REVIEW ARTICLE

blood advances

Anthracycline-related cardiotoxicity in older patients with acute myeloid leukemia: a Young SIOG review paper

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The incidence of acute myeloid leukemia (AML) increases with age. Intensive induction chemotherapy containing cytarabine and an anthracycline has been part of the upfront and salvage treatment of AML for decades. Anthracyclines are associated with a significant risk of cardiotoxicity (especially anthracycline-related left ventricular dysfunction [ARLVD]). In the older adult population, the higher prevalence of cardiac comorbidities and risk factors may further increase the risk of ARLVD. In this article of the Young International Society of Geriatric Oncology group, we review the prevalence of ARLVD in patients with AML and factors predisposing to ARLVD, focusing on older adults when possible. In addition, we review the assessment of cardiac function and management of ARLVD during and after treatment. It is worth noting that only a minority of clinical trials focus on alternative treatment strategies in patients with mildly declined left ventricular ejection fraction or at a high risk for ARLVD. The limited evidence for preventive strategies to ameliorate ARLVD and alternative strategies to anthracycline use in the setting of cardiac comorbidities are discussed. Based on extrapolation of findings from younger adults and nonrandomized trials, we recommend a comprehensive baseline evaluation of cardiac function by imaging, cardiac risk factors, and symptoms to risk stratify for ARLVD. Anthracyclines remain an appropriate choice for induction although careful risk-stratification based on cardiac disease, risk factors, and predicted chemotherapy-response are warranted. In case of declined left ventricular ejection fraction, alternative strategies should be considered.

Introduction

More than 60% of acute myeloid leukemia (AML) cases are diagnosed in adults aged ≥60 years.[1] Anthracyclines have been part of the upfront and salvage treatment of AML since the 1970s.[2] In the upfront setting, anthracycline is traditionally given over 3 days (eg, daunorubicin 45-90 mg/m^2 per day, idarubicin 12 mg/m^2 per day) in combination with cytarabine (100-200 mg/m^2 per day continuously over 7 days) ("7+3" regimen). Other strategies include the use of mitoxantrone and/or high-dose cytarabine (1-3 g/m^2). Anthracyclines are associated with cardiotoxicity; they can decrease left ventricular ejection fraction (LVEF) and contribute to the subsequent development of heart failure (HF). Compared with

Submitted 24 October 2019; accepted 13 January 2020; published online 25 February 2020. DOI 10.1182/bloodadvances.2019000955.

younger patients, anthracycline use in older patients with AML may be more challenging because of a higher prevalence of preexisting left ventricular dysfunction and an overall decreased response rate toward chemotherapy. In this narrative review, we provide an overview on anthracycline-related cardiotoxicity in older patients with AML.

Definition of anthracycline-induced cardiotoxicity

Anthracycline-induced cardiotoxicity is generally divided into acute vs chronic, the latter of which is more common and occurs in a dose-dependent manner.[3,4] Acute cardiotoxicity is typically not dose-dependent and may present as acute HF, arrhythmia, or myocarditis.[5-8] The spectrum of clinical presentation of chronic cardiotoxicity ranges from subclinical LVEF decline to HF. Cardiotoxicity is frequently found following anthracycline use and is generally defined as >10% decrease in LVEF to final LVEF <50%.[3,9,10] However, the exact cutoff values for decline in LVEF vary in published studies.[11,12] Other criteria such as decreased left fractional shortening, abnormal wall motion, global longitudinal strain, and diastolic dysfunction have also been occasionally used to define anthracycline-related cardiotoxicity but they are currently not integrated into the standard assessment and definition.[9,13,14] For the purpose of this article, we focus on anthracycline-related left ventricular dysfunction (ARLVD) that presents as a decline in LVEF.

Pathophysiology of ARLVD

There are multiple processes that contribute to development of ARLVD (Figure 1).[15] After cellular uptake, daunorubicin is intercalated into mitochondrial and nuclear DNA. This causes DNA double-strand breaks and activates topoisomerase-2β, which induces apoptosis and cellular death. It also causes mitochondrial dysfunction through the formation of reactive oxygen species and endoplasmic reticulum stress. These processes contribute to the loss of functional cardiomyocytes, myocardial disarray, and development of interstitial fibrosis.[15-17]

Risk factors of ARLVD

There are several predisposing factors for ARLVD. The most important modifiable risk factor is the cumulative anthracycline dose (CAD). Other risk factors for ARLVD include female sex, age >65 or <18 years, renal failure, concomitant or previous radiation therapy involving the heart, concomitant chemotherapy with alkylating (eg, cyclophosphamide) or antimicrotubule agents (eg, taxanes), preexisting cardiac diseases such as systemic hypertension,[18] and genetic factors (eg, the P450 oxidoreductase SNPs rs2868177, rs13240755, and rs4732513 are related to daunorubicin–induced cardiotoxicity[19]).

CAD

Chronic ARLVD is dependent on the CAD[20] and correlates with peak plasma anthracycline concentrations.[21]

Symptomatic HF does not generally develop with a cumulative (nonliposomal) doxorubicin dose of <400 mg/m^2. At a cumulative dose of 400 to 550 mg/m^2 doxorubicin, there is a 5% risk of developing HF, which increases to 25% to 43% at 700 mg/m^2.[4,18,20-22] Some studies suggest that other anthracycline analogs, such as epirubicin and idarubicin, have a lower risk of ARLVD relative to their therapeutic doses.[23] Mitoxantrone, an anthracenedione, appears to have a higher risk of ARLVD in comparison with doxorubicin.[24] In older adults, there is some evidence that the CAD needed to cause ARLVD is lower.[4,25] This was shown by the pivotal study of von Hoff et al[4] demonstrating higher incidences of ARLVD in adults >60 years even at lower CAD in comparison with younger adults (eg, incidence of ARLVD at a CAD of 250 mg/m^2: 1.5% in adults aged 40-59 years vs 2.4% in adults aged ≥60 years; CAD of 400 mg/m^2: 2.3% vs 4.6% and at 600 mg/m^2 14.9% vs 22.4%).

A few studies suggest that ARLVD may develop at lower doses and may occur at a higher frequency than reported in the pivotal trials.[3,26] Noteworthy, the data of and recommendations for maximum CAD are mostly derived from solid cancer and lymphoma regimens (Table 1) and may not be representative for the ARLVD risk in patients with AML undergoing induction therapy.[27] Nonetheless, the incidence of ARLVD after AML induction therapy varies and was previously reported to be as high as 12% to 18% for standard "7+3" regimen.[28-30] This is alarming considering that induction therapy generally comprises a cumulative daunorubicin dose of ~180 to 360 mg/m^2, whereas the expected CAD that leads to a >5% risk of ARLVD is between 400 and 550 mg/m^2.[20] This suggests that additional factors may contribute to the unexpected high incidence of ARLVD in AML, such as the relative dose density during induction therapy.[31] In solid cancers, the CAD is usually given over several months, whereas in AML, anthracycline is given over a short period (eg, daunorubicin 60 mg/m^2 on days 1-3). In addition, ARLVD was found to be more common in the setting of infections during AML therapy.[30,31] Severe infections are more common during therapy for AML compared with other cancer types (eg, breast). Thus, infections may augment the higher risk of ARLVD in AML (Table 1).

Other risk factors for ARLVD

Pretreatment comorbidities such as renal failure, hypertension, and preexisting cardiac diseases are common in the older adult population (Table 2) and are concomitant risk factors for the development of ARLVD.

In the broader context, frailty is a well-known risk factor for increased chemotherapy toxicities.[32] Frailty is defined as "a clinical state in which there is an increase in an individual's vulnerability for developing increased dependency and/or mortality when exposed to a stressor."[33] Frailty is more common in the geriatric population and is associated with sarcopenia, sarcopenic obesity, and hypoalbuminemia, all of which could lead to changes in pharmacokinetics of anthracyclines. Nonetheless, data on changes in pharmacokinetics of anthracycline with age are conflicting.[34-36] Daunorubicin has a high distribution volume, intensive tissue uptake, and moderate plasma protein binding.[36,37] Therefore, it is possible that a change in body composition may decrease tissue distribution leading to higher peak concentration resulting in higher risk of ARLVD.[38] In animal models, higher peak concentrations of daunorubicin were found in older rats compared with young rats.[39] In another study using a rat and rabbit model, protein malnutrition, lower body weight, and hypoalbuminemia alter pharmacokinetics of doxorubicin with a significant decrease in drug elimination.[39,40] It is unclear whether similar findings are seen in patients who are cachectic or sarcopenic but the findings in animal models could provide an explanation for the increased toxicities observed in older adults.

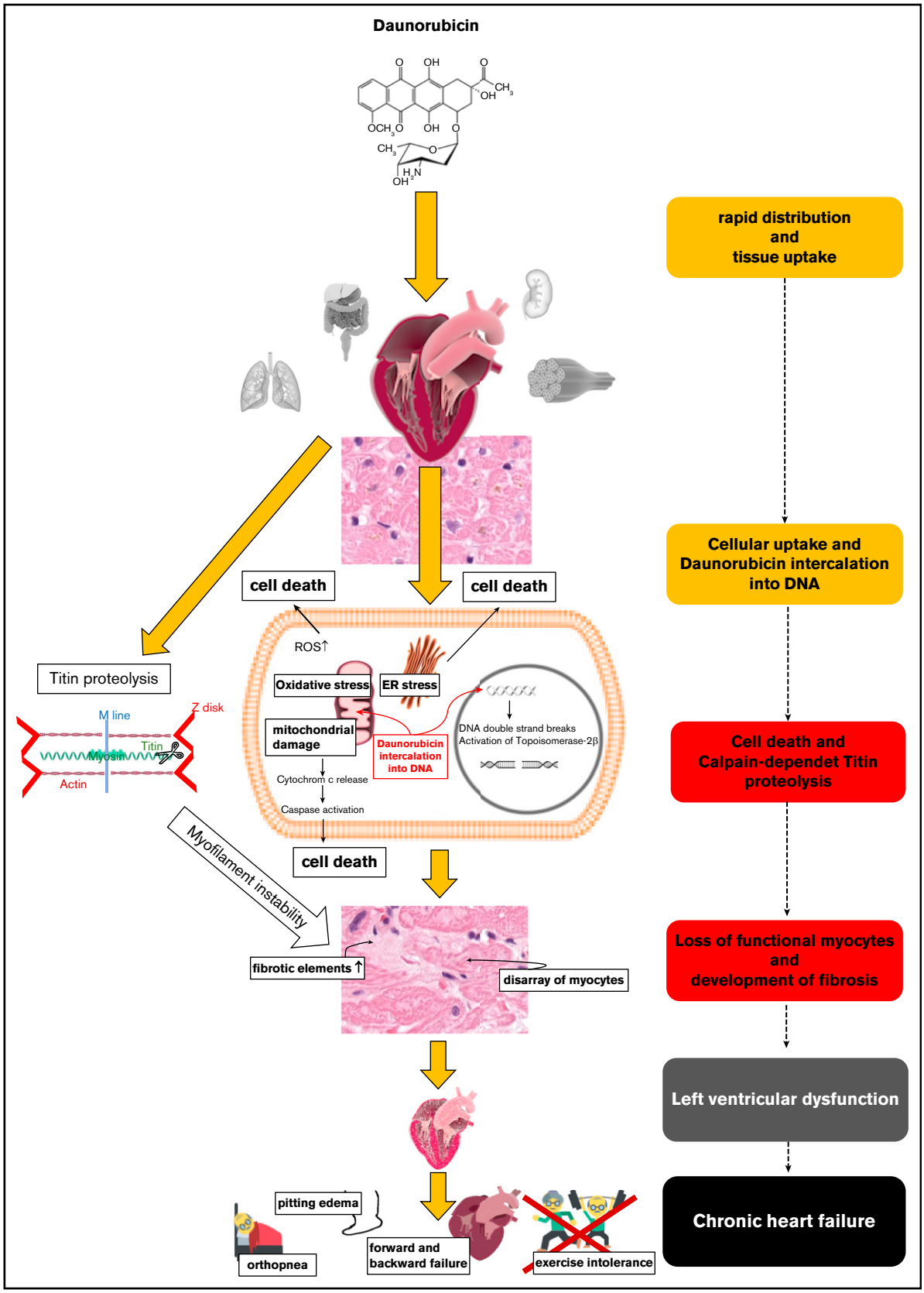

Figure 1. Mechanisms of anthracycline-related left ventricular dysfunction. The development of anthracycline-related left-ventricular dysfunction is multifactorial.[15] After injection, daunorubicin is rapidly distributed to various tissues (eg, heart, lung, kidneys, spleen, liver, lean tissue). After cellular uptake, it is intercalated into mitochondrial and

Table 1. Cumulative dose of different anthracycline agents that are associated with a >5% incidence of heart failure[18,20-22]

Anthracycline agent	Cumulative dose, mg/m^2*
Daunorubicin	400-550
Doxorubicin	400-550
Epirubicin	900
Idarubicin (IV)	90
Mitoxantrone	100-160†
Liposomal anthracyclines	>1000

*Data on cumulative doses associated with risk of heart failure are mostly derived from trials of patients with breast cancer, sarcoma, and lymphoma. Although the dose density and schedules are different in leukemia therapies, the cumulative dose for anthracycline-related toxicity is applicable in other cancer types.

†Data for mitoxantrone are mixed; reported is an ARLVD incidence of 2.6% at a cumulative dose of 140 mg/m^2 with the strict recommendation not to exceed this dose.[121]

Table 2. Prevalence of risk factors for anthracycline-related left ventricular dysfunction in the general older adult population

Comorbidity	Age, y	Prevalence in the general older adult population, %
Arterial hypertension[122]	>60	60-70
Chronic heart failure*[123-125]	60-70	~4-8
	70-79	9-12
	80+	>15
Coronary artery disease[126]	>60	15-36
Peripheral artery disease[127]	60-70	7.1
	71-80	13
	80+	>22
Chronic renal insufficiency†[128,129]	60-69	~9-13
	70+	11-46

*Including asymptomatic left ventricular ejection fraction decline, excluding those with preserved ejection fraction

†Glomerular filtration rate <60 mL/min/1.73 m^2.

Impact of preexisting cardiovascular comorbidities and ARLVD on outcomes

Preexisting cardiac comorbidities are common reasons for excluding older adults from receiving intensive chemotherapy.[41,42] An analysis of the Danish National Leukemia Registry demonstrated that either heart or renal failure are common reasons why intensive therapy was not given.[41] Even in patients ≥60 years selected for intensive induction therapy based on their overall condition, prevalence of cardiac comorbidities is high.[41,43-46] Table 3 shows the prevalence of cardiac and related comorbidities in patients with AML. Cardiovascular comorbidities are poor prognostic factors and are reflected by the Hematopoietic Stem-Cell Transplantation–Comorbidity Index (HCT-CI), which is a validated tool to predict mortality in patients with AML and those undergoing allogeneic hematopoietic stem cell transplantation (HSCT).[43,47] In this tool, several cardiac comorbidities (eg, coronary artery disease, HF, arrhythmias, heart valve abnormalities) are shown to be associated with poor outcomes.

The effect of ARLVD on outcomes was assessed in a large cohort of pediatric AML patients within the Children's Oncology Group trial AAML0531. ARLVD was associated with a reduction in event-free survival (EFS) and overall survival (OS).[30] Although the study was performed in the pediatric population, it reinforces the negative prognostic implications of ARLVD. A recent single-center retrospective analysis also demonstrated a reduction in OS after HSCT in the setting of ARLVD (including a transient LVEF decline) that developed after induction therapy (13 vs 27 months; $P = .013$).[29] Because a curative treatment approach may include an HSCT in select patients, a transient LVEF decline may potentially delay HSCT, thereby worsening outcomes.

AML biology-driven decision making on anthracycline use

When considering the use of anthracycline, it is also important to consider leukemia-related factors that are associated with a poor response to "7+3" regimen. In this case, the risk for ARLVD may exceed the potential benefit derived from anthracycline-based regimen. Factors that are related to chemoresistance include TP53 mutations, complex cytogenetic aberrations,[48] and increased expression of multidrug-resistance proteins such as *p*-glycoprotein–based efflux pumps.[49] In contrast, NPM1 mutations or core-binding factor leukemia are predictive of chemosensitive disease. Prognostic and predictive factors are summarized in Table 4.

Integration of cardio-oncology

The integration of cardio-oncology teams appears to be of utmost importance. A recent analysis of AML patients with ARLVD found that only a minority was seen by a cardiologist and received HF medication.[50] In a Canadian survey, <20% of hematologists stated that they regularly consider the indication before they stop cardiovascular medication in AML patients and up to 28% did not restart this medication after interruption.[51] This clearly illustrates that cardio-oncology specialists might better assess for risk factors of ARLVD and recommend preventive and therapeutic strategies. Nonetheless, cardio-oncologists are not broadly available. For routine practice, we recommend partnerships with cardiologists with experience in managing ARLVD to jointly follow older adults receiving anthracycline-based induction therapy who have risk factors for ARLVD.

Assessment of cardiac function before and during treatment

Although there are several guidelines in the assessment and surveillance of adults receiving anthracycline-based chemotherapy,[18,52,53] data specific to older adults with AML are limited. Strategies for assessing cardiac abnormalities include cardiac imaging (echocardiography,

Figure 1. (continued) nuclear DNA. This causes double-strand breaks and activates topoisomerase-2β, which induces apoptosis and cellular death. It also causes mitochondrial dysfunction through the formation of reactive oxygen species (ROS) and endoplasmic reticulum (ER) stress. Other contributing mechanisms include titin proteolysis and inhibition of the neuregulin/ErbB pathway.[15-17] All these processes contribute to the loss of functional cardiomyocytes, myocardial disarray, and development of interstitial fibrosis leading to left ventricular dysfunction and finally chronic heart failure.[15,17,68] The histopathological pictures are a courtesy of Karin Klingel, Department of Cardiopathology, University Hospital Tübingen (Tübingen, Germany).

Table 3. Prevalence of risk factors for anthracycline-related left ventricular dysfunction in patients with AML

AML cohort	Age group	Comorbidity	Prevalence, %
Danish National Leukemia Registry*[41]	Median age 59 y (range: 15-83 y)	Myocardial infarction	24.6
		Chronic heart failure†	12.5
		Peripheral vascular disease	21.9
		Moderate to severe renal disease†	19.2
MD Anderson Cancer Center (HCT-CI validation cohort)*[45]	>60 y	Cardiac disease (chronic heart failure, coronary artery disease, valvular dysfunction)	41.0
		Prior cerebrovascular accident	6.0
Comprehensive Cancer Center of Wake Forrest University*[44]	≥60 y	Cardiac disease†	12.5
		Renal disease†	15.3
Surveillance, Epidemiology, and End-Results Medicare linked database[45]	>65 y; mean age 77.26 y ± 6.96	Chronic heart failure‡	21.5
		Cerebrovascular disease‡	18.2
		Prior myocardial infarction‡	8.2

*Includes only patients preselected to receive intensive chemotherapy.
†As defined by Charlson Comorbidity Index (chronic heart failure defined by symptomatic dyspnea; chronic renal disease defined as creatinine >3 mg/dL).
‡Based on International Classification of Diseases-9- and Current Procedural Terminology-4 codes.

nuclear imaging, magnetic resonance imaging) and biomarkers (troponin, natriuretic peptides).[18]

Transthoracic echocardiography is a widely available and noninvasive modality to assess cardiac function. Although multiple-gated acquisition is also commonly used, it involves radiation exposure and is not able to assess atrial pressures, right ventricular, and valvular functions.[54] Cardiac magnetic resonance imaging (CMRI) can be used to assess cardiac function, especially when other noninvasive imaging is inconclusive. Although the availability of CMRI may be more limited in certain health care situations compared with other modalities, CMRI has been suggested to be more sensitive at detecting asymptomatic ARLVD than echocardiography in long-term follow-up[55] and very early changes after treatment.[56]

Serial monitoring of LVEF by repetitive transthoracic echocardiography is recommended before, during, and after anthracycline treatment to monitor for ARLVD without consensus for timing.[12,18,52,53] However, measuring only LVEF detects changes that may already be irreversible at the time of diagnosis. Advanced imaging techniques such as echocardiography-derived measures of global longitudinal strain and CMRI may detect early stages of cardiac dysfunction and predict future ARLVD.[57,58] For detailed recommendations on imaging, please refer to the joint American and European recommendations.[12]

Cardiac biomarkers are currently being investigated for their role in predicting ARLVD and to identify patients who could benefit from cardioprotective therapy.[59] Studies involving adults receiving high-dose chemotherapy have linked early increases in troponin to subsequent ARLVD.[60,61] However, in these trials, troponin was mostly determined weeks after prior anthracycline application, which was given over several treatment cycles. In AML, anthracyclines are usually given in a dose-dense manner (eg, days 1-3/3-5 of

Table 4. Response rates to "7+3"-like regimens according to molecular and cytogenetic risk groups in older adults

Source	Study population	CR 1, %	Long-term survival, %
Vasu et al, 2019[130]	944 pts with de novo AML >70 y, enrolled on intensive therapy CALGB/Alliance protocols without HSCT		At 10 y:
	CBF AML	~92	~17
	Cytogenetically normal AML	~68	~2.4
	Abnormal karyotype AML	~51	~1.1
Prebet et al, 2009[131]	CBF leukemia >60 y, received intensive induction therapy	88	At 5 y: 31
Eisfeld et al, 2018[132]	423 pts with de novo AML age 60-85 y having received intensive induction therapy without HSCT in CR		At 3 y:
	ELN 2017 favorable risk	82	30
	ELN 2017 intermediate risk	54	12
	ELN 2017 unfavorable risk	38	6
	NPM1mut + IDH2/SF1/SRSF2mut	NA	45
	FLT3-ITDmut/TP53mut/BCORmut/U2AF1mut/WT1mut/complex karyotype/t(9;11)	NA	4
Ostronoff et al, 2015[133]	Pts ≥55years with NPM1+ AML, received intensive induction therapy		At 2 y:
	55-65 y	67	39
	>65 y	53	19

CBF, core binding factor; CR 1, first complete remission; ELN 2017, European Leukemia Net risk stratification 2017; mut, mutated; NA, not addressed; pts, patients.

chemotherapy) and not over repetitive cycles of treatment. In addition, troponin may be elevated due to acute change in clinical status (eg, hyperleukocytosis,[62] pneumonia[63]) but still indicates the extent of related myocardial damage. Despite its promising role as predictive biomarker, there are currently not enough data to support a cardiac risk stratification in AML patients based on troponin measurements, and more research is warranted.

Preventive strategies

Several strategies have been investigated to minimize ARLVD as discussed in the following section.

Chelation therapy (eg, dexrazoxane)

Dexrazoxane is approved by the US Federal Drug Administration for prevention of cardiotoxicity in patients with breast cancer who have reached a CAD of 300 mg/m^2 and require additional doxorubicin.[64,65] In adult patients with AML, 3 case series on the use of dexrazoxane have been published to date (N = 15 patients).[66-68] All patients aged ≥60 years (N = 4) died of various reasons soon after treatment. Despite the lack of solid data on dexrazoxane use in older adults with AML, its cardioprotective properties and its safety profile in childhood leukemia are promising.[69] Dexrazoxane should be further evaluated in larger randomized trials of older individuals.

Prolonged anthracycline infusion time

High peak plasma levels of anthracyclines are associated with ARLVD. Prolonged infusion time reduces the peak plasma levels and was therefore investigated for its potential to reduce ARLVD.[70] A Cochrane meta-analysis compared an infusion duration of 6 hours or longer with a shorter duration of anthracycline doses equivalent to 30 to 60 mg/m^2 doxorubicin.[71] The risk of clinical HF was lower (risk ratio, 0.27; 95% confidence interval, 0.09-0.81).[71] Potentially, it decreases also asymptomatic LVEF decline.[71] Thus, a prolonged infusion time can be considered for individuals at risk.

Use of liposomal formulations

Liposomal formulations of anthracyclines have a prolonged plasma half-time and decreased distribution volumes compared with nonliposomal formulation.[72] This potentially reduces the likelihood of ARLVD.[72,73] There are currently pegylated and nonpegylated liposomal doxorubicin as well as liposomal daunorubicin and dual-drug liposomal formulation of cytarabine and daunorubicin (CPX-351).

A randomized phase 2 trial (GIMEMA GSI 103 AMLE) assessed the efficacy between liposomal daunorubicin (80 mg/m^2 on days 1-3) vs standard daunorubicin (45 mg/m^2 on days 1-3) in patients aged ≥60 years during AML induction.[74] There were no differences in complete remission (CR) rates, or ARLVD between the groups. Therefore, liposomal daunorubicin is not commonly used.

CPX-351 is approved by the US Federal Drug Administration for upfront treatment of patients with therapy-related AML, or AML with myelodysplasia-related changes.[75] It is a dual-drug liposomal formulation of cytarabine and daunorubicin delivered in a fixed 5:1 molar ratio. In vitro studies demonstrated that the maximal synergy is achieved by the fixed 5:1 concentration of cytarabine and daunorubicin. Furthermore, because cellular uptake of CPX-351 is mainly achieved via liposomes, P-glycoprotein–based efflux pumps are likely bypassed. The latter is a common cause of anthracycline-resistance and also occurs more often in older adult.[76] The initial phase 1 study[77] excluded patients with LVEF <50%. Among the 48 patients, 23 had both pre- and posttherapy LVEF data available; 12 patients received cumulative daunorubicin dose of >400 mg/m^2. Of those, symptomatic LVEF decline was noted in 2 patients. In the phase 3 study comparing CPX-351 with "7+3" regimen, no significant differences in ARLVD were noted between the 2 arms.[75] At this point in time, it is uncertain if CPX-351 has a lower risk of ARLVD, but we do not consider CPX-351 as less cardiotoxic so far.

Alternative daunorubicin dosing

Although it is possible that a lower CAD may be sufficient to cause ARLVD, the optimal anthracycline dose for induction therapy is still a matter of debate.[3,4,29] Interestingly, a dose reduction of doxorubicin and cyclophosphamide within the rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone regimen in adults ≥80 years with aggressive lymphoma showed a similar efficacy in comparison with the full dose in younger patients.[78] This raises the question whether the effective dose of anthracycline is different in older adults because of changes in body composition and whether the standard dose of daunorubicin (60-90 mg/m^2) is needed to achieve an equivalent efficacy.

Three trials have assessed the efficacy of different daunorubicin dosing comparing daunorubicin 35 mg/m^2 with 50 mg/m^2,[79] 60 mg/m^2 to 90 mg/m^2,[80] and 45 mg/m^2 to 90 mg/m^2,[81] without any significant impact on outcome. None of these trials included patients with a reduced LVEF, or monitored LVEF longitudinally. Therefore, an impact on subclinical and long-term cardiac function could not be specified.

Based on these studies, it appears that a lower dose of anthracycline may be as effective as standard dosing in older patients with AML. Although these studies generally excluded patients with cardiac risk factors, it may be worth considering a lower dose of anthracycline in older patients with AML, particularly those with cardiac risk factors, although this remains an individual decision.

HF medication as preventive and early therapeutic strategy

Angiotensin-converting enzyme inhibitors (ACE-Is) and β-blockers are frequently used for management of LVEF decline and HF, and have been shown to reduce mortality in older adults with HF.[82-87] ACE-Is have also been shown to delay the progression of left ventricular dysfunctions, including ARLVD.[88]

Table 5 summarizes various clinical studies evaluating primary and secondary preventive strategies using β-blockers and/or ACE-Is for ARLVD. The results are heterogeneous and are likely the result of different study populations and CAD. Only 1 study (Prevention of Left Ventricular Dysfunction with Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies trial[31]) evaluated a primary preventive strategy in a larger group of patients with acute leukemia (among other cancer types). Compared with the patients with AML in the control arm who had a significant absolute decrease in LVEF of 6.4%, patients in the treatment arm who received enalapril and carvedilol had preserved LVEF. Patients with preexisting LVEF <50% were excluded from the study. In addition, the CAD was low (mean CAD <300 mg/m^2). Although the difference

Table 5. Overview of clinical trials that assess the efficacy of an ACE-I and/or a β-blocker for primary and secondary prevention of anthracycline-related left ventricular dysfunction

Study	Trial population	Intervention	Endpoints of interest	Outcome	Findings
Primary preventive strategies and biomarker-triggered primary prevention					
Bosch et al, 2013[31] OVERCOME Trial	Acute leukemia, autologous HSCT; mean age 50 ± 13 y, LVEF >50% prechemotherapy	Enalapril and carvedilol vs no preventive medication (control group)	Death, HF, or a final LVEF decline to <45%	Death and HF 6.7% (enalapril/carvedilol group) vs 22.2% (control group), $P = .02$; prespecified subgroup analysis in leukemia pts: no LVEF change in enalapril/carvedilol group, 6.7% absolute decrease in control group ($P = .025$)	Subgroup analysis of leukemia pts included
Georgakopoulos et al, 2010[134]	Hodgkin lymphoma and NHL; mean age 49 y; ACC	Metoprolol vs enalapril vs no preventive medication	LVEF decline	Enalapril and metoprolol did not affect the probability of developing heart failure	Exclusively lymphoma pts
Kalay et al, 2006[135]	Mainly BC and lymphoma patients, mean age 46.8 ± 14 y (carvedilol group) and 49.0 ± 9.8 y (control group); ACC	Carvedilol vs no preventive medication	LVEF decline	Significantly lower LVEF and higher incidence of systolic dysfunction in control group	Small patient numbers (25+25 pts). No AML pts included as explicitly stated
Kaya et, 2013[136]	BC; mean age 51.4 ± 9.4 y (nebivolol group) and 50.5 ± 11.1 y (control group); ACC	Nebivolol vs no preventive medication	LVEF decline, NT-proBNP increase	LVESD/LVEDD increase and LVEF decline in control group, increase of NT-proBNP; no significant changes in nebivolol group	Small patient numbers (45 pts). No AML included
Gulati et al, 2017[137] PRADA Trial	BC; mean age not specified (mostly <60 y); ACC	Metoprolol vs candesartan vs metoprolol and candesartan vs placebo	LVEF decline, increase in cardiac biomarkers	Metoprolol attenuates troponin rise; no effect for candesartan; significant LVEF decline in placebo group	Exclusively BC pts
Cardinale et al, 2018[92] ICOS-ONE Trial	Various cancers; mean age 51 ± 12 y; ACC	Enalapril preventive or triggered by troponin-rise	Troponin rise; LVEF decline	No attenuation of troponin rise with enalapril; LVEF decline negligible in both arms	ACC with low cumulative doses ± trastuzumab and/or taxane, few acute leukemia pts included
Cardinale et al, 2006[91]	Various cancers; inclusion after early TnI rise; mean age 47 ± 11 y (enalapril) and 47 ± 13 y (control), various chemotherapy schemes and partially ACC	Enalapril vs no preventive medication (control group)	LVEF decline ≥10% of baseline below 50%	LVEF decline >10% in 0% (enalapril group) vs 43% (control group)	Few leukemia pts included
Secondary preventive/therapeutic strategies					
Cardinale et al, 2015[10]	Mainly BC and NHL, inclusion after drop of LVEF >10%; mean age 50 ± 13 y, ACC	Enalapril ± β blockers started after LVEF drop	LVEF recovery	82% recovered from ARC	No randomization for HF therapy; no AML pts included as explicitly stated
Cardinale et al, 2010[93]	Various cancers; inclusion after LVEF drop to ≤45% (asymptomatic and symptomatic); mean age 53 ± 12 y; ACC	Enalapril ± carvedilol	LVEF recovery	42% responders (normalization of LVEF in 42% and partial recovery in 13%). 0% recovery if HF therapy started >6 mo after ACC, frequent adverse cardiac events in nonresponders	No AML pts included
Silber et al, 2004[138] AAA Trial	Pediatric cancer long-term survivors; LVEF drop several years after ACC	Enalapril vs placebo	Exercise tolerance, LVESWS, LVEF recovery	No change in exercise tolerance or LVEF LVESWS significantly reduced within the first treatment year	Late start of HF therapy

ACC, anthracycline-containing chemotherapy; ARC, anthracycline-related cardiotoxicity; BC, breast cancer; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end diastolic diameter; LVESWS, left ventricular end-systolic wall stress; NHL, non-Hodgkin lymphoma; TnI, troponin I.

between the 2 groups was significant, only a small number of patients had their LVEF drop below 50%; most of the patients technically did not fulfill the criteria of ARLVD despite the statistically significant LVEF drop. Remarkably, in the intention-to-treat analysis, the combined endpoint of death, HF, or LVEF <45% occurred in 24.4% in the control group vs 6.7% in the intervention group.[31]

Interestingly, more patients in the control group died of infection compared with the treatment group. Furthermore, those who had sepsis and survived had a significant reduction in their LVEF. Based on these findings, the authors speculated that the use of ACE-Is as primary prevention may influence outcomes of patients who experience infections.[31] This may be related to the inhibition of the renin-angiotensin-aldosterone system that, when activated, promotes inflammation and endothelial damage during sepsis.[89] Prior study has demonstrated that prehospital ACE-Is in the general population may improve outcome in patients with septic shock.[90]

In addition to the primary preventive strategy, biomarker-triggered strategies such as initiating enalapril after detection of increased

Table 6. Overview of clinical trials that assess anthracycline-free induction strategies

Study	Trial population	Intervention	Trial design	Outcome
Vulaj et al, 2018 [97] FOSSIL Study	Secondary AML, mean age 63 y (range, 27-82) in the FLAG group (N = 40), 60 y (range, 21-76) in the 7+3 group (N = 66); no data on LVEF provided	7+3 vs FLAG	Retrospective single-center analysis	Higher RR in the FLAG group vs 7+3 (70% vs 48%, $P = .043$), no significant difference in OS (8.5 vs 9.1 mo; $P = .798$), shorter duration of neutropenia in the FLAG group (16 vs 23 d, $P < .001$)
Bashey et al, 2006 [96]	AML, aged >60 y; no previous therapy (N = 24), no data on LVEF provided	FLAG	Retrospective single-center analysis	CR rate 58%, 17% CRI
Brunnberg et al, 2012[98]	AML, ≥60 y; previously untreated (N = 119), exclusion of patients with HF NYHA III-IV	"7+3" vs "7+GO"	Randomized phase 2 trial	Both regimens were equally effective in blast clearance, CR, EFS, remission duration, and OS. Higher induction death rate from veno-occlusive disease in the "7+GO" group. No cardiac toxicities in both groups were observed
Kessler et al, 2008[99]	AML ≥60 y; TAA (N = 16) vs TAD/HAM (N = 16)	TAD/HAM vs TAA in the setting of HF (NYHA III-IV or LVEF <40%)	Single-center, matched-pair analysis	No significant difference in RR, RFS, and OS
Borthakur et al, 2008[100]	CBF-AML (age range 16-83 y)	FLAG vs FA vs IA ± G	Retrospective single-center analysis	No significant difference in RFS and OS between the groups

CBF-AML, core binding factor AML; CRI, complete remission with incomplete count recovery; EFS, event-free survival; FLAG, fludarabine 30 mg/m^2 per day on days 1-5, cytarabine 2 g/m^2 per day on days 1-5, filgrastim 300-480 μg/d on day 1-count recovery; HAM, cytarabine 1 g/m^2 every 12 hours on days 1-3, mitoxantrone 10 mg/m^2 on days 3-5; IA ± filgrastim, idarubicin 12 mg/m^2 on days 1-3, cytarabine 1.5 g/m^2 per day p.c. on days 1-4 (1-3 if age >65 years), ± filgrastim 5 μg/kg on days −1 to 5; NYHA, New York Heart Association, 7+GO, standard cytarabine 100 mg/m^2 per day days 1-7, gemtuzumab-ozogamicin 6 mg/m^2 on day 1, 4 mg on day 8; RFS, relapse-free survival; RR, response rate; TAA, 6-thioguanine 200 mg/m^2 on days 3-9, cytarabine 100 mg/m^{2}per 24 hours every 12 hours on days 1-2, and 100 mg/m^2 on days 3-8, Amsacrine 210 mg/m^2 on days 3-5; TAD, 6-thioguanine 200 mg/m^2 on days 3-9, cytarabine 100 mg/m^2 per 24 hours on days 1-2 or 100 mg/m^2, every 12 hours on days 3-8, and daunorubicin 60 mg/m^2 on days 3-5.

troponin levels have also been found to be effective in a randomized controlled trial in different cancer entities.[91,92] Nonetheless, it is unclear when and how frequent troponin should be measured, given that elevated troponin may be not anthracycline-related in the acute setting.

None of the aforementioned studies included patients aged >70 years and those aged 60 to 70 years were underrepresented.[10,31,92,93] Therefore, there is low-certainty evidence for benefit in the older population. However, ACE-Is are generally well tolerated in older adults,[94] with usual consideration given to the risk of adverse reaction (eg, hyperkalemia) in the presence of comorbidities (eg, renal insufficiency). Given the evidence for use of ACE-Is, this may be considered with or without the use of a β-blocker as a therapy for use during receipt of anthracyclines when early left ventricular dysfunction occurs.

Non-anthracycline induction and treatment strategies

Considerable numbers of older patients with AML present with already declined LVEF or cardiac comorbidity rendering the use of anthracycline containing chemotherapy regimens hazardous. Other than preventive strategies for ARLVD, several efforts have been used to avoid anthracycline use. Here, we discuss alternative treatment strategies.

No randomized data are available that compare non-anthracycline induction strategies in the presence of impaired LVEF. However, expert opinion suggests that non-anthracycline induction strategies should be considered where there is concern for tolerability of anthracycline-containing induction therapy.[95] Several anthracycline-free intensive induction regimens have shown similar efficacy in comparison with "7+3" regimen, although only a minority was tested in randomized trials.[96-100] These options are listed in Table 6.

Other non-anthracycline strategies include treatments such as hypomethylating agents (HMA [eg, decitabine, 5-azacytidine], BCL-2 inhibitors [eg, venetoclax], FLT3 or IDH inhibitors). A randomized controlled study suggests similar survival rates using HMA compared with intensive induction therapy.[101] Furthermore, certain high-risk subgroups may benefit from HMA such as those with *TP53* mutations, or complex karyotypes.[102-104] A head-to-head comparison between decitabine and "3+7" as the preferred induction strategy for older patients is currently being tested in the InDACtion trial.[105]

The BCL-2 inhibitor venetoclax in combination with HMA[106] or low-dose cytarabine[107] has shown promising results. The phase 1b study[106] that evaluated HMA and venetoclax demonstrated a CR and complete remission with incomplete recovery rate of 73% with an overall response rate of 73% (comprising CR, incomplete recovery, and partial remission).[106]

Targeted therapeutics, such as FLT3 or IDH inhibitors, represent another promising strategy for this patient group, also in novel combinations with HMAs. The FLT3 inhibitor sorafenib showed favorable risk ratios in combination with azacytidine in AML patients aged 61 to 86 years.[108] Of note, although sorafenib harbors a known risk for LVEF decline and adverse cardiovascular events,[18] none of the landmark trials for sorafenib use in AML, including those in older adults, showed a significantly increase of these adverse events. Nonetheless, the small sample sizes in these studies limited our ability to draw definite conclusions.[108-111]

IDH inhibitors (ivosidenib and enasidenib) carry the risks of QTc prolongation without any other known cardiotoxicity.[112,113] These agents are being explored in the upfront setting. They could be potential upfront therapeutic options for patients with IDH mutations with cardiac risk factors that preclude the use of anthracycline-based regimens.

These combination strategies will likely replace single-agent therapy alone and appear to be reasonable options for patients not candidates for anthracycline-containing induction therapy, also as a possible bridging strategy to HSCT.[106,114]

Table 7. Recommendations for assessment, alternative strategies, and management of anthracycline-related left ventricular dysfunction in older adults with AML

Baseline assessment
• Assess for preexisting cardiac comorbidities, risk factors for anthracycline-related left ventricular dysfunction, and frailty before therapy.
• Further assessment of clinical signs of HF and cardiac echocardiography should be performed before, during, and after therapy to evaluate for LVEF and if available, global longitudinal strain.
Prevention
• If anthracycline can be administered safely with a prolonged infusion time, this should be considered, especially in patients with preexisting risk factors for anthracycline-related left ventricular dysfunction besides age, or a HF with mid-range reduced ejection fraction.
Choice of induction regimens according to disease biology and risk factors for anthracycline-related left ventricular dysfunction
• In patients with chemotherapy-sensitive leukemia (eg, core-binding factor leukemia, or NPM1-mutated AML), a mild decrease in LVEF should not abrogate a curative approach and standard "7+3" regimen should be considered with the previously mentioned preventive strategy. Other options include reducing daunorubicin dose to 45 mg/m^2 or use alternative intensive induction strategies (eg, anthracycline-free, high-dose cytarabine-based regimens).
• In patients with chemotherapy-resistant disease (eg, TP53 mutations, complex cytogenetic aberrations, RUNX1 mutations), alternative therapies instead of anthracycline-containing induction therapy should be considered.
• Patients with LVEF decline before and after anthracycline-containing therapy should not be excluded from receiving allogeneic HSCT if the patient is otherwise regarded as fit. Induction therapy in patients with preexisting LVEF decline should be guided by the molecular subtype of AML and can comprise of nonintensive strategies (eg, hypomethylating agent ± venetoclax) depending on the local availability and reimbursement of these therapies.
Follow-up assessment
• Patients who have received anthracycline-containing chemotherapy should have close monitoring of cardiac function, preferably by a cardiologist with experience in managing anthracycline-related left ventricular dysfunction.
• Patients should receive longitudinal echocardiograms and clinical reviews for the control of cardiovascular risk factors.
Integration of cardiology
• Comanagement with a cardio-oncologist or a cardiologist with experience in managing anthracycline-related left ventricular dysfunction is strongly encouraged at all stages of therapy and surveillance.
Considerations for non-anthracycline-based regimens
• High probability of induction failure due to AML biology (eg, TP53 mutation, complex cytogenetic aberrations).
• Favorable-risk AML and symptomatic heart failure with reduced ejection fraction (LVEF <40%).

Who is not suitable for intensive therapy containing an anthracycline?

A baseline LVEF ≤50% is most commonly used as an exclusion criterion in clinical trials containing an anthracycline.[81,115] Outside clinical trials, this threshold might differ depending on the center and physician's preferences. Often, there is a concern that anthracycline use in patients with mild LVEF decline could lead to acute HF. However, an asymptomatic HF with mid-range reduced ejection fraction (LVEF, 40% to 49%) should not abrogate a curative approach if the patient is otherwise regarded as fit for intensive therapy and the cardiac comorbidity is well-controlled.[95] This is especially true for patients with a favorable-risk AML such as those with NPM1 mutations or CBF aberrations. If a curative approach includes an HSCT, a history of cardiac comorbidity increases the risk of nonrelapse mortality as predicted by the surrogate assessment tool HCT-CI.[47,116] HSCT in patients with decreased LVEF in the range of HF–mid-range reduced ejection fraction is probably feasible.[117-119] Therefore, patients who are not eligible for anthracycline-based chemotherapy may still be able to receive HSCT. A patient judged as "unfit for anthracycline and fit for HSCT" could benefit from an alternative induction strategy, as described previously. Nonetheless, this remains an individualized decision, taking account into patient preference and goals. In patients who are less likely to respond to anthracycline-containing therapy, such as patients with TP53 mutation, we encourage consideration of non-anthracycline-containing therapy as the potential risk for ARLVD exceeds the potential benefit.

Management of ARLVD during or after treatment

Emerging studies have suggested the role for advanced imaging techniques and biomarkers in early detection of ARLVD. However, there is a lack of consensus on their application in routine cardiac surveillance. Large, prospective, multi-institutional studies are needed to determine whether these imaging techniques and biomarkers allow an improved early detection of ARLVD, predict cardiovascular and OS, and inform early intervention strategies to reduce cardiovascular morbidity.[120] Most patients develop ARLVD within the first year after therapy,[10,29] and the recovery rate decreases rigorously after 6 months.[10] Therefore, close cardiac monitoring is important. In case of ARLVD, the standard therapy for HF including ACE-Is, β-blocker, and eventually mineralocorticoid receptor antagonist should be started promptly.[93] In case of ongoing therapy, a rigorous fluid management should be provided together with a close cardiac monitoring. Because a substantial number of patients develop ARLVD after completion of therapy, we recommend a continued comanagement with a cardiologist to optimize the cardiovascular risk profile.

Conclusions

In conclusion, older adults with AML are at risk of experiencing ARLVD. Based on our review, we summarized our recommendations in Table 7. There is high-certainty evidence to support the need to consider lifetime CAD and for serial monitoring for ARLVD. Several preventive strategies have been evaluated including alternative dosing, use of cardioprotective medications, liposomal formulation, and alternative induction strategies. More high-quality randomized controlled trials are required to elucidate the effectiveness of strategies in the prevention and treatment of ARLVD in older adults with AML.

Acknowledgments

The authors gratefully thank Karin Klingel, Department of Cardiopathology, University Hospital Tübingen (Tübingen, Germany), for providing histopathological pictures of anthracycline-related cardiomyopathy.

This work was supported by a research scholarship from the University of Heidelberg (N.R.N.), the Wilmot Research Fellowship Award (K.P.L.), a National Health and Medical Research Council Postgraduate Scholarship (APP10774676) (W.-K.S.), and Eastern Health Clinical School Scholarship (W.-K.S.).

Authorship

Contribution: N.R.N., K.P.L., A.S.M., K.C., W.-K.S., B.B., and C.O.A. wrote the manuscript; and H.D.K. and W.G.H. supervised the work and edited the manuscript.

Conflict-of-interest disclosure: N.R.N. has received honoraria and travel support from Janssen-Cilag, Medac, and Jazz Pharmaceutical. A.S.M. served on the scientific advisory boards of Agios, Astellas,

Abbvie, and Jazz Pharmaceuticals. The remaining authors declare no competing financial interests.

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