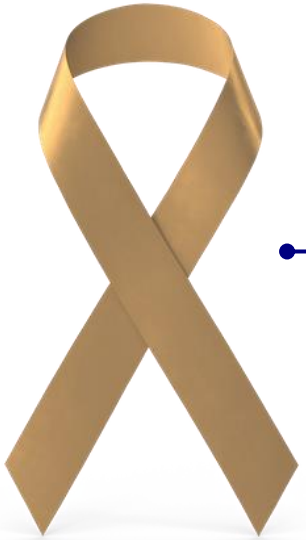
Real-World Data in Prevention of Cardiotoxicity in Childhood Sarcoma

Bridging Evidence to Clinical Practice

Focus on Dexrazoxane in Prevention of Childhood Cardiotoxicity in Sarcoma



Mohammad Faranoush
Professor of Pediatric Hematology Oncology
Iran university of Medical Sciences

Overview/Agenda

- Introduction & Burden of Cardiotoxicity
- Common Cardiotoxic Treatments in Sarcoma
- Primary Prevention Strategies
- Real-World Evidence on Prevention
- Risk Prediction & Stratification
- Clinical Implications & Future Directions
- Conclusion

Introduction
The Challenge of Cardiotoxicity

- Approximately 400,000 children and adolescents (aged 0-19 years)develop cancer annually
- Childhood sarcoma survivors:
- >80% 5-year survival rate
- Growing population:
- 150,000 -160,000 childhood cancer survivors in the world per years
- >500,000 childhood cancer survivors in US
- >20,000 childhood cancer survivors in Iran
- **High risk group: Sarcoma patients due to anthracyclines & radiation**
- **Spectrum of cardiotoxicity:**
- ***Cardiomyopathy, heart failure***
- ***Coronary artery disease, valvular disease***
- ***Arrhythmias, pericardial disease***
- Need for lifelong surveillance

Background

- Anthracyclines (e.g., doxorubicin) are central in sarcoma therapy
- Cardiotoxicity is dose-dependent, cumulative
- Dexrazoxane: iron-chelator & topoisomerase IIβ inhibitor
- Pediatric survivors: 25% subclinical, 5–10% clinical HF
- Lifelong cardiac risk → need for primary prevention

Background

- Aim: reduce risk of heart failure without compromising efficacy
- Context: High-dose anthracycline therapy (e.g., doxorubicin 450–600 mg/m²) is standard in treating pediatric osteosarcoma and Ewing sarcoma.
- Issue: Cardiotoxicity remains a significant concern, with potential for both acute and long-term cardiac complications.
- Objective: Evaluate the role of dexrazoxane in mitigating these risks based on real-world data

Cardiotoxic Treatments in Sarcoma

- **Anthracyclines**
- Mechanism: ROS generation, topoisomerase 2β disruption
- Dose-dependent: Risk ↑ significantly >300 mg/m²
- No safe dose: Subclinical abnormalities even <100 mg/m²
- Agents: Doxorubicin, Daunorubicin, Epirubicin

- **Radiation Therapy**
- Mechanisms: Endothelial damage, fibrosis, atherosclerosis
- Dose-response: No safe threshold (risk even at 5 Gy)
- Modern techniques: Conformal RT, proton therapy reduce exposure

Cardiotoxic Treatments in Sarcoma

Novel/Targeted Therapies

Therapy Class	Agents	Cardiovascular Effects
TKI	Pazopanib , Imatinib	Hypertension , Arrhythmias , HF
Immune Checkpoint Inhibitors	Atezolizumab	Myocarditis, arrhythmias
mTOR inhibitors	Temsirolimus	Hypertension, pericardial effusion

Primary Prevention Strategies

- **Dexrazoxane**
- Mechanism: Iron chelation, reduces oxidative stress
- Evidence: Significantly reduces cardiotoxicity
- Recommendation: For high cumulative anthracycline doses (>250 mg/m²)

- **Radiation Techniques**
- Conformal radiotherapy
- Proton beam therapy
- Intensity-modulated RT (IMRT)
- Deep inspiration breath-hold

Primary Prevention Strategies

- Treatment Modification & Surveillance
- Limit cumulative anthracycline doses
- Use continuous infusion (limited evidence in children)
- COG guidelines: Regular cardiac monitoring (echocardiography)
- Risk-adapted approaches

Standard Dosing

- Typical ratio: 10:1 dexrazoxane to doxorubicin
- Example: 30 mg/m² doxorubicin → 300 mg/m² dexrazoxane
- Route: Intravenous only
- Maximum dose: ~1000 mg/m² per dose (institution dependent)
- Infusion: 15–30 minutes
- Timing: Administer dexrazoxane 15–30 min before doxorubicin

Practical Notes

- Do not mix dexrazoxane and doxorubicin in the same line
- Central line preferred for infusion
- Monitor: CBC, renal function, cardiac function (echo/strain)
- Can potentiate myelosuppression
- Shown not to compromise tumor efficacy in pediatric sarcoma trials

Key Pediatric Evidence

- Lipshultz SE et al., JCO 2021: Osteosarcoma, up to 600 mg/m² doxorubicin with dexrazoxane
- Chow EJ et al., JACC 2020: Dexrazoxane mitigates LV remodeling in sarcoma
- Armenian SH et al., Lancet Oncol 2022: Guidelines recommend use ≥250 mg/m²
- EMA, Cardioxane® product info 2023: Confirms 10:1 ratio

Real-World Evidence
COG Osteosarcoma Cohort

- Study: Children’s Oncology Group (COG) study involving 315 patients.
- Findings: Dexrazoxane administration resulted in preserved left ventricular ejection fraction (LVEF) and no clinical heart failure.
- Outcome: No increase in second malignant neoplasms (SMNs) observed.
- Schwartz et al., 2015

Retrospective Cohort Analysis

- Study: Retrospective analysis of 85 pediatric sarcoma patients.
- Findings: Dexrazoxane use was associated with reduced left ventricular strain decline and better preservation of LVEF over 1–2 years Kopp et al., 2019

Institutional Comparison
MD Anderson

- Study: Comparison between bolus doxorubicin with dexrazoxane and prolonged infusion doxorubicin without dexrazoxane.
- Findings: Higher cumulative anthracycline doses were tolerated in the dexrazoxane group, with better preservation of LVEF.
  Huh et al., 2010

Single-Center Retrospective Cohort

- Ewing + Osteosarcoma, n≈63
- Dexrazoxane group received higher cumulative doxorubicin doses
- Better preserved LVEF (higher nadir)
- One CHF death occurred in non-dexrazoxane group

  Asselin BL et al., 2023

Retrospective Sarcoma Cohort (n=85)

- Serial echocardiography before, early, and 1–2 yrs post-therapy
- Dexrazoxane mitigated LV remodeling
- Protective effect most evident in girls
  Chow EJ et al., 2020; van Dalen EC et al., 2019

Children's Oncology Group Osteosarcoma Trials

- Doxorubicin 375–600 mg/m² + dexrazoxane
- No clinical HF observed
- Subtle LV structural changes persisted (esp. in girls)
- No increase in second malignancies
  Lipshultz SE et al., JCO 2021; Shaikh F et al., 2022

Safety Profile

- Adverse Effects: Mild infusion-related reactions and hematologic effects.
- Long-Term Risks: No significant increase in second malignancies or impact on overall survival.
  Baat et al., 2022

Gender-Specific Considerations

- Observations: Females may experience more pronounced left ventricular remodeling.
- Implication: Dexrazoxane may offer more significant cardioprotection in female patients.

  Narayan et al., 2019

Long-Term Survivorship Data

- Adults >10 years post anthracycline+dexrazoxane
- Preserved LVEF and GLS
- Supports sustained cardioprotection

  Blanco JG et al., 2021

Guidelines & Health Economics

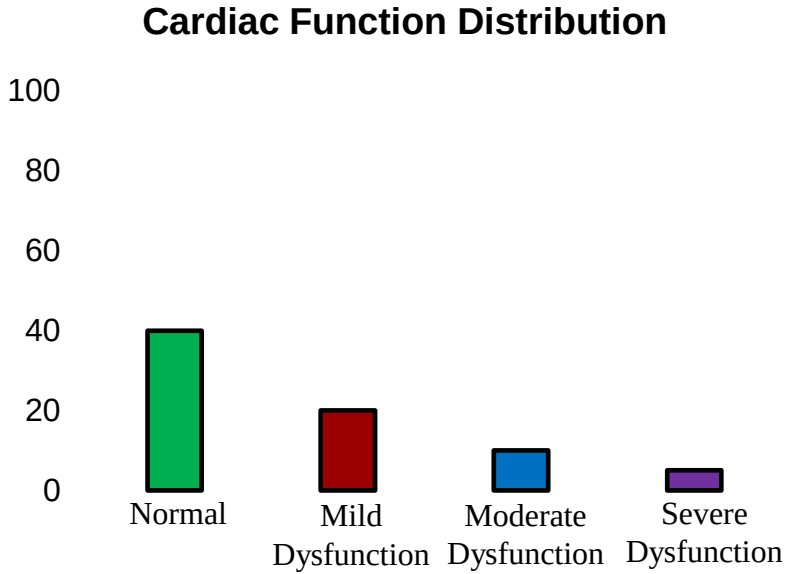
- International panel (2022): recommend dexrazoxane when cumulative dose ≥250 mg/m²
- Cost-effective for pediatric sarcoma/hematologic cancers (European model) Armenian SH et al., Lancet Oncol 2022; Lyu H et al., 2023

Dexrazoxane Cardioprotection Simulation

How can we protect children's hearts from life-saving chemotherapy without increasing their risk of developing second cancers?

Heart Function Visualization

LV Ejection Fraction : **46%**



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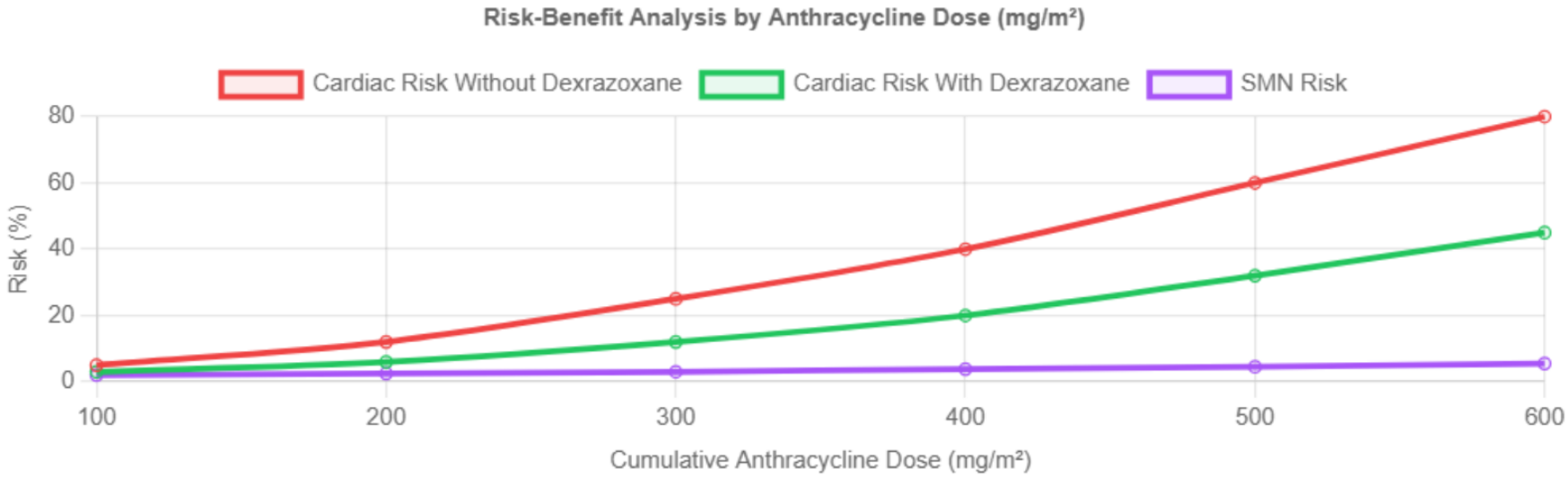
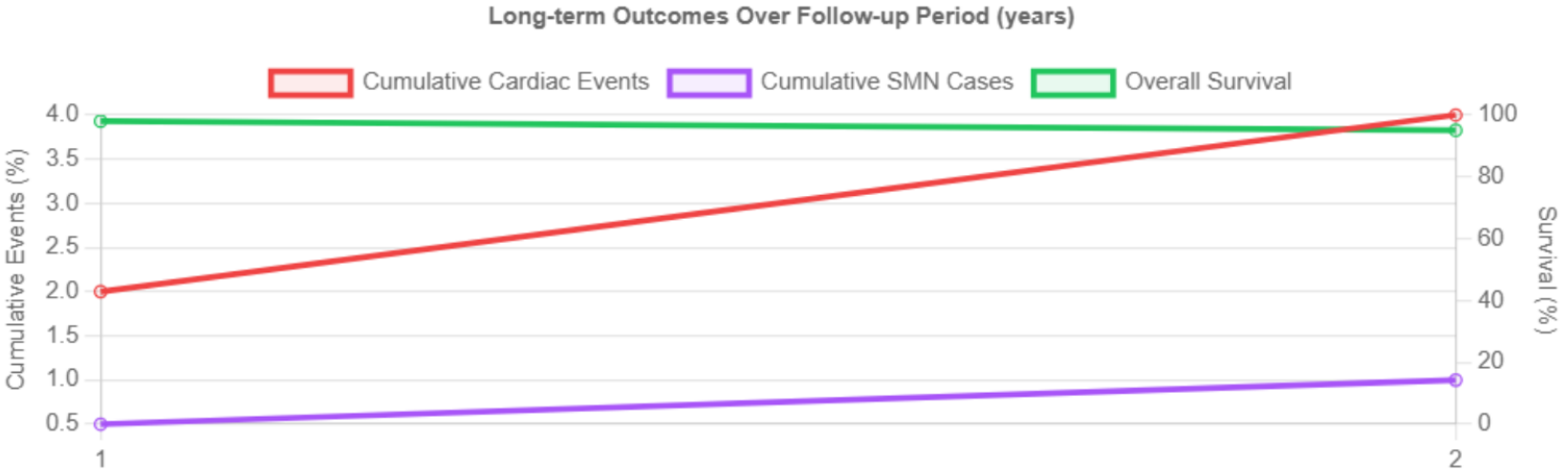
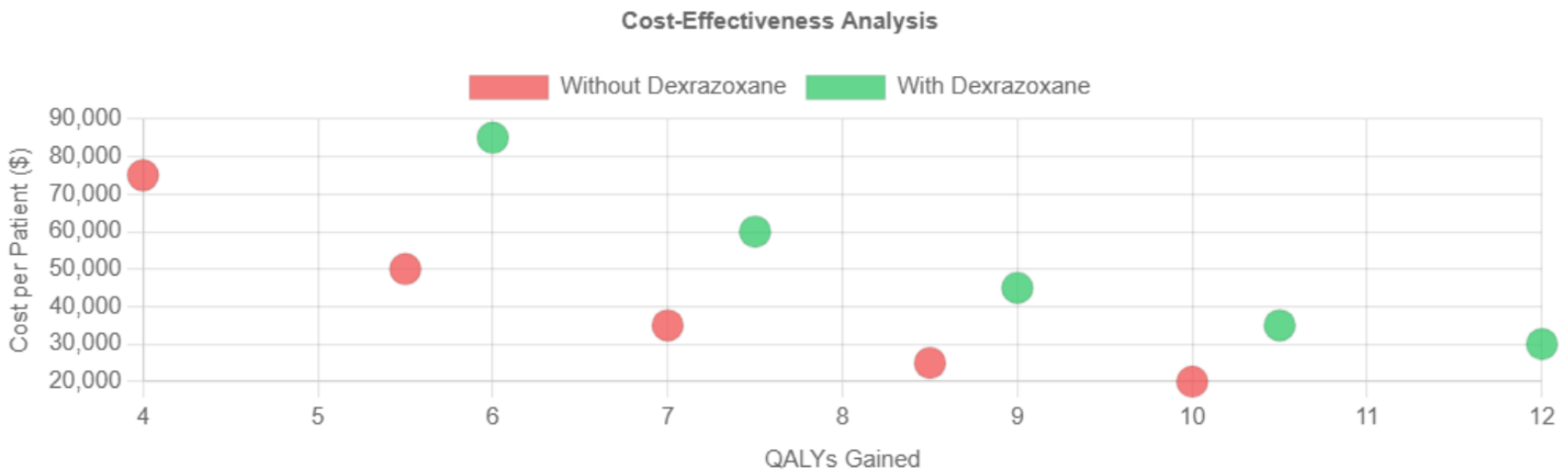


This chart shows the trade-off between cardiac protection and SMN risk at different anthracycline doses.



Long-term outcomes over the follow-up period, showing cumulative risks and benefits.



Cost-effectiveness analysis showing the relationship between costs and quality-adjusted life years.

Evidence Summary

- Schwartz et al., COG report (2016)
- Osteosarcoma cohort with dexrazoxane showed reduced LV dysfunction and allowed higher cumulative doses without clinical heart failure. No increase in SMN vs historical controls.

- Chow et al., 2021/2022
- Mixed pediatric cancers with dexrazoxane showed cardioprotective effects at ≥5 years follow-up with preserved LVEF/GLS. No adverse impact on second cancer risk or overall survival.

- Dewilde et al., Cost-effectiveness 2020
- Model predicts reduced cardiotoxicity and improved QALYs with dexrazoxane. Cost-effective even with SMN uncertainty.

Comparison pf Cohorts : Anthracycline Dose , Cardiac Outcomes , and SMN Indcidence (Dexaroxane)

Study (ref)	Cancer Type / Cohort	Dexrazoxane use	Cumulative Anthracycline Dose	Cardiac Outcome (summary)	SMN incidence (summary)
Schwartz et al., COG report (2016). cite turn0search7	Osteosarcoma (COG multi-center)	Dexrazoxane used with intensified chemo	Doxorubicin up to ~375–600 mg/m² in intensification	Reduced LV dysfunction; allowed higher cumulative doses without clinical HF	No increase in SMN vs historical controls. cite turn0search7
Kopp et al., 2019 (CardioOncology). cite turn0search10	Osteosarcoma (single/multi cohorts)	Dexrazoxane used	High cumulative doses (varied by protocol)	Prevention of LV dysfunction; subtle LV structural changes persist (esp. girls)	No increased SMN signal in cohorts analyzed. cite turn0search10
Chow et al., 2021/2022 (Late outcomes). cite turn0search6 turn0search23	Mixed pediatric cancers (trial cohorts)	Dexrazoxane-containing trials	Varied (trial-based doses)	Cardioprotective effect observed at ≥5 years follow-up; preserved LVEF/GLS	No adverse impact on second cancer risk or overall survival. cite turn0search6 turn0search23
Lipshultz et al., (2010, commentary 2023). cite turn0search4 turn0search8	High-risk ALL and other pediatric cancers	Dexrazoxane used in trial settings	Cumulative doses variable; cardioprotection seen even at higher doses	Long-term cardioprotection; greater effect observed in girls	No clear increase in SMN in long-term follow-up. cite turn0search4
Shaikh et al., JNCI 2016 (pooled analysis). cite turn0search14	Mixed pediatric cohorts (meta-analyses included)	Included studies with/without dexrazoxane	Varied across studies	Dexrazoxane protective for LV dysfunction; effect sizes vary	Reported a statistically borderline increase in SMN in pooled analysis (interpret cautiously). cite turn0search14

Real-World Evidence Effectiveness

- **Dexrazoxane**
- Systematic review: Reduces subclinical cardiac dysfunction
- Prevalence of systolic dysfunction: 0.0% to 56.4% (variable definitions)
- **Cumulative Burden**
- CCSS data: 18.7% cumulative incidence of CVD at 30 years

- **Advanced Radiation Techniques**
- Real-world data: ↓ cardiovascular complications in modern era

Real-World Evidence Monitoring Adherence

- Gaps in Care
- 40% of survivors: No cardiac testing within 5.25 years post-therapy
- Young adults (18-28 years): Less likely to receive monitoring (HR=0.42)
- Disparities: By cancer type, treatment, and region
- Factors Influencing Adherence

Factor	Category	Hazard Ratio (95% CI)
Age Groups	Young Adults	0.42(0.35-0.49)
Cancer Type	Bone/ Soft tissue	1.64 (1.30-2.07)
Treatment	HSCT Recipients	2.23 (1.63-3.03)

Risk Prediction & Stratification

- Clinical & Treatment Factors
- Anthracycline dose ≥250 mg/m²: HR = 2.31 (2.09-2.55)
- Chest radiation ≥20 Gy: HR = 1.84 (1.66-2.05)
- Demographics: Older age, male sex, African-American ancestry
- Comorbidities: Obesity, Hypertension, Diabetes

Genetic Susceptibility

- Polymorphisms: CBR1, CBR3 (drug metabolism); HFE (iron); SOD2 (antioxidant)
- Biomarkers: Troponin, natriuretic peptides (early detection)

Clinical Implications Recommendations

- Use dexrazoxane for high-risk patients (e.g., >250 mg/m² anthracycline)
- Employ heart-sparing radiation techniques
- Adhere to COG monitoring guidelines with risk-adapted frequency
- Manage modifiable risk factors (hypertension, dyslipidemia, obesity)
- Facilitate care transitions (pediatric to adult)
- Implement risk-stratified approaches: Using prediction models
- Monitoring: Regular echocardiographic assessments, including LVEF and strain imaging, during and post-treatmen

Future Directions & Research Priorities

- Long-term outcomes of novel therapies (TKIs, ICIs)
- Genotype-guided prevention (prospective validation)
- Pediatric-specific interventions (heart failure medications)
- Interventional trials (preventive pharmacotherapy, lifestyle)
- Standardized definitions for cardiotoxicity in children
- Leverage data initiatives (e.g., Childhood Cancer Data Initiative)

Summary

- Real-world cohorts support dexrazoxane as effective cardioprotection in pediatric sarcoma
- Preserves EF, reduces severe HF events
- No clear increase in second cancers
- Subtle structural changes can persist, esp. in girls
- Widely recommended in guidelines at higher anthracycline doses

Summary

- Standard dose: 10:1 ratio to doxorubicin
- Give IV, 15–30 min before anthracycline
- Use when cumulative dose ≥250 mg/m² (per guidelines)
- Strong evidence for cardioprotection, no increase in second cancers

Discussion & Questions

- Cardiotoxicity remains a significant cause of morbidity/mortality in childhood sarcoma survivors
- Dexrazoxane and advanced radiation techniques are effective prevention strategies
- Real-world data reveals gaps in monitoring adherence, especially during care transitions
- Risk prediction models enable personalized prevention and surveillance
- Future work should focus on pediatric-specific interventions and long-term outcomes of novel therapies

Thanks

Discussion & Questions

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Payk Daru Tosseh Co.
(P.J.S)