Role of NT-proBNP in Late-onset Anthracycline-induced Cardiotoxicity Screening in Adult Survivors of Pediatric Cancer

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Introduction:

- Anthracyclines, a commonly used chemotherapeutic agent in treating pediatric cancer, have well-established cardiotoxic effects [1].
- Prior studies in leukemia survivors have demonstrated that even the lowest effective doses of anthracyclines can lead to cardiotoxicity[2].
- These cardiotoxic effects can occur acutely during treatment or, most commonly, at least 1 year following treatment as a subclinical non-ischemic cardiomyopathy (NICM) that can progress to overt heart failure [3].
- Noninvasive techniques such as echocardiography and radionuclide ventriculography (MUGA) are used in NICM surveillance, but this approach is limited in that cardiotoxicity is only detected after pathogenic remodeling and decline in LV contractility.
- Efforts are focused on identifying alternative screening techniques. Of particular interest as an early marker is NT-proBNP, a neurohormone released from the ventricles in response to volume overload and stretch [4].
- NT-proBNP is a widely available, non-invasive test that imposes less burden on patients and the healthcare system.
- We analyzed a cohort of adult pediatric cancer survivors to better understand the relationship of NT-proBNP to the development of anthracycline-induced NICM.

Methods:

- This is a retrospective chart review of adult survivors of pediatric cancer presenting to the UT Southwestern After Cancer Experience (ACE) Clinic between the dates of November 1, 2007 to June 1, 2017.
- Data recorded included: gender, age, cancer diagnosis, age at diagnosis, age at follow-up, dates of cardiac imaging studies and lab draws, cumulative anthracycline dosage, radiation location and dosage, and cardiac medications (limited to beta-blockers, renin-angiotensin-aldosterone system (RAAS) modifying medications, thiazide or loop diuretics, K+ sparing diuretics).
- Indicators of traditional cardiac risk factors (BMI, A1C, Blood Pressure, Total Cholesterol, HDL Cholesterol) between the first encounter and last encounter were recorded.
- An encounter was defined as a NT-proBNP lab draw or a cardiac imaging study. Observation Period was defined as time between first encounter and last encounter.
- Cardiac imaging studies were limited to conventional echocardiograms. LVEF value was reported as the most accurate available value, in the order of descending preference: bi-plane Simpsons, single plane, Teicholz, and visual estimate. 3D values were prioritized when available.
- NICM was defined as an LVEF of <55%.
- Data were summarized using means and standard deviations for numerical data and proportions for categorical data. Groups were compared using analysis of variance followed by Tukey's Studentized Range test. Stepwise multivariate regression was utilized to predict delta EF. Analyses were carried out using SAS software.

Methods and Results:

Figure 1. Flow Chart of study protocol and group formation

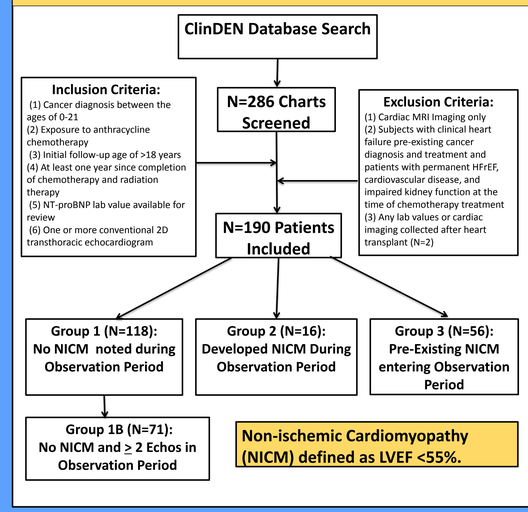


Table 1. Patient Demographics

Criterion	N (%)
Patients	190(100)
Male	80 (42)
Age at Diagnosis, years, mean ± SD (range)	9.0 ± 5.7 (0.17-20)
Age at Follow-Up, years, mean ± SD (range)	25.8± 6.3 (19-49)
Time Since Completion of Therapy, years, mean ± SD (range)	15.0 ± 8.2 (1.4-38)
Cumulative Dosage of Anthracycline (mg/m^2), mean ± SD	252.2 ± 138.1
Radiation Exposure	96 (50.5)
Cardiac Radiation Exposure	54(28.4)
Treated with Dextrazoxane	15 (7.9)
Received Bone Marrow or Peripheral Stem Cell Transplant	13 (6.8)
Diagnosis	
Hodgkin's Lymphoma	28 (14.7)
Non-Hodgkin's Lymphoma	20 (10.5)
Burkitt's Lymphoma	6 (3.2)
Osteogenic sarcoma	11 (5.8)
Non-Osteogenic Sarcoma	29 (15.3)
ALL	58 (30.5)
AML	14 (7.4)
Neuroblastoma	10 (5.3)
Nephroblastoma [Wilms' Tumor]	13 (6.8)
Pancreaticoblastoma	1 (0.5)
Treated with Statin Therapy	9 (4.7)
Cardiac Medication (Any)	36 (19)
β-Blocker	4 (2)
RAAS Modifying Agent or Diuretic	16(8)
B-Blocker & RAAS modifying Agent or Diuretic	8(4)
Other Anti-HTN medications	8(4)

Table 2. Clinical Characteristics of NICM Groups

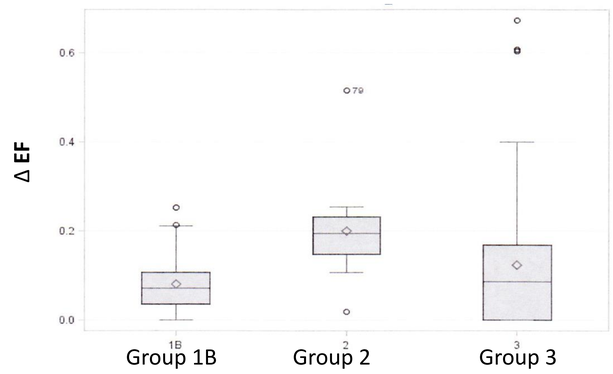
Criterion	Group 1 (n=118)	Group 2 (N=16)	Group 3 (N=56)	p-value
Male Patients (%)	52 (44)	4 (25)	24 (43)	0.326
Age at First Follow-Up in years, mean ± SD	25.3 ± 6.28	24.8 ± 3.1	27.2 ± 6.85	0.140
Age at Diagnosis in years, mean ± SD	9.8 ± 5.8*	9.41 ± 5.36	7.29 ± 5.29*	0.022
Time since Completion of Therapy, years, mean ± SD	13.7 ± 7.8*	14.4 ± 7.7	17.9 ± 8.7*	0.006
Cumulative Dosage of Anthracycline, mg/m^2, mean ± SD	229 ± 142.4*	251.3 ± 120.8	302.2 ± 121.2*	0.006
Dosage Range, N(%)				
<100 mg/m^2	21 (17.8)	2 (12.5)	9 (16.1)	<0.002
≥ 100 mg/m^2 and >200 mg/m^2	36 (30.51)	5 (31.3)	4 (7.1)	
≥200 mg/m^2 and >300 mg/m^2	27 (22.9)	2 (12.5)	10 (17.9)	
≥300 mg/m^2	34 (28.8)	7 (43.8)	33 (58.9)	
Exposed to Cardiac Radiation (%)	30 (25.4)	7 (43.8)	17 (30.4)	0.311
Hypertension [1]	8 (6.8)	1(6.3)	3 (5.4)	0.134
Total Cholesterol ≥ 200 mg/dL	32 (31.7)	5 (35.7)	20 (39.2)	0.651
HDL <40 mg/dL	22 (20)	0	13 (23)	0.026
BMI ≥ 25	63 (53.4)	10 (62.5)	22 (39.4)	0.133
Hg A1C ≥ 6.5	2 (1.7)	0	1 (1.8)	0.500
Greatest NT-proBNP Value in pg/mL, mean ± SD	69.4 ± 107.9*	206.13 ± 408.9	302.2 ± 121.2*	0.043
Maximum hsCRP	4.04 (± 4.7)	4.67 (± 4.8)	3.99 (± 4.64)	0.869
Minimum EF, mean (± SD)	59.3 (± 2.9)**	50.5 (± 5.7)	47.1(± 9.2)	<0.001

1: HTN defined as two or more BP measures of ≥ 140/90 mmHg during the period of observation.

Table 3 & Fig 3. Analysis of Δ EF in Patients with Multiple Echos

	Group 1B (N=71)	Group 2 (N=16)	Group 3 (N=56)	P value
Δ EF [2] mean ± SD	0.08 ± 0.25	0.20 ± 0.10**	0.12 ± 0.15	0.0002
Patient Years Observed, mean ± SD	4.96 (± 2.59)	5.71 (± 2.56)	4.75 ± 2.96	0.470

2: Δ EF is defined as $\frac{\text{Maximum EF- Minimum EF}}{\text{Maximum EF}}$



Regression Analysis of Δ EF

We assessed whether independent variables (age at diagnosis, age at first follow-up, time since completion of therapy, cumulative cardiac radiation dosage, CAD, greatest NT-proBNP, hsCRP) were predictive of ΔEF. A greater max NT-proBNP (R^2 =0.23) was most strongly associated with greater ΔEF values. Longer time since completion of therapy (R^2 =0.05), greater CAD (R^2 =0.04), and elevated hs-CRP (R^2 =0.03) were also associated with greater ΔEF values. R^2 of the model was 0.35.

Conclusions:

- Those who developed NICM during follow-up did have a significantly elevated ΔEF. Mean maximum NT-proBNP was increased in the subjects that developed NICM (Group 2), but not to a level achieving statistical significance.
- Maximum NT-proBNP was significantly elevated in those with NICM prior to observation (Group 3). This group had more severe heart failure, with lowest minimum EF. This could indicate that NT-proBNP elevation occurs later in the course of NICM, after significant decline in cardiac function.
- Though NT-proBNP was not clearly supported as a predictor of early change in cardiac function, maximum NT-proBNP was the most heavily weighted variable in predicting Δ EF.

Limitations

- EF was used as the sole parameter for cardiac function; there is intrinsic error, given the range of methods used to measure it and technician-to-technician variability.
- Given the retrospective design of this study, imaging and lab draws were often on different days, compromising correlation studies.
- Those who did not receive multiple images were not included Δ EF comparison studies (N=47). Those with less frequent imaging requirements are a generally lower risk population, introducing selection bias.
- This is a single-center, pilot study. Replication in a higher powered, multi-center study would be ideal.

References

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[4] Chow SL, Maisel AS, Anand I, *et al.* Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the American Heart Association. *Circulation.*2017; 135(24). doi: 10.1161/CIR.0000000000000490