IDARUBICIN & MITOZANTRONE & CUMULATIVE LIFETIME DOSES OF ANTHRACYCLINES

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QUESTION

What is the dose conversion factor of Idarubicin and Mitozantrone when calculating maximum lifetime cumulative doses of anthracyclines?

SEARCH LIMITS

Adult cancer patients.

SEARCH METHODOLOGY

A systematic search was conducted for literature. The results were screened by two librarians using Covidence. See the Appendix for the PRISMA chart, search terms, and Medline search strategy.

DATABASES SEARCHED

- Medline – index of peer reviewed articles across health sciences and medicine.
- Embase – index of biomed and pharmacological peer reviewed journal articles.
- UpToDate & BMJ Best Practice – synthesised evidence for patient care.
- Medicines databases – AMH, MIMS, Lexicomp, Martindale, Micromedex.
- Grey literature – Google, Google Scholar, Trip database, Biomed Central Proceedings.

LITERATURE RESULTS

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GENERAL RESOURCES

GREY LITERATURE (PRACTICE GUIDELINES)

UpToDate – **Risk and prevention of anthracycline cardiotoxicity**, last updated Feb 2023.

- Table - Lifetime cumulative dose thresholds for cardiotoxicity from anthracyclines and related agents in adults. Includes lifetime limits for Idarubicin and Mitoxantrone.
- In general, cardiotoxicity rates are relatively higher with mitoxantrone and idarubicin than with doxorubicin; they are both considered to be four to five times as cardiotoxic as doxorubicin, on a mg per mg basis. These cardiotoxicity rates relative to doxorubicin form the basis for recommendations about cumulative lifetime doses that should not be exceeded to avoid clinically significant cardiotoxicity.
- Cumulative anthracycline exposure is a consistent risk factor for cardiotoxicity, and the risk of toxicity increases substantially above the upper cumulative lifetime limit of each agent.
- Idarubicin – There is disagreement about the upper limit for the cumulative lifetime dose of idarubicin. The US prescribing information for idarubicin does not state a particular cumulative lifetime dose. Some suggest limiting cumulative doses to <150 mg/m2, others suggest <225 mg/m2 [45], and still others state that, given the rarity of cardiotoxicity, there is no definable cumulative dose beyond which rates of cardiotoxicity are higher than for lower doses.
- Mitoxantrone – The US Food and Drug Administration (FDA) prescribing information for mitoxantrone suggests a lifetime cumulative dose no higher than 140mg/m2.

Communities Oncology Network Pharmacy Educators. (2022) **Anthracycline and Bleomycin Cumulative Doses - Pharmacy FAQs**. Provisional Health Services Authority. BC, Canada. Web link

- Conversion factors – table 1 page 2: Recommended Conversion Factors, Monitoring Thresholds and Cumulative Doses for Anthracyclines
- Adapted from BC Cancer Drug Manual Index – Idarubicin monograph and Mitoxantrone monograph.

Alexander, et al. (2022). **ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS).** European Heart Journal, Volume 43, Issue 41, 1 November 2022, Pages 4229–4361. Web link

- This guideline provides guidance on the definitions, diagnosis, treatment, and prevention of cancer therapy-related CV toxicity (CTR-CVT), and the management of CV disease (CVD) caused directly or indirectly by cancer.
- In the case of patients scheduled to receive anthracycline chemotherapy, the total planned cumulative anthracycline dose is also relevant, and ≥250 mg/m2 of doxorubicin or equivalent should be considered higher risk.
- Table 5: Anthracycline equivalence dose

NSW Government. (2004, reviewed 2019). **Cardiac toxicity associated with anthracyclines**. eviQ Cancer Treatments Online. Web link

- Management – Table: Recommended maximum cumulative anthracycline doses.

MEDICINES DATABASES

IDARUBICIN

- **Australian Medicines Handbook**:
  - Maximum cumulative dose: Adult, should not exceed 160 mg/m2 by IV route.
  - Contraindicated if cardiac toxicity due to an anthracycline occurs or if the maximum cumulative dose has been reached. When calculating cumulative dose include all anthracycline treatment.
  - Previous radiotherapy to the chest region increases the risk of cardiac toxicity as may cardiac disease, reduced cardiac reserve or treatment with other cardiotoxic drugs.

- **Lexicomp**:
  - Drug Monograph - IDArubicin Hydrochloride (Adult and Pediatric)
  - The relative cardiotoxicity of idarubicin compared to doxorubicin is unclear. Some investigators report no increase in cardiac toxicity for adults at cumulative oral idarubicin doses up to 540 mg/m2; other reports suggest a maximum cumulative intravenous dose of 150 mg/m2.
  - Monitor cumulative (lifetime) anthracycline/idarubicin dose. CBC with differential and platelet count (frequently), cardiac function (LVEF; prior and during treatment), serum electrolytes, renal function (serum creatinine; prior to and during treatment), uric acid, liver function (ALT, AST, bilirubin; prior to and during treatment). Evaluate pregnancy status prior to use in patients who could become pregnant. Monitor infusion site for signs of extravasation; monitor for GI toxicity and infection.

- **MIMS**:
  - Precautions: 150-290 mg/m2 IV or ≥ 400 mg/m2 oral cumulative dose (incr cardiomyopathy risk); concomitant, prior radiation to mediastinal/ pericardial area, high cumulative anthracycline dose (cardiotoxicity risk).

- **Micromedex**:
  - Precautions: Cardiovascular: Evaluate the benefit-to-risk ratio of idarubicin before initiating therapy in patients with pre-existing heart disease and previous therapy with high cumulative doses of anthracyclines or other potentially cardiotoxic agents

- **Martindale Medicines Complete**:
  - A total cumulative oral dose of 400 mg/m2 should not be exceeded.
  - A cumulative total dose limit has not yet been defined. UK licensed product information states that total cumulative oral doses up to 400 mg/m2 have a low probability of cardiotoxicity. Cardiomyopathy has been reported in some patients with cumulative intravenous doses of 150 to 290 mg/m2. It has been suggested that idarubicin may be associated with less cardiotoxicity than doxorubicin. Idarubicin should be given with caution, and in reduced doses, to patients with renal or hepatic impairment.

MITOZANTRONE

- **Australian Medicines Handbook**:
  - Single agent, IV 14 mg/m2 for 1–5 days. Combination therapy or debilitated patients, IV 10–12 mg/m2 for 1–5 days. Further courses depend on response and toxicity.
  - Maximum cumulative dose: 140 mg/m2 or 100 mg/m2 with predisposing risk factors

such as previous anthracycline courses, mediastinal radiation or cardiac disease.

- **Lexicomp**:
  - Drug Monograph - mitoXANTRONE Hydrochloride (Adult and Pediatric)
  - Myocardial toxicity: May cause myocardial toxicity and potentially fatal heart failure (HF); risk increases with cumulative dosing. Cardiotoxicity may occur during therapy or may be delayed (months or years after completion of therapy). Predisposing factors for mitoxantrone-induced cardiotoxicity include prior anthracycline or anthracenedione therapy, prior or current cardiovascular disease, concomitant use of cardiotoxic drugs, and mediastinal/pericardial irradiation, although may also occur in patients without risk factors.
  - Do not administer mitoxantrone if LVEF falls below LLN or if a significant decrease in LVEF is observed during treatment. Evaluate potential risk versus benefit in patients who have previously received anthracycline therapy. If signs/symptoms of heart failure develop, evaluate LVEF and ECG.

- **MIMS**:
  - Dose: Dilute to ≥ 50 mL with glucose 5% or NaCl inj; admin over ≥ 3-5 min through free running glucose 5% or NaCl IV infusion, then flush with diluent
  - Precautions: dose > 140 mg/m2

- **Martindale Medicines Compete:**
  - UK licensed product information states that cardiac monitoring should also be performed in patients without identifiable cardiac risk factors who receive a total cumulative dose of mitoxantrone in excess of 160 mg/m2; US licensed product information states that the risk of symptomatic congestive heart failure is higher after a cumulative dose of 140 mg/m2 and that multiple sclerosis patients should not receive a total cumulative dose greater than this.
  - Previous anthracycline therapy increases the risk, and congestive heart failure is more likely in patients exposed to a cumulative mitoxantrone dose of 160 mg/m2, or 100 mg/m2 in those already given anthracyclines. The risk of symptomatic congestive heart failure in cancer patients has been estimated to be 2.6% for patients receiving a cumulative dose of up to 140 mg/m2; patients with multiple sclerosis should not receive a total cumulative dose greater than this.

PEER-REVIEWED LITERATURE - IN REVERSE CHRONOLOGICAL ORDER

Articles are grouped by theme:

- Conversion factor
- Cardiotoxic effect
- Individualised care
- Modelling studies
- Prevention and risk management
- Safe dose - anthracyclines

Each article summary contains excerpts from the abstract and an online link.

CONVERSION FACTOR

Adige et al. (2019). **Equipotent doses of daunorubicin and idarubicin for AML: a meta-analysis of clinical trials versus in vitro estimation.** Cancer Chemother Pharmacol. 2019 Jun;83(6):1105-1112. Article link
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 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.

Teuffel, et al. (2013) **Anthracyclines during induction therapy in acute myeloid leukaemia: a systematic review and meta-analysis. [Review]** British Journal of Haematology. 161(2):192-203, 2013 Apr. Article link
This systematic review and meta-analysis compared the efficacy of different anthracyclines and anthracycline dosing schedules for induction therapy in acute myeloid leukaemia in children and adults younger than 60 years of age. Twenty-nine randomized controlled trials were eligible for inclusion in the review. Comparisons of several other anthracycline derivates did not reveal significant differences in outcomes. Survival estimates in adults suggest that both high-dose DNR (90 mg/m(2) daily x 3 or 50 mg/m(2) daily x 5) and IDA (12 mg/m(2) daily x 3) can achieve 5-year survival rates of between 40 and 50 percent.

Dodos, et al. (2008). **Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults**. Clin Res Cardiol. 2008 May;97(5):318-26. Article link
Anthracyclines of the therapeutic regimens were doxorubicin (53%), epirubicin (29%), daunorubicin (15%), mitoxantrone (2%), and idarubicin (1%). The mean cumulative anthracycline dose estimated with the conversion factor for assessment of equivalent doses (Table 2) was 226.1 ± 8.3 mg/m2 (range 90–400 mg/m2). Table 2, page 320.

CARDIOTOXIC EFFECT

Jeyaprakash, et al (2021). **Cardiotoxic Effect of Modern Anthracycline Dosing on Left Ventricular Ejection Fraction: A Systematic Review and Meta-Analysis of Placebo Arms From Randomized Controlled Trials**. Journal of the American Heart Association, 10(6), e018802. Article link
Anthracyclines are a key chemotherapeutic agent used against hematological and solid organ malignancies. However, their benefits in cancer survival are limited by cumulative, dose-related cardiotoxicity. The impact of anthracyclines on left ventricular ejection fraction (LVEF), in the era of modern chemotherapy regimens, remains unclear. A doxorubicin equivalent anthracycline dose metric was calculated to compare different anthracyclines. A random-effects model was used to pool mean difference in LVEF after anthracycline. Meta-regressions were calculated to identify variation sources. We included 660 patients from 19 trials. The magnitude of LVEF impairment post-anthracycline therapy appears less than previously described with modern dosing regimens. This may improve the accuracy of power calculation for future clinical trials assessing the role of cardioprotective therapy.

Antolin, et al. (2020). **Incidence and clinical evolution of long term anthracycline cardiotoxicity.** Journal of the American College of Cardiology, 75(11), 927. Article link

Anthracycline cardiotoxicity (AC) may manifest years after treatment (long-term AC). There are few data on the incidence and natural history of AC in the current context. We evaluated incidence, onset time and clinical correlates of long-term AC and the evolution of systolic function in patients (pts) with breast cancer treated with anthracyclines (A). Incidence of long-term cardiotoxicity in patients treated with low-cumulative dose of anthracyclines is high, 16.5 % at 4.5 years, and in most cases appears after the first year of follow-up. Therefore, long-term monitoring may be recommended.

Conyers, et al. (2017). **Chemotherapy-related cardiotoxicity: are Australian practitioners missing the point?** Internal Medicine Journal, 47(10), 1166-1172. Article link
It has long been established that cardiotoxicity occurs as a result of exposure to certain chemotherapeutics, particularly anthracyclines. Historically, clinicians equate cardiotoxicity with a poor prognosis, in a small percentage of patients and deem long-term surveillance as optional. Emerging evidence suggests that anthracycline cardiotoxicity (ACT) is a life-long risk with an incidence approaching 20%. This study demonstrates, in keeping with modern literature, the higher incidence of anthracycline associated cardiac toxicity and a need for better surveillance and follow up.

Levis, et al. (2017). **Cardiotoxic effects of anthracycline-based therapy: what is the evidence and what are the potential harms?** The Lancet. Oncology, 18(8), e445-e456. Article link
Despite the known cardiotoxic effects of doxorubicin and other anthracyclines, no evidence-based guidelines exist for the surveillance and prevention of chemotherapy-induced cardiotoxicity in adult survivors of breast cancer who have had limited previous doses of anthracyclines (ie, total cumulative dose 240 mg/m2), or limited-dose anthracyclines followed by trastuzumab-based regimens. Nonetheless, some national and international cardio-oncology and cardiac-imaging organisations recommend increased cardiac surveillance during or after treatment, measurement of cardiac biomarkers and other surrogate endpoints, and in some cases initiation of cardioprotective drug therapy in asymptomatic women. However, two unintended potential harms of such approaches are medicalisation and increased health-care costs when the value of providing that care is unknown. Further research is needed to assess the long-term benefits, harms, and value of expanded cardiac surveillance, use of surrogate cardiac biomarkers, and prophylactic cardioprotective therapy in asymptomatic women with limited exposure to anthracyclines.

Lotrionte, et al. (2013). **Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity.** The American journal of cardiology, 112(12), 1980-4. Web link
The management of individual patients requiring anthracyclines remains challenging because uncertainty persists on predictors of cardiotoxicity. We aimed to perform a systematic review and meta-analysis on incidence and predictors of anthracycline chemotherapy in patients with cancer. Appraisal of independent risk factors of cardiotoxicity showed that cumulative anthracycline dose was most consistently reported as an accurate and robust predictor of cardiotoxicity, with an acceptable prognostic role also for chest radiotherapy, African-American ethnicity, very young or very old age, diabetes, hypertension, very high or very low body weight, or severe co-morbidities. In conclusion, despite ongoing refinements in chemotherapy regimens, anthracyclines still pose a significant risk of cardiotoxicity, especially in those requiring a high cumulative dose or chest radiotherapy.

Smith, et al. (2010) **Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomised controlled trials.** BMC Cancer 10, 337 (2010). Article link
We conducted a systematic review and meta-analysis to clarify the risk of early and late cardiotoxicity of anthracycline agents in patients treated for breast or ovarian cancer, lymphoma, myeloma or sarcoma. Evidence is not sufficiently robust to support clear evidence-based recommendations on different anthracycline treatment regimens, or for routine use of cardiac protective agents or liposomal formulations. There is a need to improve cardiac monitoring in oncology trials. Cumulative doses of anthracyclines received are shown in Additional file 4; Table S2.

INDIVIDUALISED CARE

Sallustio and Boddy. (2021). **Is there scope for better individualisation of anthracycline cancer chemotherapy?** British Journal of Clinical Pharmacology, 87(2), 295-305. Article link
Cardiotoxicity, particularly heart failure, is a leading cause of morbidity and mortality in cancer survivors. Cumulative anthracycline dose is a significant predictor of cardiotoxicity risk, suggesting a role for anthracycline pharmacokinetic variability. Population pharmacokinetic models in adults have not adequately addressed older ages, obesity, hepatic and renal dysfunction, and potential drug-drug interactions to enable clinical application. Precision-dosing of anthracyclines is currently hindered by lack of clinically useful pharmacokinetic targets and models that predict cumulative anthracycline exposures. Combined with known risk factors for cardiotoxicity, the use of advanced echocardiography and biomarkers, future validated pharmacokinetic targets and predictive models could facilitate anthracycline precision dosing that truly maximises efficacy and provides individualised early intervention with cardioprotective therapies in patients at risk of cardiotoxicity.

Oliveira, et al. (2016). **Maximizing anthracycline tolerability in hematologic malignancies: Treat to each heart's content.** Blood Reviews, 30(3), 169-178. Web link
Anthracyclines are the cornerstone of therapy for a wide spectrum of malignancies and have improved patient survival. Concern for anthracycline-related cardiotoxicity often leads to dose reductions or use of second-line regimens, which may adversely impact survival. Development of cardiotoxicity depends on a combination of cumulative dose modulated by individual patient characteristics, which we have termed individual cardiotoxic threshold (ICT). Prophylaxis with cardioprotective agents and other strategies have shown promising results in randomized trials and may improve tolerance to anthracyclines. In this review we introduce the concept of ICT and critically analyze the evidence supporting existing strategies to modulate it and increase cardiovascular tolerability of anthracyclines.

MODELLING STUDIES

Bozza, et al. (2021). **Anthracycline-Induced Cardiotoxicity: Molecular Insights Obtained from Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes (hiPSC-CMs).** AAPS Journal, 23(2), 44. Article link
Here, we describe an assay platform by coupling hiPSC-CMs and impedance measurement, which allows real-time monitoring of cardiomyocyte cellular index, beating amplitude, and beating rate. Using this approach, we have performed comparative studies on a panel of four anthracycline drugs (doxorubicin, epirubicin, idarubicin, and daunorubicin) which share a high degree of structural similarity but are associated with distinct cardiotoxicity profiles and maximum cumulative dose limits. The results provide molecular insights into anthracycline cardiac interactions and offer a novel assay system to more robustly assess potential cardiotoxicity during drug development.

Salvatorelli, et al. (2018). **Low-dose anthracycline and risk of heart failure in a pharmacokinetic model of human myocardium exposure: Analog specificity and role of secondary alcohol metabolites**. Journal of Pharmacology and Experimental Therapeutics, 364(2), 323-331. Article link
Recently, a pharmacokinetic model was developed that simulated clinical exposure of human myocardium to anthracyclines and incorporated simulations of CBR3 polymorphism. It was shown that HF risk could occur after lower doxorubicin doses than previously reported, particularly for patients with CBR3 polymorphism. In this study, we show that also daunorubicin and idarubicin, but not epirubicin, might cause HF after reportedly safe cumulative doses. These results support concerns

about HF risk from low-dose anthracycline, characterize the analog specificity of HF risk, and illuminate the role of secondary alcohol metabolites.

PREVENTION & RISK MANAGEMENT

Fogarassy, et al. (2020). **Analysing the risk factors of doxorubicin-associated heart failure by a retrospective study of integrated, nation-wide databases**. Orvosi Hetilap, 161(26), 1094-1102. Article link

The incidence of dilated cardiomyopathy after anthracycline chemotherapy is mainly influenced by anthracycline cumulative dose. Previous research showed doxorubicin treatment under cumulative dose of 450 mg/m2 associated with a low incidence of heart failure. Nowadays, doxorubicin is administered with a lower dose, the development of heart failure is largely determined by other factors. Our purpose was to identify the risk factors for heart failure due to doxorubicin therapy. Among the analysed 3288, doxorubicin-treated patients, heart failure cumulative incidence was 6.2%. Doxorubicin cumulative dose over 400 mg/m2 increased the risk. The heart failure incidence was essentially influenced by age, even over 50 years the risk rose. Diabetes mellitus and the treatments with pyrimidine-analogues, carboplatin or bevacizumab were also associated with higher risk. By the integration of national financial and clinical databases, we could identify the risk factors for doxorubicin-associated heart failure.

Conway, et al. (2015). **The prevention, detection and management of cancer treatment-induced cardiotoxicity: a meta-review.** BMC cancer, 15(100967800), 366. Article link

The benefits associated with some cancer treatments do not come without risk. A serious side effect of some common cancer treatments is cardiotoxicity. The aim of this meta-review is to appraise and synthesise evidence from only high quality systematic reviews focused on the prevention, detection or management of cancer treatment-induced cardiotoxicity. The following strategies might reduce the risk of cardiotoxicity: 1) The concomitant administration of dexrazoxane with anthracylines; 2) The avoidance of anthracyclines where possible; 3) The continuous administration of anthracyclines (>6 h) rather than bolus dosing; and 4) The administration of anthracycline derivatives such as epirubicin or liposomal-encapsulated doxorubicin instead of doxorubicin. In terms of management, one review focused on medical interventions for treating anthracycline-induced cardiotoxicity during or after treatment of childhood cancer. Neither intervention (enalapril and phosphocreatine) was associated with statistically significant improvement in ejection fraction or mortality. This review highlights the lack of high level evidence to guide clinical decision-making with respect to the detection and management of cancer treatment-associated cardiotoxicity. There is more evidence with respect to the prevention of this adverse effect of cancer treatment. cardiotoxicity.

Volkova & Russell. (2011). **Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment**. Current Cardiology Reviews, 7(4), 214-220. Article link

Anthracyclines, such as doxorubicin and idarubicin, remain an important class of chemotherapeutic agents. Unfortunately, their efficacy in treating cancer is limited by a cumulative dose-dependent cardiotoxicity, which can cause irreversible heart failure. In this review, we discuss the pathogenesis and incidence of anthracycline-induced cardiotoxicity as well as methods to detect, prevent and treat the condition. Includes table 1: Dose Related Risk of Doxorubicin-Induced Congestive Heart Failure and Table 2: Factors Associated with Increased Risk of Anthracycline-Induced Cardiotoxicity.

SAFE DOSE OF ANTHRACYCLINES

Abbas and Alazmi. (2019). **Anthracycline-induced cardiac toxicity: A clinical review.** Indian Journal of Medical and Paediatric Oncology, 40(4), 465-475. Article link

Anthracyclines (ATCs) have a great efficacy against many types of cancer and is currently considered a cornerstone in the treatment of numerous pediatric and adult hematological and solid tumors. The clinical use of ATC such as doxorubicin and daunorubicin can be viewed as a sort of double-edged sword. The most common side effect of the ATC group is cardiotoxicity (CTX). The clinical use of ATC is limited by unique maximum total cumulative dose (approximately 350 mg/m2) limiting CTX. ATC CTX is cumulative dose-dependent and is in most of the occasions irreversible. Lowering the cumulative dose has been proved to be useful in minimize the risk of heart failure (HF), but, yet, there is a growing concern that HF might occur following doses that were thought to be safe. The average incidence of HF is around 5% at a cumulative dose of 400 mg/m2 that becomes higher above 500 mg/m2, albeit with substantial individual variation. The newer generations ATC medications such as epirubicin, idarubicin, and mitoxantrone were thought to be safer; however, subsequent clinical studies showed more or less similar toxicity profiles. In this review article, we present a comprehensive account on the ATC and provide up to date data on their clinical use and toxicity profile. In addition, we provide a contemporary approach on the early detection, diagnosis, and treatment of ATC CTX.

Bradstock, et al. (2017). **Idarubicin dose escalation during consolidation therapy for adult acute myeloid leukemia.** Journal of Clinical Oncology, 35(15), 1678-1685. Article link
Higher doses of the anthracycline daunorubicin during induction therapy for acute myeloid leukemia (AML) have been shown to improve remission rates and survival. We hypothesized that improvements in outcomes in adult AML may be further achieved by increased anthracycline dose during consolidation therapy. Patients with AML in complete remission after induction therapy were randomly assigned to receive two cycles of consolidation therapy with cytarabine 100 mg/m2 daily for 5 days, etoposide 75 mg/m2 daily for 5 days, and idarubicin 9 mg/m2 daily for either 2 or 3 days (standard and intensive arms, respectively). The primary end point was leukemia-free survival (LFS). An increased cumulative dose of idarubicin during consolidation therapy for adult AML resulted in improved LFS, without increased nonhematologic toxicity.

Aronoson. (2016). **Anthracyclines and related compounds**, Chapter in Meyler's Side Effects of Drugs, pp 511-521. Chapter link
Dose-relatedness : The development of anthracycline-induced cardiomyopathy is closely related to the cumulative lifetime dose of the anthracycline. The recommended maximum cumulative lifetime dose of doxorubicin is 450–550 mg/m 2 and of daunorubicin 400–550 mg/m 2 intravenously in adults [1 , 2]. About 5% of doxorubicin-treated patients develop congestive cardiac failure at this dose; however, the incidence approaches 50% at cumulative doses of 1000 mg/m 2. These figures are derived from experience with doxorubicin administered as a bolus or by infusion of very short duration (under 30 minutes). The incidence of clinical cardiotoxicity falls dramatically with other schedules of administration (that is weekly doses or continuous infusion for more than 24 hours).

Santos, et al. (2015). **Cardiac status of patients treated with anthracyclines-a brazilian osteosarcoma study**. Journal of Cardiac Failure, 21(8 SUPPL. 1), S22.
Despite the proven benefits of anthracyclines in curing various cancers in adult and pediatric population, there is an intimate relationship with cardiovascular complications (cardiotoxicity-CTX) .The evidence points to the concept that there is no safe dose of antracyclines. This study aims to retrospectively evaluate the behavior of left ventricular (LV) myocardial function during the treatment of osteosarcoma based on the current Latin American protocol (GLATO 2006) and the present cardiac status of these patients. This study demonstrates the lack of safe dose of anthracyclines and emphasizes the importance of cardiac monitoring before, during and after treatment. CTX was a frequent finding, unrelated to symptoms of HFor cumulative dose of anthracycline. Diastolic dysfunction was associated to progression of systolic dysfunction. Although the anticipation of DEX and recovery of systolic function at the end of treatment, it is assumed that the injuries occurred with

the initial doses of Doxo were responsible for myocardial injuries. Thus, we demonstrated the importance of the use of dexrazoxane since the first dose of anthracyclines.

Jensen. (2006). **Cardiotoxic consequences of anthracycline-containing therapy in patients with breast cancer**. Seminars in oncology, 33(3 Suppl 8), S15-21. Web link
The successful use of anthracyclines is restricted by the risk of developing life-threatening congestive heart failure. This risk increases exponentially with cumulative dose, and is further augmented by the addition of trastuzumab. Studies have reported that 10% to 26% of patients administered cumulative anthracycline doses above those recommended (> or =500 mg/m2 for doxorubicin and 1,000 mg/m2 for epirubicin) develop congestive heart failure, and that more than 50% of patients administered these doses will experience measurable functional impairment months to years after the end of therapy. The susceptibility of patients to anthracycline-induced cardiotoxicity varies widely, with a dramatic increase with advancing age. Possible future treatment options for managing anthracycline-induced cardiotoxicity include agents such as dexrazoxane that prevent oxygen-free radical generation. Further investigation is required into the use of angiotensin-converting enzyme inhibitors to redress cardiac damage and new methods of identifying patients at high risk of congestive heart failure before cardiac damage has occurred.

SEARCH TERMS

Concept	MeSH headings	Keywords
Cumulative lifetime dose of anthracyclines	Anthracyclines with Administration & Dosage, Adverse Effects sub headings	anthracycline* near cumulative or total or maximum or lifetime. conversion or convert* or cumulative and idarubicin* or mitozantrone* and anthracycline*.
Drug therapies	Idarubicin, Mitoxantrone, Doxorubicin	mitozantrone* or mitoxantrone* or idarubicin* or doxorubicin*
Cancer	Neoplasms with Drug Therapy sub heading	cancer* or neoplasm* or oncolog* or anticancer
Conversion factor	Therapeutic Equivalency	dose conversion or conversion factor or equivalence ratio or drug* within 2 words of conver* cumulative within 3 words of schedule or dose maximum within 5 words of lifetime
Drug effects	Cardiotoxicity, Incidence, Risk Factors, Dose-Response Relationship, Drug	dose and dysfunction or injur* or harm or adverse or toxic* or cardiotoxic*

MEDLINE SEARCH STRATEGY

1 Anthracyclines/ad, ae [Administration & Dosage, Adverse Effects] (2502)

2 (anthracycline* adj10 (cumulative or total or maximum or lifetime)).ti,ab. (779)

3 ((conversion or convert* or cumulative) and (idarubicin* or mitozantrone*) and anthracycline*).tw. (48)

4 1 or 2 or 3 (3068)

5 Idarubicin/ad, ae, to [Administration & Dosage, Adverse Effects, Toxicity] (1136)

6 Mitoxantrone/ad, ae, to [Administration & Dosage, Adverse Effects, Toxicity] (2471)

7 Doxorubicin/ad, ae, to [Administration & Dosage, Adverse Effects, Toxicity] (31572)

8 (mitozantrone* or mitoxantrone* or idarubicin* or doxorubicin).ti,ab. (58281)

9 5 or 6 or 7 or 8 (73714)

10 Neoplasms/dt [Drug Therapy] (88171)

11 (cancer* or neoplasm* or oncolog* or anticancer).tw. (2400668)

12 10 or 11 (2420879)

13 (dose conversion or conversion factor or equivalence ratio or (drug* adj2 conver*)).mp. (2555)

14 (cumulative adj3 (schedule or dose)).mp. (12397)

15 (maximum adj5 lifetime).mp. (428)

16 Therapeutic Equivalency/ (8139)

17 13 or 14 or 15 or 16 (23473)

18 (dose and (dysfunction or injur* or harm or adverse or toxic* or cardiotoxic*)).tw. (286746)

19 Cardiotoxicity/ or Incidence/ or Risk Factors/ or Dose-Response Relationship, Drug/ (1565727)

20 18 or 19 (1800231)

21 4 and 12 and 17 and 20 (92)

APPENDIX

PRISMA CHART