Effect of Mineralocorticoid Receptor Antagonists on Secondary Prevention of Cardiomyopathy Progression in Childhood Cancer Survivors

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Abstract

BACKGROUND

The effect of mineralocorticoid receptor antagonists (MRA) on secondary prevention of late anthracycline-induced cardiomyopathy in childhood cancer survivors is unknown, while other heart failure therapies showed only transient effect. This study sought to assess whether MRA's may prevent the left ventricular systolic dysfunction caused by latent anthracycline cardiotoxic effects.

METHODS

Cross-sectional, proof of concept study of adult survivors of childhood cancer followed up at the After Cancer Experience and Cardio-Oncology clinics, UT Southwestern Medical Center, after completing anthracycline treatment at least two years prior to this study, in the prior decade. Cross-sectional symptom questionnaires administered during the study and retrospective clinical, laboratory, and imaging data extracted from the electronic medical records were analyzed in 3 groups of patients: on MRA therapy, on heart failure therapy regimen without MRA, and not on therapy for heart failure.

RESULTS

Of 105 enrolled, 67 patients completed the study. At baseline, the MRA group demonstrated lower LVEF (46% (30-51), n=8 MRA therapy vs 61% (57-63), n=46 no therapy; p<0.01) and higher ESV (59mL (41-90), n=8 MRA therapy vs 36mL (29-43), n=40 no therapy, p<0.05). The MRA group reported a decreased ability to walk one block compared with the non-MRA and no therapy groups (p=0.013). Administration of MRA resulted in a significant improvement in LVEF (52% (34-56), p=0.031 compared to baseline).

CONCLUSIONS

MRA administration as single drug therapy or in combination with standard of care heart failure therapy may prevent the progression of left ventricular dysfunction in childhood cancer survivors with late anthracycline-induced cardiomyopathy.

Introduction

More than 500,000 adult survivors of childhood cancer live in the United States in 2020[1]. At least three-fourths of them experience a chronic health condition as a result of their cancer treatment, often latent cardiotoxic effects secondary to exposure to alkylating agents, anthracyclines, and radiation therapy [2-5]. Childhood cancer survivors have more than 11 times higher risk to develop heart failure and more than 8 times increased risk for cardiovascular mortality compared with the general population[6, 7].

Up to 65% of patients have evidence of subclinical cardiotoxicity following anthracycline treatment; the risk for anthracycline-induced heart failure increases over time with a cumulative incidence of about 7.5% over 30 years [8-10]. Childhood cancer survivors may present with evidence of cardiotoxicity as early as one year after completion of therapy[11-13]. Current treatment of anthracycline-induced heart failure is based on general heart failure guidelines. However, the structural changes seen in these patients vary from restrictive to dilated cardiomyopathies and thus therapy may need to be individualized for each patient[2]. Studies of enalapril and growth hormone have shown only transient improvements in cardiac function and survival in childhood cancer survivors and the use of beta-blockers (BB) has not been well studied in this population[14-18].

Aldosterone is known to play a role in the development of heart disease by promoting cardiac fibrosis, hypertrophy, cell death, and inflammation [15, 16, 19-26]. Mineralocorticoid receptor antagonists (MRA) have demonstrated efficacy and safety in treating heart failure, and recent animal and human studies have supported the use of spironolactone in the prevention of anthracycline-induced cardiotoxicity [20, 23-29]. Another aldosterone antagonist, eplerenone, has demonstrated similar efficacy in treating heart failure with greater selectivity for aldosterone receptors than spironolactone. Due to its selectivity, the side effect profile of eplerenone is more favorable than that of spironolactone with a lower incidence of side effects such as gynecomastia and vaginal bleeding, a distinction with adherence and quality of life implications for young childhood cancer survivors requiring therapy for cardiomyopathy[30]. The few studies on mineralocorticoid receptor antagonists for the prevention and treatment of anthracycline-induced cardiomyopathy in adult cancer survivors have largely been promising[20, 23, 24, 31]. Studies demonstrated preservation of ejection fraction in human and mouse models receiving MRA therapy in conjunction with anthracycline-based chemotherapy[20, 23, 24, 31, 32]. One of the most promising

studies to date demonstrated preservation of left ventricular ejection fraction in adult females with breast cancer receiving anthracycline treatment in a prospective, randomized control trial comparing concurrent treatment with spironolactone versus placebo [20].

The use of MRA therapy for treatment of delayed-onset cardiomyopathy in childhood cancer survivors has not been studied. This retrospective study evaluated clinical, laboratory, and imaging data from 67 adult survivors of childhood cancer to test the hypothesis that MRA therapy prevents progression of anthracycline- induced cardiomyopathy in childhood cancer survivors.

Methods

STUDY COHORT: This cross-sectional, single center, proof of concept study, included adult survivors of childhood cancer under care at the After Cancer Experience childhood cancer survivors' clinic or the Cardio-Oncology clinic, University of Texas Southwestern Medical Center, Dallas, Texas, USA. The study was reviewed and approved by the Institutional Review Board and the Protocol Monitoring and Review Committee at UT Southwestern Medical Center.

PROTOCOL DESIGN: Patient charts were initially screened in the Clinical Research Data Warehouse at UT Southwestern, from documented visits to the After Cancer Experience and the Cardio-Oncology clinic for the following inclusion criteria: 1) cancer treatment with anthracyclines in the period January 2009 – December 2018, 2) an echocardiogram before and after cancer treatment, 3) completed anthracycline therapy at least 2 years prior to this study, and 3) valid contact information on file. Patients were excluded from this study if they had clinical heart failure prior to or concurrent with the cancer diagnosis and treatment. Of 377 patient charts screened, 182 (49%) patients were determined eligible for enrollment and were contacted by phone. Of these, 105 patients agreed to participate and were sent a link to an online questionnaire; 67 participants completed the questionnaire (response rate = 64%).

PATIENT DATA: Enrolled participants completed an online questionnaire regarding history and current symptoms of heart disease. Following questionnaire completion, data were collected on demographics, cancer diagnosis and treatment history, and cardiac function. Change over time and current symptoms were analyzed and compared in 3 groups of patients: patients on MRA therapy, patients on alternative heart failure therapy (non-MRA therapy), and patients not on therapy for cardiomyopathy (no therapy**, Figure 1)**.

To evaluate symptoms of cardiotoxicity, 14 multiple-choice questions were selected from the Childhood Cancer Survivor Study Questionnaire[5].The web-based data collection system REDCap (Research Electronic Data Capture) was employed to build and administer the survey[33, 34]. The modified questionnaire is included in **Appendix 1**.

Vital signs, the 5 most recent cardiac imaging studies and laboratory data were recorded for each patient. For the MRA group, vital signs and imaging data were compared before and after initiating MRA treatment. For the non-MRA group, the most recent documented set of vital signs was used for comparison; the oldest and most recent imaging parameters were compared. For the no therapy group the most recent imaging data available were used. The following cardiac imaging parameters were extracted: end-diastolic volume (EDV), end-systolic volume (ESV), shortening fraction (SF) left-ventricular ejection fraction (LVEF), and global longitudinal strain (GLS), prioritized from cardiac MRI and 3D-echocardiography to linear echocardiographic quantitation. Laboratory data included N-terminal pro b-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive Protein (hs-CRP) and lipid profile.

DATA ANALYSIS: Kruskal-Wallis non-parametric test was used to detect differences among the three groups, with post hoc analysis performed using the Dunn test[35]. In addition, within groups changes in LVEF with therapy were assessed via Wilcoxon Signed Ranks Test. Fisher's Exact test was employed for evaluation of cardiomyopathy symptoms between the groups. Mann-Whitney U test was performed to compare LVEF of patients with and without radiation exposure history. Spearman correlation was used to detect association between any pair of the following measures: cumulative doxorubicin dose, radiation dose, GLS, LVEF, NT-proBNP, HS-CRP, and symptoms assessed via questionnaire. Statistical analyses were conducted using IBM SPSS V24, significance was set at $p<0.05$, and all statistical tests were two-sided.

Results

Patient characteristics are described in **Table 1**. Of the 67 participants involved in the study, there were 8 participants in the MRA group, 11 in the non-MRA group, and 48 in the no therapy group.

CUMULATIVE DOXORUBICIN DOSE AND DEXRAZOXANE: There was a significant difference in the cumulative doxorubicin dose between the three groups on initial evaluation (Table 1) (p=0.008). The non-MRA therapy group showed a significantly lower average rank anthracycline exposure than the no therapy group. The majority of patients in the no therapy group received cumulative doxorubicin doses of $\leq$ 200 mg/m^2, whereas six of eight patients in the MRA therapy group and six of eleven patients in the non-MRA therapy group were exposed to a cumulative doxorubicin dose >300 mg/m^2. Five of the participants in the study were treated with dexrazoxane at the time of chemotherapy administration, all in the no therapy group.

LVEF showed a negative correlation with cumulative anthracycline dose (r^2 = -0.396; p=0.002) (Figure 2). NT-proBNP and ESV correlated positively with increasing cumulative anthracycline dose, (r^2 = 0.285; p=0.039 and r^2 = 0.138 p=0.024) (Figure 3). In contrast, there were no relationships detected between the cumulative doxorubicin dose and reported symptoms, GLS, or hs-CRP.

CARDIAC IRRADIATION: Cumulative therapeutic radiation doses ranged from 900-5220 cGy, with no significant difference in exposure among the groups (Table 1). Other than a weak correlation between increasing radiation dose and reported limitation in walking uphill/climbing a few flights of stairs (r^2 = -0.245; p=0.049), there were no relationships between radiation and other data.

MEDICATION HISTORY: Of the eight participants in the MRA therapy group, four were taking spironolactone and four were taking eplerenone. Two patients had long-standing cardiomyopathy for >10 years, and the remaining patients had new onset or subclinical cardiomyopathy. Only three patients were on MRA monotherapy; the remaining five were concurrently taking an ACEI/ARB with or without a BB. Most patients started the drug within the year prior to enrollment in doses ranging from 12.5 to 50 mg daily and most patients were on a dose of 25 mg daily. Two patients taking spironolactone were prescribed the medication for acne. Of the eleven patients in the non-MRA therapy group, there were three patients on ACEI monotherapy, one on ARB monotherapy, and two on BB monotherapy. Two patients were taking a combination of ACEI and BB, and three were on both an angiotensin receptor blocker and BB. Three of the patients were receiving the medications for a diagnosis of hypertension rather than heart failure. Most of the patients in the non-MRA therapy group had been on their respective medications for a longer period than patients in the MRA therapy group (Table 1). Given the patients' longstanding treatment, there were limited study data available prior to initiation of cardiac medication in this group. Baseline cardiac imaging studies were only recorded for 4 of the 11 patients in this group, and there were similarly limited baseline laboratory data.

EVALUATION OF SYMPTOMS OF CARDIOMYOPATHY: Due to the small sample size, the presence or absence of symptoms was analyzed in lieu of symptom severity. The only difference in symptoms detected between the three groups was a limitation in walking one block (p=0.013), with 38% of the MRA therapy group reporting this symptom, in comparison with no patients in the non-MRA therapy group and 4% of patients in the no-therapy group. In addition to this finding, there was also a non-significant trend towards higher prevalence of shortness of breath and limitations in moderate physical activities, such as walking uphill or carrying groceries. All three patients on MRA monotherapy reported no symptoms. Although not tested for statistical significance due to the small number of patients receiving dexrazoxane, patients with a history of dexrazoxane therapy reported fewer symptoms of cardiac disease.

There was a statistically significant correlation between lower ejection fraction and limitation in moderate physical activity (r^2 = 0.290, p=0.022) and limitation in walking one block due to health (r^2 = 0.428, p<0.001). Similarly, there was a relationship with higher NT-proBNP and limitation in moderate physical activity (r^2 = -0.387, p =0.003), limitation in walking uphill or climbing a few flights of stairs (r^2 = -0.272, p =0.039), and limitation in walking one block (r^2 = -0.488, p <0.001).

VITALS: At baseline prior to initiation of MRA, the heart rate was higher in the MRA group compared with most recent heart rate in the no-therapy group (p=0.01); lack of baseline vitals data in the non-MRA therapy group precluded comparison. This difference in heart rate between the MRA therapy group and the no therapy group persisted after treatment with MRA (p<0.05), but heart rate and blood pressure did not significantly change with MRA administration. There was no difference in other recorded sets of vitals between the MRA therapy group and the non-MRA therapy group.

LEFT VENTRICULAR VOLUMES: Baseline ESV differed between groups (p=0.008), with post hoc analysis revealing that ESV was significantly higher in the MRA group when compared with the no therapy group (59mL (41-90), n=8, MRA therapy vs 36mL (29-43), n=40, no therapy, p<0.05), but not compared with the non-MRA therapy group (n=4, non-MRA therapy). There were no differences in the baseline and most recent EDV, as well as the most recent ESV among the three groups. Although median ESV and EDV decreased

with MRA administration, the change was not significant (ESV 59mL (41-90), to 48mL(33-68), p=0.092 and EDV 104mL (79-133) to 81mL (71-152), p=0.208) **(Figure 4)**.

LEFT VENTRICULAR EJECTION FRACTION: There was a significant difference in baseline LVEF between groups (p=0.001), with post-hoc analysis indicating lower LVEF in the MRA therapy compared with the no therapy group (46%(30-51), n=8, MRA therapy vs 61% (57-63), n=46, no therapy, p<0.01). There was a significant increase in LVEF with administration of MRA therapy (46% (30-51) to 52% (34-56), p=0.031), **(Figure 4)**.

Baseline LVEF was only available for 4 of the 11 patients in the non-MRA therapy group, as these patients were initiated on therapy prior to adoption of electronic medical records and echocardiogram data were no longer available at the time of data collection. Due to this lack of data, most recent echocardiogram was compared against both the penultimate and oldest recorded echocardiograms, with neither comparison demonstrating a change in LVEF.

GLOBAL LONGITUDINAL STRAIN: There were limited data on global longitudinal strain (GLS) due to the only recent incorporation of the parameter as standard of care. GLS measurements for the MRA therapy group are listed in **Table 2.**

CARDIAC LABORATORY PARAMETERS NT-proBNP was higher in the MRA therapy group prior to administration of MRA than in the no therapy group (p=0.05). NT-pro BNP was also different between groups after MRA administration (p=0.029), and by post hoc analysis it was significantly higher in the MRA group (p<0.05) than in the no therapy group. In contrast, most recent NT-proBNP did not differ between the MRA therapy and non-MRA therapy groups. Similarly, hs-CRP was not different among groups. Within the MRA therapy group, only three patients had NT-proBNP measured after initiation of the medication, with one patient experiencing an 81% decrease, another a 23% increase, and the third a 90% increase. hs-CRP after initiating therapy was only recorded in two patients, both showing an increase. There was a significant difference in the triglyceride levels (p=0.04), and by post hoc analysis the non-MRA therapy group had significantly higher triglyceride levels than the no therapy group (124mg/dL (78-224), non-MRA therapy vs 78mg/dL (57-97), no therapy, p<0.05).There were no differences in the most recent total cholesterol, LDL, or HDL among the three groups.

Discussion

Aldosterone receptor antagonists are commonly used in the guideline directed medical therapy of adults with heart failure; however, research has not explored the use of MRA therapy for secondary prevention of anthracycline-induced cardiomyopathy in childhood cancer survivors. This retrospective study demonstrates that MRA administration as monotherapy or in combination with standard of care heart failure therapy may improve left ventricular dysfunction among childhood cancer survivors exposed to anthracycline based chemotherapy. The findings of this study suggest that at-risk survivors of childhood cancer may benefit from MRA therapy for secondary prevention of anthracycline-induced cardiomyopathy progression, and these findings have the potential to change how physicians manage the late cardiotoxic effects of anthracycline based chemotherapy.

he population of survivors of childhood cancer with cardiovascular disease continues to grow as 5- year survival rates in childhood cancer are greater than 85%, and about 40-50% of childhood cancer survivors are exposed to anthracyclines as part of their chemotherapeutic regimen[36-38]. Anthracycline-induced cardiotoxicity most commonly manifests progressively, evolving gradually towards heart failure after onset at greater than one year following completion of cancer therapy. Patients with cardiomyopathy related to anthracycline exposure in childhood are generally younger than patients with more common forms of cardiomyopathy [11-13]. This is demonstrated by the relatively young age of the study population in the present study, ranging 25-44 years of age.

The study population had varying doses of anthracycline exposure, cardiac dysfunction, and subjective physical debility. Consistent with the known relationship between cardiomyopathy and the cumulative anthracycline dose, there were significant differences in cumulative doxorubicin dose between the three groups, and patients exposed to a lower median dose of doxorubicin not requiring therapy for heart failure. Compared with patients on no heart failure therapies, patients on an MRA had already worse baseline cardiac function and decreased ability to walk one block. Although LVEF was still significantly lower after MRA initiation, the difference in ESV between the two groups appeared to resolve with MRA initiation.

It has been previously demonstrated using mammalian model systems that the renin-angiotensin-aldosterone system (RAAS) plays an important role in anthracycline-induced cardiomyopathy. In a study using a rabbit model, 8 weeks of administration of doxorubicin was associated with activation of the RAAS pathway as evidenced by doubling of plasma renin activity over the first four weeks of

anthracycline treatment, a change that was maintained for the remaining four weeks [21] After treatment with anthracycline, LVEF was not impaired in mice with cardiac myocyte mineralocorticoid receptor (MR) gene deletion, but was impaired in control mice with the wild type MR gene [24]. Mice pretreated with eplerenone who were exposed to doxorubicin had significantly higher EF and contractility compared with those not receiving eplerenone [24]. Also in a rat model, treatment with spironolactone prior to doxorubicin exposure prevented QT prolongation and LVEF decline compared to control [23]. These studies exploring MRA therapy for primary prevention of anthracycline-induced cardiomyopathy are promising; however, there are no experimental models of secondary prevention of anthracycline-induced cardiotoxicity using antialdosterone therapy.

Studies involving human participants have been so far limited by small size and variable timelines of cardiomyopathy onset. LVEF was preserved in a group of female breast cancer patients receiving pre-treatment with spironolactone, with demonstration of a significant acute decrease in LVEF in the placebo group in comparison to the spironolactone group [20]. However, a study evaluating the effect of eplerenone on diastolic function in women receiving anthracycline-based chemotherapy was terminated early after an interim analysis showed no significant evidence of cardiomyopathy in the placebo group, concluding lack of power and proposing larger scale trials[39].

In our retrospective study patients in the MRA group on guideline directed medical therapy had already worse baseline cardiac function and higher prevalence of symptoms in comparison to patients in the non-MRA therapy and no therapy groups. Guideline directed medical therapy for heart failure with reduced ejection fraction includes MRA therapy at LVEF <35%. Given the retrospective nature of this study, this difference in baseline cardiac function was expected. For the MRA group, there was a significant improvement in LVEF despite this group continuing to have worse cardiac function after initiation of MRA therapy. Due to the lack of available data prior to initiating ACEI/ARB or BB therapy in the non-MRA therapy group, the effect of MRA therapy alone or in combination with these drugs could not be directly compared to the effect of these drugs without MRA. Patients taking ACEI/ARBs or BBs had stable ejection fraction and fewer reported symptoms of cardiac decompensation, but the duration of this study was relatively short and may have also included patients on ACEI/ARBs or BBs for management of alternative indications such as hypertension, compared with studies that showed decreasing efficacy of ACE inhibitors over time in survivors of childhood cancer with cardiomyopathy [14, 15].

Also, of note is that the average increase in LVEF while on an MRA was higher when the cohort was restricted to women only. This finding is compatible with experimental evidence that suggests mineralocorticoid antagonists are more effective in females in the treatment of cardiovascular disease [22]. Female childhood cancer survivors exposed to anthracyclines have a higher incidence of heart failure than their male counterparts[40] and, given that these female childhood cancer survivors are frequently treated for heart failure during their child-bearing years, MRA may be a reasonable alternative to teratogenic RAAS pathway inhibitors, such as ACEI/ARB medications.

Radiation dose was not associated with objective evidence of worsening cardiac function in this study. However, there was a significant correlation of radiation dose exposure with a limitation in effort tolerance walking uphill or climbing a few flights of stairs and with the severity dyspnea on exertion. Manifestations of radiation-induced cardiac and pulmonary disease include coronary artery disease, valvular disease, and pulmonary fibrosis, all of which could lead to a decrease in effort tolerance [36]. However, a systematic assessment of radiation induced comoplications was not available in this cohort.

STUDY LIMITATIONS: This study has several limitations primarily related to the retrospective nature of the clinical data and small sample sizes in the medication groups. Patients in the MRA group had already worse baseline cardiac function and functional status before MRA administration in comparison to patients in the no MRA group. This is likely related to their severely depressed ejection fraction at baseline, where MRA therapy is included as guided by current evidence-based heart failure treatment guidelines. Many of the patients in the MRA group were concurrently on ACEI/ARB or BB around the time of MRA initiation it was not possible to accurately attribute an effect among these classes. Additionally, the limited availability vital sign and imaging data, varied duration of treatment, and lack of standardized evaluation modalities and time intervals precluded baseline and direct comparison of treatment effect in the medication groups. Small sample sizes resulted in limited ability to analyze some parameters for statistical significance. As medication history was obtained via chart review, confirmation of drug adherence was not obtained. Finally, the questionnaire did not distinguish the source of a reported symptom, such as limited physical activity. These limitations emphasize the necessity of future prospective, multicenter studies to further elucidate the benefit of MRA therapy in this unique population.

Conclusions And Future Directions

This study demonstrates an improvement in LVEF in childhood cancer survivors receiving MRA therapy for anthracycline-induced cardiomyopathy. This finding suggests that MRA as monotherapy or in combination with GDMT may reverse the left ventricular functional decline associated with anthracycline-induced cardiomyopathy in this unique patient population. A prospective, multicenter study with standardization of medication regimens, cardiac imaging data, and longitudinal clinical surveillance is necessary to better understand the effect of mineralocorticoid receptor antagonists in the treatment of anthracycline-induced cardiotoxicity in childhood cancer survivors.

Abbreviations

ACEI, angiotensin converting enzyme inhibitor

ARB, angiotensin receptor blocker

BB, beta blocker

cGy, centigray

MRA, mineralocorticoid receptor antagonist

Declarations

CLINICAL PERSPECTIVE:

Childhood cancer survivors who required anthracycline chemotherapy are at risk of latent cardiotoxic effects, progressive cardiomyopathy and heart failure. This proof-of-concept, cross-sectional study provides evidence suggesting that mineralocorticoid receptor antagonists may prevent the left ventricular dysfunction caused by latent anthracycline cardiotoxic effects. A prospective trial is necessary to formally test this effect.

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Tables

Table 1: Demographic Characteristics of the Study Groups.

	MRA Therapy	Non-MRA Therapy	No Therapy	Total
N	8	11	48	67
Male	1	7	14	22
Female	7	4	34	45
Diagnosis				
Leukemia	1	3	19	23
Hodgkin's disease	1	0	4	4
Non-Hodgkin's lymphoma	2	2	9	12
Neuroblastoma	0	0	4	4
Wilm's tumor	1	2	1	4
Sarcoma	3	4	3	10
Age	37 (27-43.5)	41 (25-44)	30 (25.3-33)	31 (26-39)
Years since treatment	24 (15-32.1)	24 (11.3-30)	17 (10.4-23.8)	18 (11.4-26.2)
Cumulative doxorubicin dose (mg/m^2)	360 (300-375)*	416 (178-452)	188 (101-326)*	200 (135-363)
Patients with doxorubicin dose >300 mg/m2	6 (75%)	6 (55%)	14 (29%)	26 (39%)
Received dexrazoxane	0	0	5	5
Received cardiac irradiation	4	2	13	19
Radiation dose (cGy)	1575 (1200-1950)	3210 (2204-4215)	2100 (2100-2415)	2100 (1200-2205)
On ACEI therapy	3	5	0	8
Average time on ACEI therapy (months)	3	5	N/A	8
On ARB therapy	2	4	0	6
Average time on ARB therapy (months)	50.5 (30.3-70.8)	54 (8.3-90.8)	N/A	54 (8.5-91.3)
On BB therapy	4	7	0	11
Average time on BB therapy	10.5 (7-86)	83 (23-108)	N/A	63 (10-108)
On MRA	8	0	0	8
Average time on MRA therapy (months)	8.5 (8-11.3)	N/A	N/A	8.5 (8-11.3)

Values are median, with the interquartile range in parentheses. * $p<0.5$. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; cGy, centigray.

Table 2: Mineralocorticoid Receptor Antagonist Therapy Group (n=8). Patient Characteristics.

Patients Characteristics									Median (IQR)
Gender	F	F	F	F	F	F	F	M	-
Age	33	46	26	42	41	22	30	44	37 (27-43.5)
Age at diagnosis	11	5.5	12	16	14	14.5	5	8	12 (6-14)
Dose of doxorubicin(mg/m^2)	400	300	160	-	365	375	320	360	360 (300-375)
Cardiac radiation exposure (cGy)	N/A	1200	1950	1200	N/A	N/A	N/A	1950	1575 (1200-1950)
MRA drug	S	E	E	E	S	S	E	S	-
Months on MRA	7	9	8	8	9	12	8	45	8.5 (8-11.3)
Months on ACEI-ARB	10	-	4	91	10	-	-	198	10 (7-104)
Months on BB	11	-	-	6	10	-	-	111	10.5 (7-86)
Heart rate before MRA	84	85	111	101	100	-	117	96	100 (85-111)
Heart rate after MRA	81	121	109	94	84	75	98	96	95 (81.8-106.3)
LVGLS (%) before MRA	-	-17	-16	-15.6	-	-	-16.2	-	-16.1 (15.7-16.8)
LVGLS (%) after MRA	-	-	-16.3	-18.4	-	-13.8	-16.8	-	-16.6 (14.4-18)
LVEF (%) before MRA	30	50	52	49	20	51 [a]	43	30	43 (30-50)
LVEF (%) after MRA	52	55	52	56	29	56	47	25	52 (33.5-55.8)
NT pro-BNP (pg/ml) before MRA	267	273	24	84	2437	-	21	1005	267 (24-1005)
NT pro-BNP (pg/ml) after MRA	-	-	-	-	459	53	-	1914	459 (256-1186)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; cGy, centigray; E, eplerenone; IQR, interquartile range; LVGLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; [a] LVEF was 3 months after spironolactone initiation; NT pro-BNP, N-terminal pro b-type natriuretic peptide; S, spironolactone.
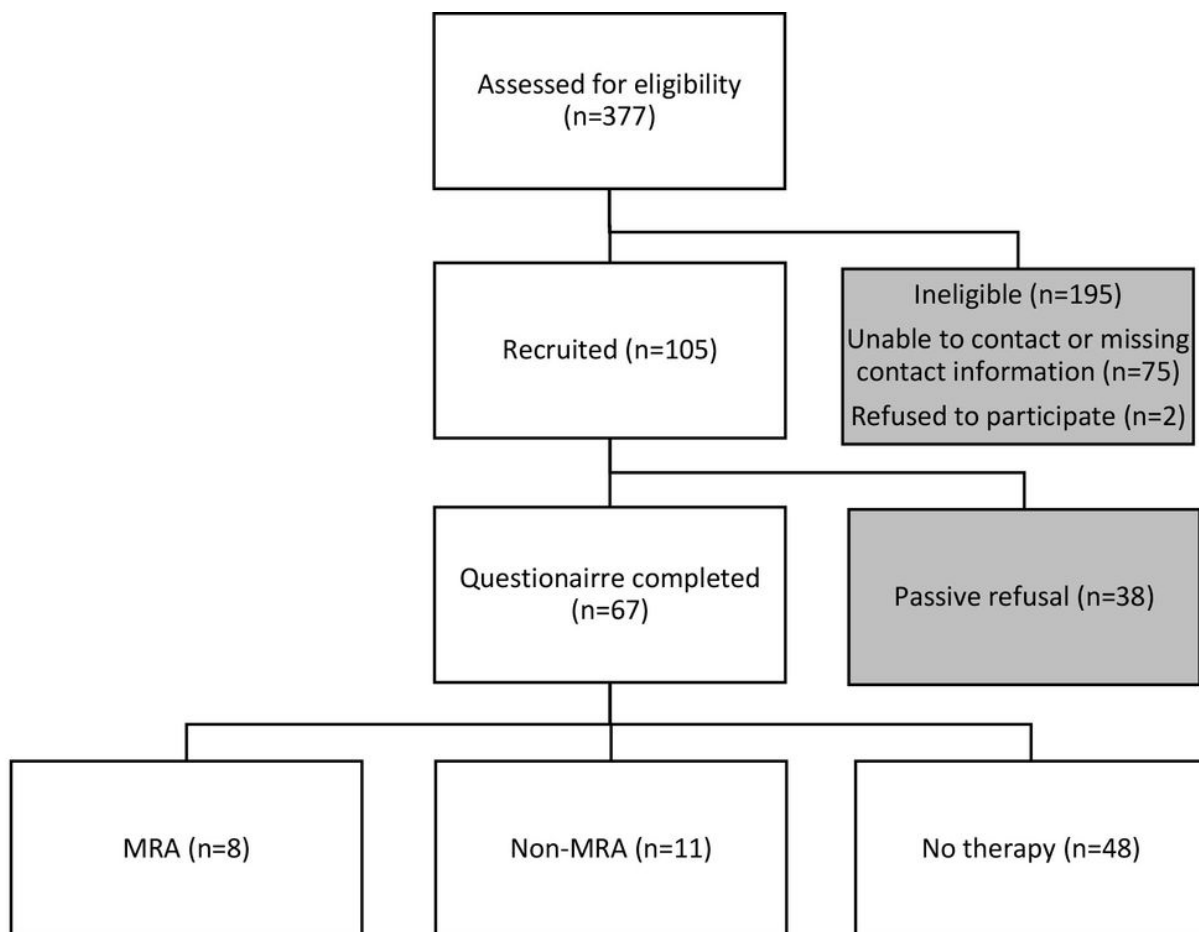
Figures

Figure 1

Participant selection and inclusion criteria. Eligible patients were adults with a history of childhood cancer who completed treatment greater than two years prior to study initiation.
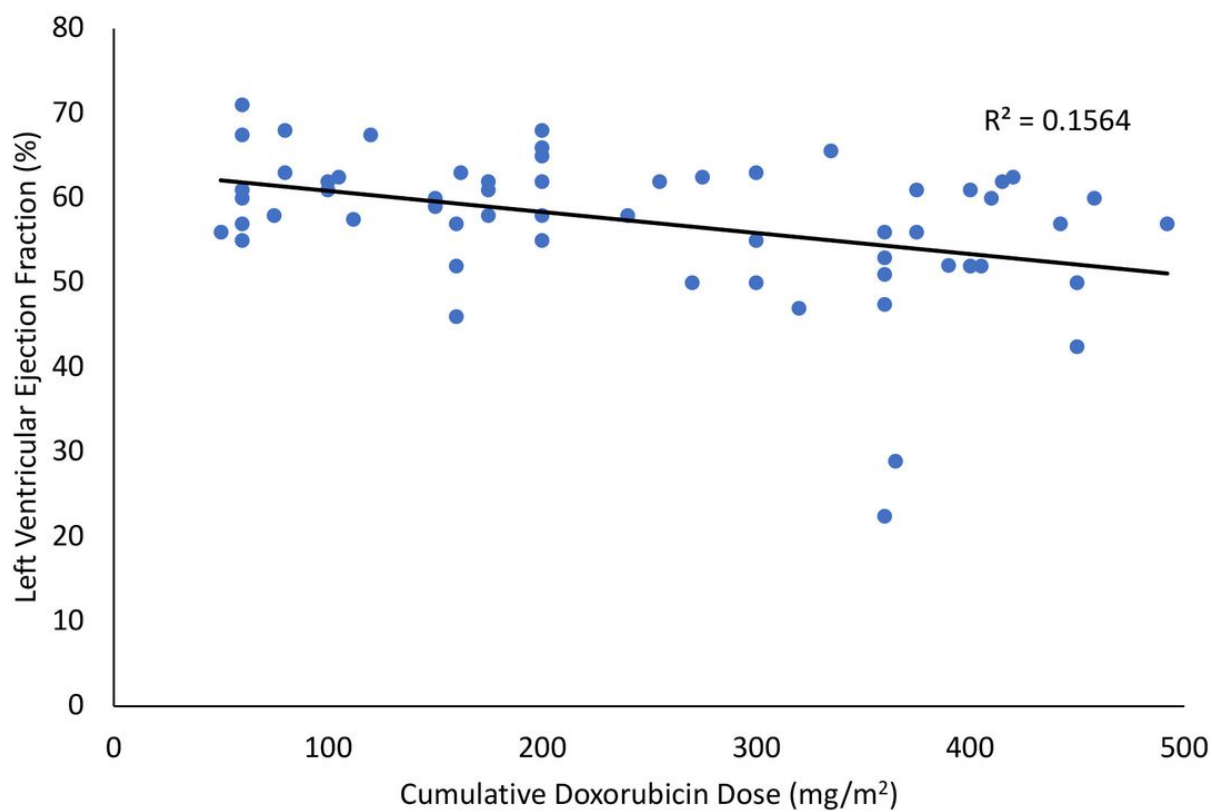
Figure 2

Figure 2

Correlation between the cumulative doxorubicin dose and baseline LVEF for all participants (n=67). Reduced baseline LVEF was associated with a higher cumulative doxorubicin dose (p=0.002).
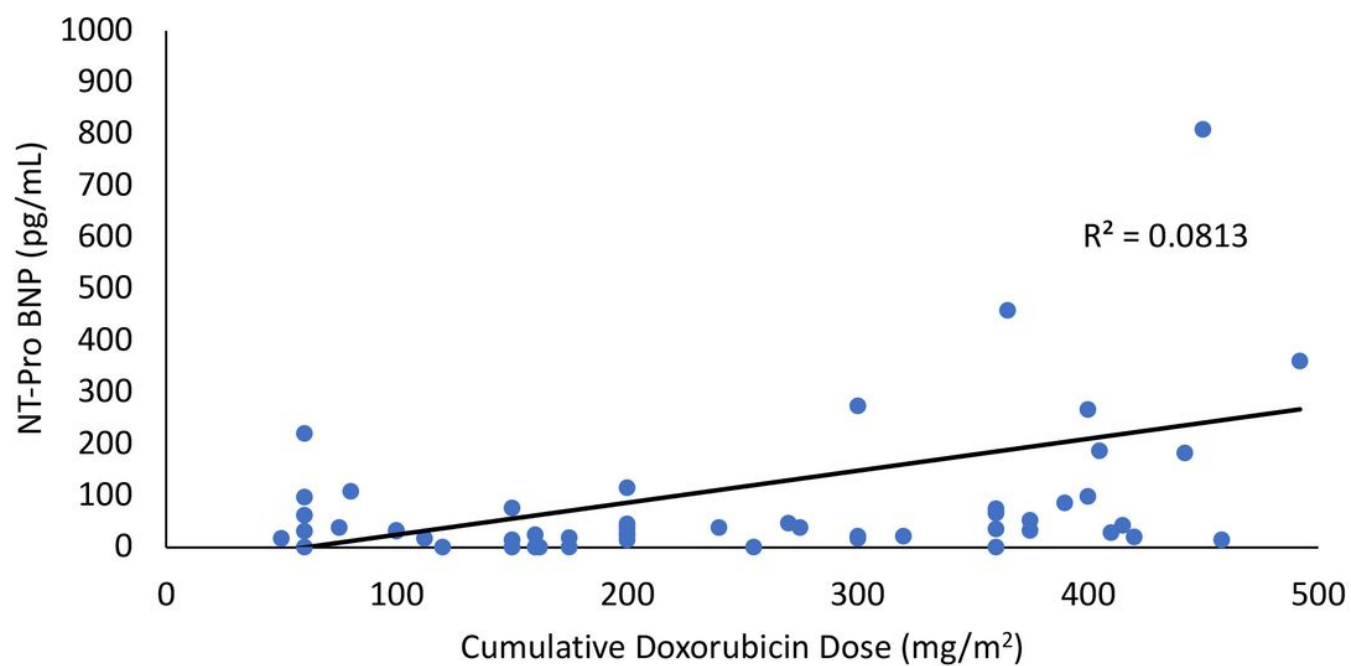
Figure 3

Figure 3

Correlation between cumulative doxorubicin dose and most recent NT pro-BNP for all patients (n=67). Increased NT pro-BNP was associated with a higher cumulative doxorubicin dose (p=0.039).
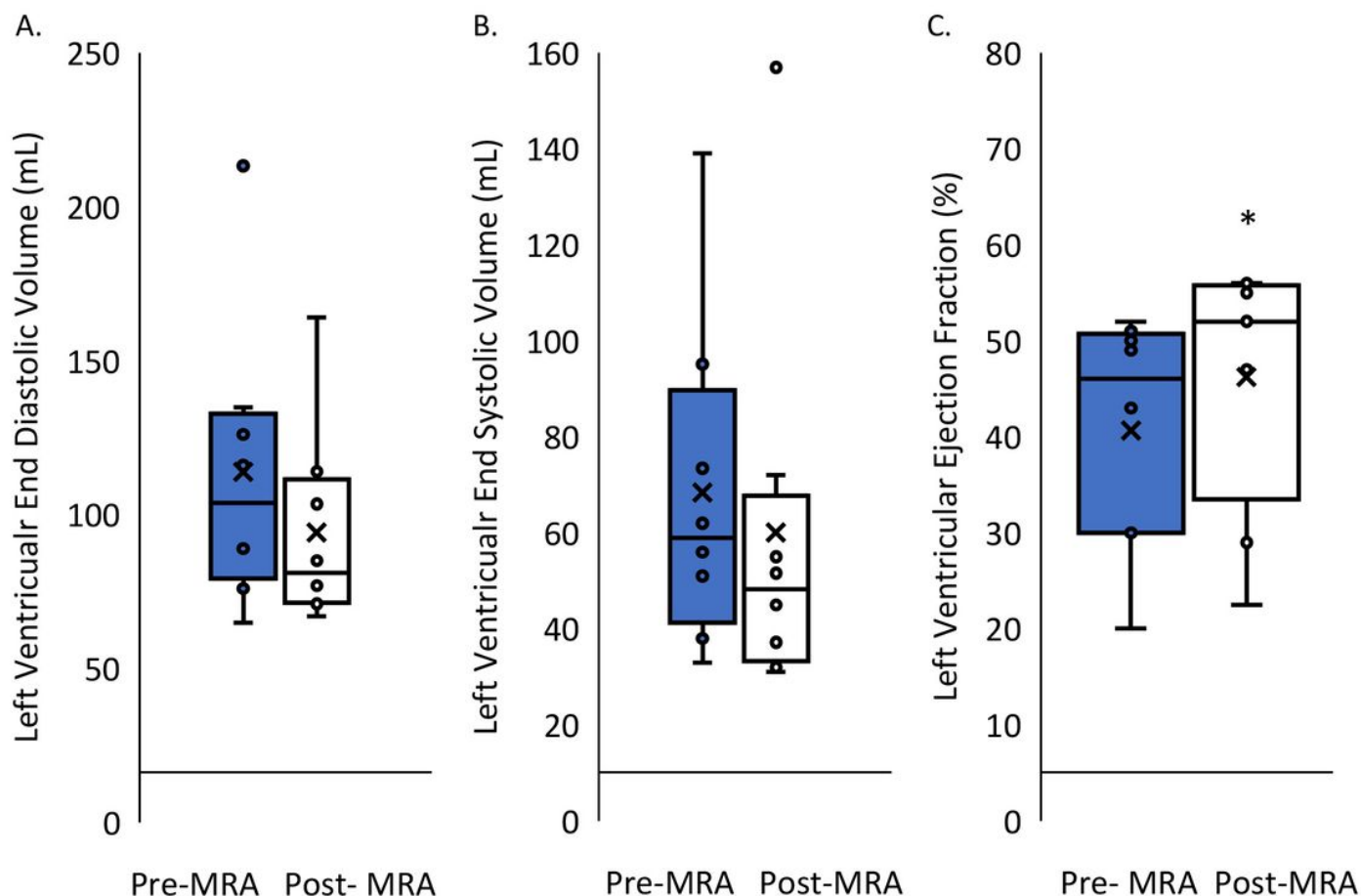
Figure 4

Figure 4

Echocardiographic parameters in the mineralocorticoid receptor antagonist (MRA) therapy group (n=8). A. Left ventricular end diastolic volume before and after MRA administration, no statistical difference (p=0.208). B. Left ventricular end systolic volume before and after MRA administration, no statistical difference (n=8, p=0.092). C. Significant increase in left ventricular ejection fraction from baseline in patients that received MRA therapy (p=0.016).

Supplementary Files

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