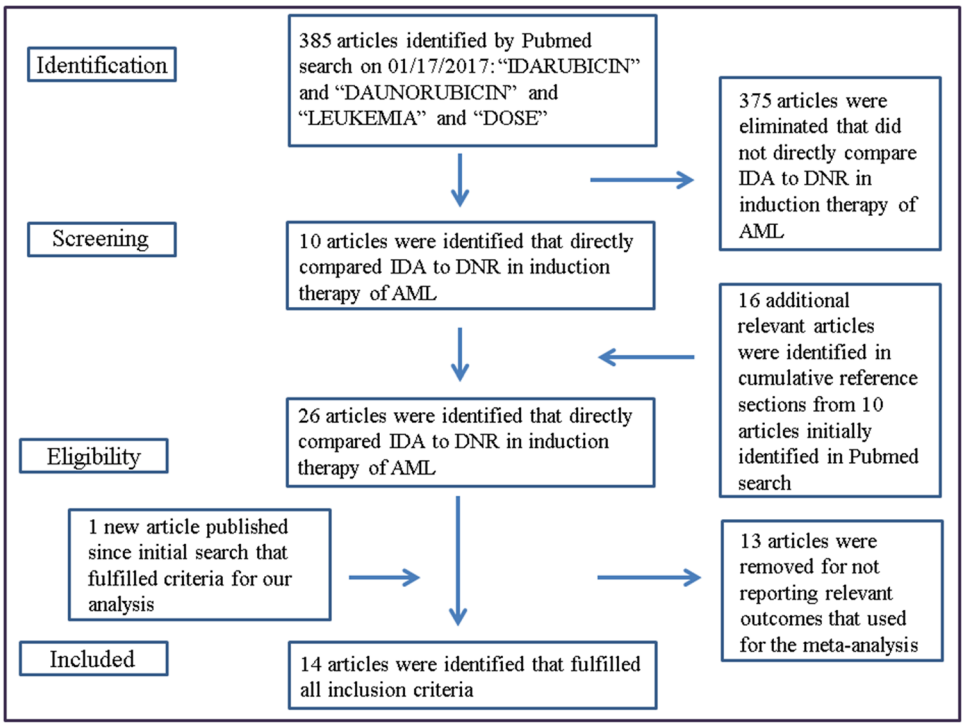

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses statement flow diagram of search methods

Cell lines and culturing

THP-1, MV4-11, MonoMac-6, HL-60, and K562 cells were purchased from the American Type Culture Collection (ATCC, Manassas, VA). MOLM-14 cells were the kind gift of Dr. Mark Levis from Johns Hopkins University. All cell lines were grown at 37 °C with 5% CO_2 atmosphere with Roswell Park Memorial Institute (RPMI) 1640 (Life Technologies, Carlsbad, CA) supplemented with heat-inactivated 10% (v/v) fetal bovine serum (FBS). Cell lines were grown and maintained following ATCC recommendations. We performed in-house karyotyping and molecular analyses on the cell lines and report them in Supplementary Table 2.

Primary human leukemia cells (primary AML) derived from patients were obtained through the institutional (IRB approved) Tumor and Cell procurement Bank at the University of Maryland. Primary AML cells, which had been previously isolated through ficoll separation and frozen viably, were thawed into room temperature RPMI 1640 with 10% FBS and supplemented with DNase I 20 U/ml. Viable cell numbers were obtained using trypan blue exclusion, and cells were plated into 96-well dishes at 5×10^4 cells/well in RPMI/10% FBS.

IC_{50} proliferation assay

To measure the concentrations of DNR and IDA required for decreasing viable cell numbers by 50% (i.e., IC_{50}) in vitro, cells were seeded onto 96-well plates the afternoon prior to treatment. Approximately 18 h later, IDA (LC labs, Woburn MA) and DNR (LC Labs) semi-serially diluted in dimethyl sulfoxide (DMSO) and growth medium were added to cells. Treated cells were grown in appropriate cell culture conditions for 72 h prior to addition of Alamar Blue (Sigma, St. Louis MO). Plates were read using a BioTek Synergy HT plate reader (BioTek, Winooski, VT) after 4 additional hours of incubation at 37 °C. IC_{50} was estimated using GraphPad Prism Software (GraphPad, La Jolla, CA).

For IC_{50} proliferation assay studies, primary AML cells were thawed and plated in this manner the day prior to drug treatment. Treatment durations were 48 h, after which time plates were terminated with Alamar Blue (Life Technologies, Carlsbad, CA). Four hours after termination, fluorescence measurements were taken using a Synergy H1 plate reader (Biotek, Winooski, VT) and IC_{50} values were calculated using Graphpad Prism software (Graphpad, San Diego, CA).

Statistics and data analysis

Data extraction from published trial data

Each trial report was reviewed with respect to calculation of the ratio between the cumulative doses of DNR and IDA as well as the empirical hazard ratio (HR) for overall survival (OS) between the two trial arms, $HR_{DNR/IDA}$. The latter ratio was estimated through a hierarchy of approaches. If a trial reported the estimated HR between OS in the trial arms directly together with its 95% confidence interval (CI), then these estimates were used in the analysis. When the HR was not specified, we estimated it as the ratio between the logarithms of the survival in the two trial arms at a specified point in time. If the proportional hazards assumption seemed to be violated by graphical inspection of the survival plot in the original trial report, an average HR was estimated by reading off the survival rates at several time points along the available follow-up time. In these cases, the confidence interval for the hazard ratio was estimated from the two-tailed *P* value as described in Parmar et al. [19] and Diez et al. [20].

Meta-regression of literature dose–effect data

Least squares regression weighted by the inverse variance of the $HR_{DNR/IDA}$ estimate as a function of the ratio of the cumulative dose of DNR/IDA was performed using SPSS ver. 25.0. The intercept between the regression line and $HR_{DNR/IDA} = 1$ was calculated from the estimated regression coefficients. Fieller's theorem was used to estimate the equipotency dose ratio with 95% CI as derived from the variance–covariance matrix.

Estimation of IC_{50} from in vitro assay

All in vitro IC_{50} assays were repeated five or six times for both drugs in each cell line. IC_{50} was estimated using the curve-fitting procedure in Graphpad Prism®. The arithmetic mean of IC_{50} and the standard error of the mean (SEM) were calculated for each drug/cell line. From these data, we derived the equipotency dose ratio; 95% confidence limits on this ratio were estimated using standard propagation of error techniques. These equipotency dose ratios were subsequently synthesized across cell lines using inverse variance weighting in a meta-analysis assuming a fixed effects model. This analysis was conducted using the "metagen" package in R version 3.3.2.

Results

The full results of the search strategy are provided in a PRISMA flowchart (Fig. 1). A total of 385 articles were found during the initial search, 375 of which did not directly compare DNR to IDA in induction therapy for patients with AML, and thus were eliminated from our meta-analysis. We went through the reference sections of the remaining 10 articles and identified 16 other articles that met the above

inclusion criteria. Thirteen of the 26 articles were eliminated due to not reporting the time-to-event outcomes with hazard ratios that we used for statistical analysis [21–33]. After the initial query, another article was published that met our criteria and it was added to our dataset [34]. We then used statistical analyses to compare the dose ratios of DNR:IDA with regard to OS to identify the equipotent doses of the drugs.

One article included two separate data sets and was therefore used as two separate studies for our analysis [30]. Our final analysis therefore included 15 studies. For detailed information on the included clinical trials, see Supplementary Table 1.

Figure 2 shows a plot of the within-trial hazard ratio for OS between the DNR and IDA arms of trials (with 95% CI) as a function of the ratio of cumulative doses of the drugs in the two arms during remission induction therapy. We used weighted linear regression, weighting the HR in each trial with the inverse variance of the estimate, to estimate an empirical relationship between HR and the corresponding dose ratio. We used the regression equation to estimate the dose ratio corresponding to an HR = 1, i.e., the equipotency dose ratio of the two drugs; the estimate was 5.90 with 95% CI 1.7, 20.7. The rather wide 95% confidence interval of the equipotency dose estimate reflects considerable trial-to-trial variability in the estimated HR, most of which seems to result from the statistical uncertainty in HR in most trials.

In addition to the meta-analysis of published survival data, we also undertook an analysis of odds ratios for response rates to DNR and IDA as a function of the cumulative doses of the two drugs in each trial. The regression analysis did not find a significant dose–response relationship and did not produce a meaningful estimate of the equipotent dose ratio (data not shown).

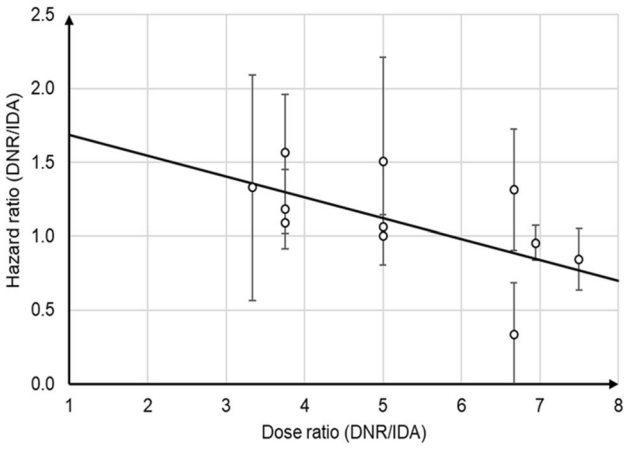

Fig. 2 Within-trial hazard ratio for overall survival between the DNR and IDA arms of a trial (with 95% CI) as a function of the ratio of cumulative doses of the drugs in the two arms

To validate our meta-analysis biologically, we conducted in vitro tests that compared cytotoxic activity of DNR and IDA in six AML cell lines and two primary AML cells from patients with different karyotypes and mutations. Table 1 shows the IC_{50}s of DNR and IDA and the DNR:IDA ratio for each of the myeloid leukemia cell lines. The ranges of IC_{50}s of DNR and IDA in the AML cell lines were 8.1–56.7 nanomolar (nM) and 2.6–17.8 nM, respectively. IDA was 3.05 to 5.52 times more potent than DNR in killing the cells across this panel. Figure 3 is a forest plot of the equipotency dose ratio derived from in vitro IC_{50} estimates from five or six repeat experiments for each drug in each AML cell line. The error bars denote 95% confidence intervals on the mean ratio. The size of each square is proportional to the weight of that data point, i.e., the inverse variance of the estimate. The stippled line indicates the overall best estimate of the equipotency ratio, with the corners of the blue diamond indicating the 95% confidence limits of the estimate: 4.06 with 95% CI 3.64–4.49.

Inverse-variance weighting was used to synthesize the clinical and the in vitro estimates of the equipotency dose ratios. This yielded an overall estimate of the DNR/IDA equipotency dose ratio of 4.1 with 95% CI 3.9–4.3.

Discussion

Notwithstanding the availability and approval of small molecules and an immunotherapeutic targeted agent for treatment of AML, anthracyclines remain an indispensable component of treatment regimens for young and medically fit patients. In early studies, DNR at 30 mg/m^2 daily was inferior to 45 mg/m^2 daily in the 7 + 3 induction regimen, demonstrating lower complete remission (CR) rate in patients younger than 60 years of age [35]. Two randomized phase 3 clinical trials conducted in the USA and South Korea established the clinical benefit of DNR dose intensification

Table 1 IC_{50} proliferation assay: results after each leukemia cell line was exposed to either DNR or IDA in vitro and the resulting ratio

Cell lines	DNR IC_{50} (nM)	IDA IC_{50} (nM)	IC_{50} ratio (DNR:IDA)	SEM
K562	21.7 ± 5.6	4.7 ± 1.3	4.57	0.77
MOLM-14	8.1 ± 1.2	2.6 ± 0.9	3.05	0.53
MV4-11	17.1 ± 1.7	4.1 ± 0.7	4.10	0.35
HL-60	56.7 ± 18.3	11.8 ± 3.9	4.81	0.95
THP-1	56.1 ± 26.0	17.8 ± 4.5	3.16	0.73
MonoMac-6	37.3 ± 14.7	9.3 ± 1.4	4.00	0.69
AML29	28.0 ± 5.7	5.1 ± 1.1	5.52	0.72
AML31	16.7 ± 8.5	3.3 ± 0.4	5.14	1.21

Mean ± standard deviation IC_{50} values are reported from five to six experiments for each cell line

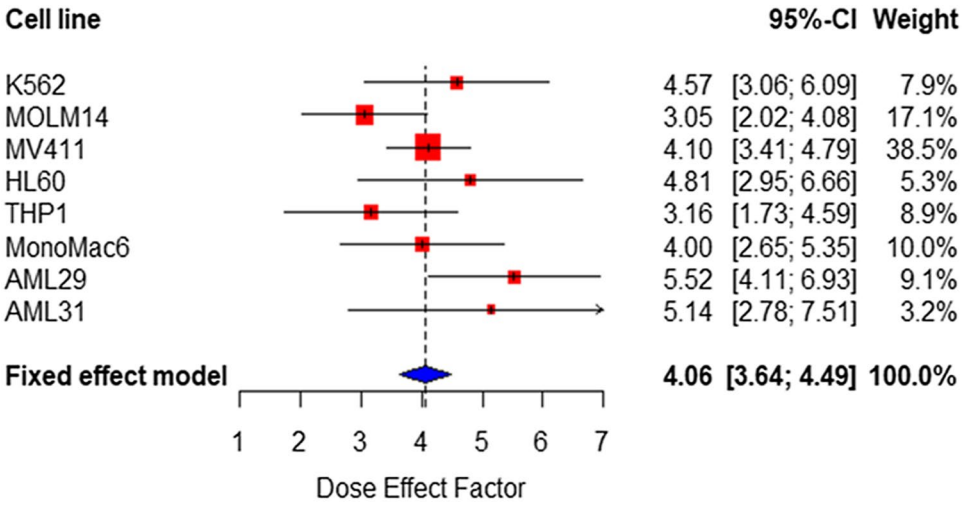

Fig. 3 Forest plot of the equipotency dose ratio derived from in vitro IC_{50} estimates from five to six repeat experiments for each drug with each AML cell line

(90 mg/m^2 versus 45 mg/m^2), when used in the 7 + 3 regimen, in patients younger than 60 years of age with newly diagnosed AML [15–17]. In these studies, the cumulative doses of DNR during induction were 270 (90 × 3) mg and 135 (45 × 3) mg. In the US study, 90 mg/m^2, compared with 45 mg/m^2, DNR led to a significantly higher CR rate (71% vs. 57%, $P < 0.001$) and improved OS (median, 23.7 versus 15.7 months, $P = 0.003$). The update on the long-term follow-up of this study (median, 80 months among survivors) demonstrated that 90 mg/m^2 DNR was associated with statistically significant improvement in OS, with hazard ratios of 0.5–0.74 in all subgroups of patients including patients younger than 50 years of age, patients with unfavorable, intermediate, and favorable cytogenetic findings, and patients with *FLT3*-ITD, *DNMT3A*, and *NPM1* mutations [15]. In the South Korean study [16], the CR rate was higher (83% vs. 72%, $P = 0.014$) with 90 mg/m^2, compared to 45 mg/m^2, DNR, and with approximately 4.5 years median follow-up, OS was significantly longer with 90 mg/m^2, compared to 45 mg/m^2 (47% vs. 35%, $P = 0.03$). In another clinical trial supported by the United Kingdom National Cancer Research Institute (UK NCRI AML17), with a median follow-up of 28 months, re-analysis of data by intention to treat showed that DNR at 90 mg/m^2, compared with 60 mg/m^2, in induction course 1, statistically significantly improved cumulative incidence of relapse (44% vs 60%, HR 0.58), relapse-free survival (45% vs 33%, HR 0.63), and OS (54% vs 34%, HR 0.65) in patients with *FLT3*-ITD AML [36]. The original report of the NCRI AML17 trial concluded that there was no evidence of overall clinical benefit with 90 mg/m^2 of DNR compared with 60 mg/m^2 [13]. Of note, in this study, patients received the second course of induction with DNR 50 mg/m^2 on days 1, 3, and 5, resulting in DNR cumulative doses of 420 (140 [90 + 50] × 3) and 330 (110 [60 + 50] × 3) mg, respectively, during induction [13]. The cumulative dose of DNR in 60 mg/m^2 arm of NCRI AML17 trial is similar to the cumulative dose of 90 mg/m^2 arms in other studies. In all studies, treatment-related toxicities were similar in the groups receiving higher and lower DNR doses.

When DNR is not available because of manufacturing shortages or needs to be substituted with IDA for clinical trials, determining the most accurate equipotent dose ratio between the two agents may have a substantial impact on the clinical outcomes of patients with AML. Three systematic reviews and meta-analyses compared the efficacy of different anthracyclines and anthracycline dosing schedules for induction therapy in AML in children and adults younger than 60 years of age [14, 37, 38]. Twenty-nine randomized controlled trials were eligible for inclusion in these analyses. IDA, in comparison to DNR, was found to decrease CR failure rates [risk ratio (RR) 0.81; 95% CI, 0.66–0.99, $P = 0.04$], but IDA use did not alter the rates of overall mortality or early death. Interestingly, clinical trials in which DNR:IDA dose ratio was less than 5:1 were the only trials demonstrating the superiority of IDA for remission induction (ratio < 5:1, RR 0.65; 95% CI, 0.51–0.81, $P < 0.001$; ratio ≥ 5:1, RR 1.03; 95% CI 0.91–1.16, $P = 0.63$).

In the current study, we used a novel approach to try to identify the equipotency between IDA and DNR. We combined the results from our meta-analysis of clinical studies comparing IDA and DNR in AML induction therapy with results of comparisons of in vitro anti-AML cytotoxicity of IDA versus DNR. Comparisons derived from clinical and in vitro studies determined that IDA is approximately 5.90 and 4.06 times more potent than DNR, respectively. Combining the estimates from both the meta-analysis and the in vitro data, the best estimate of the equipotent dose ratio between DNR and IDA was found to be 4.1. Statistically, the in vitro and clinical estimates were not significantly different. However, the rather wide confidence interval from the meta-analysis of clinical trials reduces the power to detect a clinically relevant effect size between the two.

How can equipotency of 4.1 apply to clinical practice and research? First, purely from an anti-AML activity standpoint, it suggests that DNR 90 mg/m^2 is equivalent to IDA 22 mg/m^2. Secondly, IDA 12 mg/m^2 should not be substituted equally for 90, 60, or 45 mg/m^2 DNR [37]. Thirdly, a conservative approach of using an equipotency value of 5.9 (or approximately 6) derived only from clinical data would result in using 15 mg/m^2 of IDA instead of 90 mg/m^2 of DNR in both clinical practice and clinical trials. Récher and colleagues reported that patients (15–60 years) with AML who received 7 + 3 induction therapy with IDA (8 mg/m^2/day × 5 days), compared with DNR (60 mg/m^2/day × 3 days), had an improved 7-year disease-free survival (DFS) and OS and less frequently relapsed [39]. The authors concluded that higher dose of IDA (40 mg/m^2) compared with (30–36 mg/m^2) was superior to DNR (180 mg/m^2) without increasing the toxicity. DNR/IDA ratio in this study was 4.5, which is very similar to our analysis.

The main concern for dose intensification of IDA is safety, and particularly cardiotoxicity. In a study aimed at determining the maximum tolerating dose (MTD) and dose-limiting toxicities (DLT) of oral IDA in dogs, the MTD was 22 mg/m^2 [40]. In a phase II study investigating intravenous (IV) IDA for treatment of patients with non-Hodgkin's lymphoma, IDA was administered at a dose of 15 mg/m^2 to 31 patients, 29 of whom had received prior anthracycline or anthracenedione [41]. IDA was well tolerated and hematologic adverse events (AEs) were DLTs. In a study conducted in Japan, 32 patients with AML or blast crisis of chronic myeloid leukemia were treated with IV IDA daily for 3 days at doses ranging from 5 to 15 mg/m^2 daily. The MTD was 15 mg/m^2 daily for 3 days (cumulative dose per course 45 mg/m^2), with DLTs reported to be stomatitis and anorexia [42]. In this study, the terminal half-lives ($t_{1/2}$) of IDA and its active metabolite, idarubicinol, were 6.5–15 h and 43.5–51 h, respectively, in plasma. The area under the curve (AUC) of IDA and idarubicinol increased dose-dependently [42]. In a phase I study conducted in South Korea to determine the MTD of IDA daily for 3 days in combination with cytarabine in the induction treatment of AML, using a 3 + 3 design, IDA was administered at doses ranging from 12 to 18 mg/m^2/day [43]. In this trial, the MTD of IDA was not reached and no grade 4 or 5 non-hematologic AEs were observed at any dose level. In a retrospective study of 115 patients with AML or myelodysplastic syndrome who received IDA during different courses of treatment and achieved durable CR, the probability of developing cardiomyopathy was 5% (cumulative IDA dose range 150–290 mg/m^2) [44]. In this study, the probability of asymptomatic decrease in left ventricular ejection fraction to less than 45%, but more than 15%, was 7% [44]. In a Cochrane systematic review, IDA compared with DNR did not increase the risk of grade 3 or 4 cardiac toxicity [45]. In the ALFA-9801 study, patients were randomly assigned to receive induction therapy with cytarabine for 7 days and either DNR (80 mg/m^2/day × 3 days, = 240 mg) or IDA (12 mg/m^2/day × 3 days, = 36 mg) or IDA (12 mg/m^2/day × 4 days, = 48 mg) [30]. While, no differences were observed in durations of cytopenias and hospitalization, as well as ≥ grade 3 infections and bleeding among the three arms, ≥ grade 3 mucositis was reported in the 10%, 15% and 29% ($P = 0.005$) in DNR, IDA (36 mg) and IDA (48 mg) arms, respectively [30].

Our systematic review and meta-analysis of published outcome data in trials comparing IDA and DNR relies on within-study comparisons only of the hazard ratio for OS between the two drug arms as a function of the ratio of cumulative doses. Thus, the large inter-study variability in case mix and in details of therapy delivery is at least in part taken into account. It is possible; however, that between-study variability in competing causes of mortality will create a less steep relationship between dose ratio and the hazard ratio for OS. Graphical inspection of the scatter of study outcomes around the regression line in Fig. 2 and taking the confidence intervals into consideration reveal no obvious over-dispersion of the outcomes data. Conceivably, response rates might be a more direct measure of the efficacy of a drug. In this specific analysis, however, the meta-regression of response odds ratios versus dose ratios did not show a statistically significant relationship. This could possibly reflect differences in definitions and timing of response assessments among the trials included in the overview.

A limitation of in vitro studies is that they do not take into account the in vivo pharmacokinetic (PK) (e.g., AUC and half-lives of parent compounds and metabolites) and pharmacodynamic (PD) differences between DNR and IDA [46]. The highly hydrophobic IDA exhibits greater tissue penetration than DNR in vivo, given its increased lipophilicity derived from the absence of the 4-methoxyl group [47], and has also been less susceptible to cellular efflux by multidrug resistance proteins [8, 9]. Though cellular uptake may be reflected in vitro, such studies do not take into account possible in vivo differences in adsorption [8, 9], tissue penetration, metabolism, excretion, and volume of distribution. When the PK of DNR and IDA were studied in 16 patients with leukemia treated with one of these agents, the dose-independent PK parameters including total plasma clearance, total volume of distribution, and elimination $t_{1/2}$ were similar for the two anthracyclines [10]. The elimination $t_{1/2}$ of 13-dihydroderivative of IDA, idarubicinol, was twice longer than 13-dihydroderivative of DNR, daunorubicinol (81 versus 37 h), which resulted in an AUC ratio metabolite/parent drug higher for IDA than for DNR [10]. In our study, the overall estimated equipotency factor and its 95% confidence limits are close to the estimates obtained from the

in vitro data analysis alone. This is due to the much wider confidence limits for the clinical, compared to the in vitro estimate.

In conclusion, the present literature review and in vitro analysis support a daunorubicin to idarubicin conversion factor of 4.1, and conservatively 5.9. These conversions can be considered for dose substitutions in the context of drug shortages, as well as for future clinical trial design including testing of new drugs in conjunction with backbone chemotherapy regimens. This may be the right time to initiate clinical trials utilizing dose intensification of IDA for induction therapy of AML; if not for well-designed well-conducted clinical trials in the last decade, we would be still using DNR 45 mg/m^2 as a standard dose. The question of whether escalation of the IDA dose for induction therapy may improve survival in medically fit patients with AML who are under the age of 65 years remains unanswered.

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Author contributions SA performed the literature search, designed, created Supplementary Table 1 and Figure 1, and helped to write the manuscript. RGL and BACC performed in vitro studies and helped to write the manuscript. AD and CP provided consultation on pharmacy-related issues and helped to write the manuscript. JYL developed the second draft of the manuscript under the direction of AE. MRB helped to write the manuscript. YZ and NPA performed cytogenetic and molecular analyses. SMB developed the statistical design and performed statistical analysis and co-authored the final result section with AE. AE developed the study design, supervised data collection and all aspects of the study, helped with data analysis, coordinated different sections of the project, and wrote and revised the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no relevant conflicts of interest.

Ethical approval This research does not involve human participants and/or animals.

Informed consent No informed consent was needed for this research.

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