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Anthracycline Cardiotoxicity in Acute Lymphoblastic Leukaemia: Standard vs. High Risk Paediatric Groups

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Ao “J” ...

SUMMARY

TABLE LIST

ABBREVIATIONS

ALL – Acute Lymphoblastic Leukaemia

CNS - Central Nervous System

DFCI - Dana Farber Cancer Institute

Dx - Diagnosis

EF – Ejection Fraction

EF1 - Ejection Fraction (1^{st} follow-up period)

EF2 - Ejection Fraction (2^{nd} follow-up period)

EF3 - Ejection Fraction (3^{rd} follow-up period)

FS – Fraction Shortening

FS1 – Fraction Shortening (1^{st} follow-up period)

FS2 - Fraction Shortening (2^{nd} follow-up period)

FS3 - Fraction Shortening (3^{rd} follow-up period)

H/VHR – High/Very High Risk

SR – Standard Risk

TAPSE - Tricuspid Annular Plane Systolic Excursion

TAPSE1 – Tricuspid Annular Plane Systolic Excursion (1st follow-up period)

TAPSE2 - Tricuspid Annular Plane Systolic Excursion (2nd follow-up period)

TAPSE3 - Tricuspid Annular Plane Systolic Excursion (3rd follow-up period)

WBC - White Blood Cell

ABSTRACT

The use of anthracyclines in the treatment of acute lymphoblastic leukaemia (ALL) is limited by its cardiotoxic effects in long-term childhood cancer survivors. The aim of this study was to evaluate and compare the effects of anthracycline therapy on cardiac function between two groups of children with standard and high/very high risk ALL. Acute, subacute and chronic toxicities were evaluated.

The study included patients aged 1 to 17 diagnosed with ALL between 2007 and 2016, treated with the Dana Farber Cancer Institute protocol in its most updated version (05-01 and 11-01) with at least one year of follow-up. They were divided into two groups according to their ALL risk category. Standard risk (SR) patients received a cumulative anthracycline dose of 60 mg/m2, while High risk and Very High Risk (H/VHR) patients were treated with a cumulative dose of 300 mg/m2.

A retrospective echocardiographic analysis was carried out over a period of 10 years (2008-2017). The parameters used to evaluate left systolic cardiac function were the fraction shortening (FS) and the ejection fraction (EF) by the Simpson's biplane method, and the tricuspid annular plane systolic excursion (TAPSE) for the right ventricular systolic function. The echocardiographic evaluation was performed at diagnosis, three, six and twelve months after the onset of chemotherapy, and then, yearly and every three years for H/VHR and SR patients, respectively.

The study included 87 patients. Among these, 8 patients were excluded [early death (n=1), refractory leukaemia (n=2) and Philadelphia positive leukaemia (n=5)]. In the SR group 53% were male and in the H/VHR group 66% were male. The cardiovascular risk

factors identified prior to therapy were arterial hypertension (n=5), type 1 diabetes *mellitus* (n=2), dyslipidaemia (n=3) and chronic kidney disease (n=2).

TAPSE during anthracycline treatment and one year after its conclusion was lower in the H/VHR group (n=25; p=0,044), suggesting that there might be a higher probability of acute/ early chronic right ventricular dysfunction in this group.

FS and TAPSE showed lower values during the late follow-up period in female subjects within the SR group (n=16; p=0,024 and n=15; p=0,010, respectively), implying that chronic biventricular systolic dysfunction would be more likely to occur in female patients. No difference was found among the H/VHR group concerning gender. Regarding the age at diagnosis within the H/VHR group, TAPSE during treatment showed lower values in older patients (n=22; p=0,008).

This study highlights the importance of cardio-oncological cooperation in the follow-up of paediatric cancer patients treated with anthracyclines in order to early diagnose and treat potential cardiovascular toxicity.

Keywords: Acute Lymphoblastic Leukaemia; Chemotherapy; Anthracyclines; Cardiotoxicity; Echocardiography; Cardio-Oncology.

SECTION 1

INTRODUCTION

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most frequent cause of childhood cancer, (1) being accountable for more than 25% of paediatric malignancies. (2) It can be classified as Standard Risk (SR), High Risk (HR) and Very High Risk (VHR) depending on several factors such as immunophenotype, chromosomal abnormalities, age at diagnosis, white blood cell (WBC) count, presence of central nervous system leukaemia and the total cumulative dose of anthracyclines administrated.

Anthracyclines are a class of antibiotics widely used as chemotherapeutic agents in the treatment of ALL. (1,3–12) Their cardiotoxic effects are well known, (6,7,10,13–16) ranging from mild myocardial thinning to congestive heart failure. (5,13,17–19) Once established, treatment discontinuation may not be sufficient to reverse the most serious complications. (1,4,6,10) Cardiotoxicity is classified as acute, if it occurs during anthracycline administration or during the subsequent two weeks; early chronic, if its onset is during the first year post-treatment; or late chronic, if it occurs after the first year post-treatment, the latter being the most common form. (2,6,15)

With the therapeutic advances seen in recent years, both the prognosis and survival of these patients are improving, reaching a 5-year survival rate above 90%. (20–22) However, with this improved survival comes a greater risk of anthracycline-induced cardiac dysfunction, which, in this group of patients, has become a major concern. Childhood cancer survivors that have been treated with anthracyclines have 10 times the mortality risk related to cardiac events when compared with age-matched control subjects. (21) This data reinforces the importance of a regular follow-up at a specialized Centre. (23)

With this in mind, the Paediatric Cardiology Department of the Hospital Centre of the University of Coimbra created the first Paediatric Cardio-Oncology consultation in Portugal in December 2015, where echocardiography plays a major role in the evaluation, risk stratification and follow-up of cardiac function. (3,6,9,15,17,21,24)

In this study, we evaluated and compared some functional echocardiographic parameters between Standard Risk and High/Very High Risk patient groups and the influence of age and gender on long-term cardiac function. Acute and subacute toxicities were also evaluated.

SECTION 2

METHODS

METHODS

Study design

This was an observational, analytical, longitudinal, retrospective cohort study, carried out between 2016 and 2017 that included children diagnosed with ALL over a 10-year period (2007-2016) and followed in the Paediatric Oncology Department of the Hospital Centre of the University of Coimbra. These patients were referred to the Cardiology or Cardio-Oncology consultation of the Paediatric Cardiology Department for cardiovascular assessment.

Patient selection

The study included patients aged 1 to 17 years, diagnosed with ALL between May 2007 and November 2016. The sample was divided into two groups according to their ALL risk. (25)

The "Standard Risk" group included patients under 10 years of age, with a WBC count less than 50.000/mm^3, B-precursor cell surface antigen predominance on lymphoblasts and no evidence of CNS infiltration neither chromosomal abnormalities. The "High/Very High Risk" group included patients who failed to meet any of the above criteria.

Although both groups were treated with the most updated version of the Dana Farber Cancer Institute (DFCI) protocol at the time of diagnosis (05-01 or 11-01 if diagnosed after 2011), the corresponding protocols differed according to the ALL oncological risk. In fact, SR patients were managed with anthracyclines over a period of one month (induction phase), while H/VHR patients were treated with anthracyclines for at least a year (induction and

consolidation phases). Objectively, the first group (SR) had a total anthracycline cumulative dose of 60 mg/m^2, whereas the second group (H/VHR) had a total cumulative dose of 300 mg/m^2. No patient received mediastinal radiotherapy.

The exclusion factors taken into consideration were early death, switch of treatment protocol and Philadelphia chromosome positive leukaemia.

Echocardiographic Study

A retrospective echocardiographic analysis was carried out over a period of 10 years (2008-2017) both before starting chemotherapy as a basal echocardiogram, and during the follow-up period. An echocardiogram was performed in both groups at three, six and twelve months after treatment initiation, then yearly in the H/VHR group and every three years in the SR group. (26,27)

The examination took place in an adequately climatized consultation room and the patients were positioned in a supine position or, when necessary, left lateral decubitus. A transthoracic echocardiographic examination was performed using a "*Vivid 7*" (*General Electrics Medical Systems*®, Milwaukee, USA) ultrasound system with a 4S MHz transducer. The parameters used to evaluate left systolic ventricular function were fraction shortening (FS) and ejection fraction (EF), the latter evaluated by the Simpson's biplane method. The systolic right ventricular function was evaluated using the tricuspid annular plane systolic excursion (TAPSE).

Both the FS and EF values are presented as a percentage. The TAPSE was converted to a z-score to eliminate age related variations using the average and standard deviation (Attachments - Table 8) of a studied North American population. (28)

Statistical Analysis

The database programme used for the statistical analysis was the *Statistical Package for the Social Sciences* (IBM SPSS Statistics®) version 24. The significance level used was 0,05.

Variable normality was determined by the *Kolmogorov-Smirnov* test or the *Shapiro-Wilk* test, depending on the size of the variable. If $n>30$, the *Kolmogorov-Smirnov* test was used, if $n<30$, the *Shapiro-Wilk* test was used instead.

The echocardiographic functional parameters analysed over a period of 10 years were summarized, using their average, into three periods, as seen in Table 1. The first, during anthracycline treatment and one year after its conclusion in order to evaluate potential acute/subacute and early chronic cardiac dysfunction; the second period included the three years of follow up post the first period; and the third period included the remaining follow-up.

Table 1 – Periods of functional echocardiographic evaluation

		1st period			**2nd period**			**3rd period**					
SR	Dx	3mths	6mths	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs	9yrs	10yrs
H/VHR	Dx	3mths	6mths	1yr	2yrs*	3yrs	4yrs	5yrs*	6yrs	7yrs	8yrs	9yrs	10yrs

*This difference is due to the "High/Very High Risk" group treatment protocol includes anthracycline treatment during Induction and Consolidation phases, while the "Standard Risk" protocol includes anthracyclines only for the Induction phase (1 month).

To compare quantitative variables (FS, EF and TAPSE) between two independent groups (SR/ H/VHR, male/female or age at diagnosis) the *t-Student test* was used if the variables followed a normal distribution and n>30, whereas the non-parametric *Mann-Whitney U test* was selected if the variables failed to meet any of the conditions mentioned previously.

To compare the age at diagnosis within the H/VHR group, the sample was divided into two subgroups. The first was composed of patients diagnosed before completing 10 years of age and the second included the patients diagnosed between 10 and 18 years of age.

Ethical Issues

The Department of Paediatric Cardiology of the Hospital Centre of the University of Coimbra granted permission for the investigators to access medical reports and all the ethical issues, including patient and data privacy, were safeguarded.

SECTION 3

RESULTS

RESULTS

1. Population

From the 79 children, aged 1 to 17 years at the time of diagnosis (7 ± 4,70 years), 38 were included in the SR group and 41 were included in the H/VHR group. The demographic characteristics are shown in Table 2.

Table 2 –Demographic characteristics

	Number of patients (n)	Age at diagnosis (years)	Male %
SR	38	3,84 ± 2,37	53%
H/VHR	41	9,93 ± 4,44	66%

From the original sample (n=87), which consisted of all the patients diagnosed during the study period (2007-2016), 8 were excluded. The exclusion criteria were early death (n=1), refractory leukaemia requiring a protocol switch (n=2) and Philadelphia chromosome positive leukaemia (n=5).

The cardiovascular risk factors identified prior to therapy were arterial hypertension (n=5), type 1 diabetes *mellitus* (n=2), dyslipidaemia (n=3) and chronic kidney disease (n=2). None of the patients included had symptomatic cardiovascular disease. The group characteristics are summarized in Table 3.

Table 3 – Group Characteristics

	Standard Risk group	High/Very High Risk group
Average age (years)	3,84 (1.1 – 9.2)	9,93 (1.2 - 17.3)
Number of patients	38	41
Gender (male/female)	20/18	27/14
Years of follow-up after diagnosis (average)	4.9 (0.3 – 10)	3.7 (0.5 – 10)
Anthracycline cumulative dose (mg/m^2)	60	300
Chemotherapy protocol	DFCI 05-01 or 11-01	DFCI 05-01 or 11-01

2. Comparison of echocardiographic functional parameters between SR and H/VHR groups

TAPSE's z-scores during anthracycline treatment and one year after its conclusion (TAPSE1) showed statistically significant differences (n=25; p=0,044), being lower in the "High/Very High Risk" group (Table 4).

Table 4 – TAPSE (z-score) in each "Oncological Risk" group

	SR	H/VHR	*p-value*
TAPSE1	**0,57** ± 0,79	**-0,65** ± 1,22	**0,044**
TAPSE2	1,10 ± 1,55	0,65 ± 1,68	0,172
TAPSE3	1,28 ± 1,78	-0,10 ± 1,73	0,123

The other variables of cardiac function (FS and EF) did not show any statistically significant differences between SR and H/VHR groups as seen in Tables 11 and 12 (see Attachments).

3. Comparison of echocardiographic functional parameters between genders within the SR group

Fraction shortening measured during the late follow-up period (FS3) showed statistically significant differences (n=16; p=0,024), being lower in the female group (Table 5).

Table 5 – FS (%) between genders in the SR group

	Male	Female	*p-value*
FS before treatment	42,67 ± 5,51	37,50 ± 3,70	0,114
FS1	35,20 ± 1,78	37,50 ± 4,50	0,194
FS2	35,86 ± 1,78	36,38 ± 3,80	0,471
FS3	**36, 95** ± 1,78	**33,00** ± 2,35	**0,024**

TAPSE's z-scores measured during the late follow-up period (TAPSE3) showed statistically significant differences (n=15; p=0,010), being lower in the female group (Table 6).

Table 6 – TAPSE (z-score) between genders in the SR group

	Male	Female	*p-value*
TAPSE1	-	0,57 ± 0,79	-
TAPSE2	0,95 ± 1,75	1,31 ± 1,35	0,426
TAPSE3	**1,96** ± 1,56	**-0,08** ± 1,45	**0,010**

The other variables did not show any statistically significant differences as seen in Table 13 (see Attachments).

4. Comparison of echocardiographic functional parameters between genders within the H/VHR group

No statistically significant differences were found between genders within the "High/Very High Risk" group as can be observed in Tables 14, 15 and 16 (see Attachments).

5. Comparison of echocardiographic functional parameters between age at diagnosis within the H/VHR group

TAPSE's z-scores during anthracycline treatment and one year after its conclusion (TAPSE1) showed statistically significant differences (n=22; p=0,008), being lower in the older group (Table 7).

Table 7 – TAPSE (z-score) between age at diagnosis in the H/VHR group

	1 – 9y	10 – 17y	*p-value*
TAPSE before treatment	3,33 ± 1,34	2,40 ± 2,97	0,238
TAPSE1	**0,16** ± 0,77	**-0,96** ± 1,23	**0,008**
TAPSE2	1,00 ± 2,18	0,47 ± 1,39	0,341

The other variables did not show any statistically significant differences (see Attachments - Tables 17 and 18).

SECTION 4

DISCUSSION

DISCUSSION

Cardiotoxicity is a well-known side effect of anthracycline chemotherapy (6,7,10,13–16) and the main goal of this study was to compare two different ALL risk groups and establish a possible relation between oncological risk and acute, early chronic or late chronic cardiotoxicity.

According to our results, the TAPSE during anthracycline treatment and one year after its conclusion (TAPSE1) showed lower values in the H/VHR group, implying that there might be a higher probability of acute/ early chronic right ventricular dysfunction in this group.

Other secondary goals were to identify the existence of any correlation between genders among each oncological risk group and age at diagnosis in the H/VHR group.

Regarding gender difference in the SR group, we found that FS and TAPSE measured during the late follow-up period (FS3 and TAPSE3) were both lower in female patients, suggesting that chronic biventricular systolic dysfunction would be more likely to happen in girls among the SR group. However, when analysing the database, none of these values were compatible with cardiac dysfunction, supporting only the hypothesis that girls may have lower, but still within normal range, values. Nonetheless, this potentially implies a higher predisposition to cardiac dysfunction in female patients as observed in various studies. (16,29) Perhaps, as the follow-up continues (further than 10 years), these values could eventually fall below the normal range.

On the other hand, when analysing the correlation between age at diagnosis we found that TAPSE during anthracycline treatment and one year after its conclusion (TAPSE1) in H/VHR group showed lower values in the older subjects, possibly meaning that there might be a higher probability of acute/ early chronic right ventricular dysfunction in these patients.

The results of this study need to be carefully analysed. Despite being statistically true for this population, we cannot make general assumptions, and further prospective studies are necessary to validate our findings.

In fact, from a total sample of 79 patients, we were not able to have some echocardiographic parameters measured in more than 30 patients, limiting the statistical analysis to only non-parametric tests (*Mann-Whitney U test*). This was due to the limited data provided in the medical reports, which were frequently incomplete. The cardiac follow-up of oncological patients in a specific setting started in December 2015 with the creation of the Cardio-Oncology consultation in the Paediatric Hospital of Coimbra in which patients are followed according to specific guidelines (26,27) that will allow for a more complete and reliable study in the future.

On the other hand, the fact that the echocardiogram is an operator-dependent exam means the results may vary according to the physician performing it. Once again, the creation of the specialized Cardio-Oncology consultation carried out by only one physician at the moment will help to standardize this exam and overcome this bias in upcoming studies.

Another limitation of this study was the average and standard deviation used to convert the TAPSE to a z-score were from a North American reference population, which is different from our population. Nevertheless, even admitting this difference, its effect would be similar in all the groups studied, thus, not interfering directly with the comparisons made.

Despite all these limitations and possible bias, the authors see this study as a launching pad to years of hard work and follow-up of cardio-oncological patients. More echocardiographic parameters should be evaluated and cardiac biomarkers like cardiac troponins and cardiac natriuretic peptides (6,10,12,17,21,24) could also be included. A

prospective study would be the best way to determine and compare anthracycline cardiotoxicity in Acute Lymphoblastic Leukaemia in different risk groups.

Finding correlations between anthracycline cardiotoxicity and echocardiographic or analytical parameters during the follow-up of oncological patients would allow us to initiate some preventive strategies, (15,30) and reduce the incidence of anthracycline-induced cardiotoxicity in oncological patients.

SECTION 5

CONCLUSION

CONCLUSION

This study focused primarily on finding a relation between anthracycline total cumulative dose and cardiotoxicity in a paediatric Portuguese population.

We do not consider our findings sufficiently substantial to make general assumptions based on small sample sizes. Nonetheless, we found significant differences in some echocardiographic parameters between some groups which may lead us in an important direction.

TAPSE during anthracycline treatment and one year after its conclusion showed lower values in the H/VHR group, highlighting that there might be a higher probability of acute/ early chronic right ventricular dysfunction in this group, especially in the older subjects.

FS and TAPSE measured during the late follow-up period were both lower in the female patients, suggesting that chronic systolic dysfunction would be more likely to happen in girls among the SR group.

As a future perspective, the recently created specialized Cardio-Oncology consultation has a substantial value in the follow-up of patients diagnosed with any childhood cancer and will allow more in-depth and detailed prospective studies.

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REFERENCES

1. Lipshultz SE. Exposure to Anthracyclines During Childhood Causes Cardiac Injury. Semin Oncol. 2006;8–14.

2. Bayram C, Çetin I, Tavil B, Yarali N, Ekici F, Isik P, et al. Evaluation of Cardiotoxicity by Tissue Doppler Imaging in Childhood Leukemia Survivors Treated with Low-Dose Anthracycline. Pediatr Cardiol. 2015;36:862–6.

3. Vandecruys E, Mondelaers V, De Wolf D, Benoit Y, Suys B. Late cardiotoxicity after low dose of anthracycline therapy for acute lymphoblastic leukemia in childhood. J Cancer Surviv. 2012;(6):95–101.

4. Prestor V V, Rakovec P, Kozelj M, Jereb B. Late cardiac damage of anthracycline therapy for acute lymphoblastic leukemia in childhood. Pediatr Hematol Oncol. 2000;17:527–40.

5. Rammeloo LAJ, Postma A, Sobotka-Plojhar MA, Bink-Boelkens MTE, van der Does-van der Berg A, Veerman AJP, et al. Low-Dose Daunorubicin in Induction Treatment of Childhood Acute Lymphoblastic Leukemia : No Long-Term Cardiac Damage in a Randomized Study of the Dutch Childhood Leukemia Study Group. Med Pediatr Oncol. 2000;35:13–9.

6. Ruggiero A, Rosa G De, Rizzo D, Leo A, Maurizi P, Nisco A De, et al. Myocardial performance index and biochemical markers for early detection of doxorubicin-induced cardiotoxicity in children with acute lymphoblastic leukaemia. Int J Clin Oncol. 2013;18:927–33.

7. Rathe M, Lauritz N, Carlsen T, Oxhøj H, Nielsen G. Long-Term Cardiac Follow-Up of Children Treated With Anthracycline Doses of 300 mg/m2 or Less for Acute Lymphoblastic Leukemia. Pediatr Blood Cancer. 2010;54:444–8.

8. Rathe M, Carlsen NLT, Oxhøj H. Late Cardiac Effects of Anthracycline Containing Therapy for Childhood Acute Lymphoblastic Leukemia. Pediatr Blood Cancer. 2007;48:663–7.

9. Avelar T, Pauliks LB, Freiberg AS. Clinical Impact of the Baseline Echocardiogram in Children With High-Risk Acute Lymphoblastic Leukemia. Pediatr Blood Cancer. 2011;57:227–30.

10. Lipshultz SE, Miller TL, Scully RE, Lipsitz SR, Rifai N, Silverman LB, et al. Changes in Cardiac Biomarkers During Doxorubicin Treatment of Pediatric Patients With High-Risk Acute Lymphoblastic Leukemia : Associations With Long-Term Echocardiographic Outcomes. J Clin Oncol. 2012;30(10):1042–9.

11. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med. 1991;324(12):808–15.

12. Lee HS, Son CB, Shin SH, Kim YS. Clinical Correlation between Brain Natriutetic Peptide and Anthracyclin-induced Cardiac Toxicity. Cancer Res Treat. 2008;40(3):121–6.

13. Stapleton GE, Stapleton SL, Martinez A, Ayres NA, Kovalchin JP, Bezold LI, et al. Evaluation of Longitudinal Ventricular Function with Tissue Doppler Echocardiography in Children Treated with Anthracyclines. J Am Soc Echocardiogr. 2007;20:492–7.

14. Collaborative Group CALL. Beneficial and harmful effects of anthracyclines in the treatment of childhood acute lymphoblastic leukaemia : a systematic review and meta-analysis. Br J Haematol. 2009;145:376–88.

15. Mahoney DH. Evaluation of Left Ventricular Function in Asymptomatic Children About to Undergo Leukemia : An Outcome Study. J Pediatr Hematol Oncol. 2001;23(7):420–3.

16. Lipshultz SE, Lipsitz SR, Sallan SE, Dalton VM, Mone SM, Gelber RD, et al. Chronic Progressive Cardiac Dysfunction Years After Doxorubicin Therapy for Childhood Acute Lymphoblastic Leukemia. J Clin Oncol. 2005;23(12):2629–36.

17. Dolci A, Dominici R, Cardinale D, Sandri MT, Panteghini M. Biochemical Markers for Prediction of Chemotherapy- Induced Cardiotoxicity Systematic Review of the Literature and Recommendations for Use. Am J Clin Pathol. 2008;130:688–95.

18. Sorensen K, Levitt GA, Bull C, Dorup I, Sullivan ID. Late Anthracycline Cardiotoxicity after Childhood A Prospective Longitudinal Study. Cancer. 2003;97:1991–8.

19. Zalewska-Szewczyk B, Lipiec J, Bodalski J. Late cardiotoxicity of anthracyclines in children with acute leukemia. Klin Padiatr. 1999;211:356–9.

20. Bhatia S. Long-term Complications of Therapeutic Exposures in Childhood : Lessons Learned From Childhood Cancer Survivors. Pediatrics. 2012;130(6):1141–3.

21. Sherief LM, Kamal AG, Khalek EA, Kamal NM, Soliman AAA, Esh AM. Biomarkers and early detection of late onset anthracycline-induced cardiotoxicity in children Biomarkers and early detection of late onset anthracycline-induced cardiotoxicity in children. Hematology. 2012;17(3):151–6.

22. Silverman LB. Balancing cure and long-term risks in acute lymphoblastic leukemia. Hematology. 2014;190–7.

23. Fiuza M, Ribeiro L, Sousa AR, Menezes MN. Organização e implementação de uma consulta de cardio-oncologia. Rev Port Cardiol. 2016;35(9):485–94.

24. Mavinkurve-groothuis AMC, Marcus KA, Pourier M, Loonen J, Feuth T, Hoogerbrugge PM, et al. Myocardial 2D strain echocardiography and cardiac biomarkers in children during and shortly after anthracycline therapy for acute lymphoblastic leukaemia (ALL): a prospective study. Eur Heart J. 2013;14:562–9.

25. Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Gaynon P, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14(1):18–24.

26. Armenian SH, Hudson MM, Mulder RL, Chen MH, Constine LS, Dwyer M, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Cildhood Cancer Guideline Harmonization Group. Lancet Oncol. 2015;16:e123-36.

27. Kremer LCM, Mulder RL, Oeffinger KC, Bhatia S, Landier W, Levitt G, et al. A Worlwide Collaboration to Harmonize Guidelines for the Long-Term Follow-Up of Childhood and Young Adult Cancer Survivors: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group. Pediatr Blood Cancer. 2013;60:543–9.

28. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gamillscheg A, et al. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiogr. 2009;22(6):715–9.

29. Goldberg JM, Scully RE, Sallan SE, Lipshultz SE. Cardiac Failure 30 Years after Treatment Containing Anthracycline for Childhood Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol. 2012;34(5):395–7.

30. Cruz M, Duarte-rodrigues J, Campelo M. Cardiotoxicidade na terapêutica com antraciclinas: estratégias de prevenção. Rev Port Cardiol. 2016;35(6):359–71.

ATTACHMENTS

Table 8 – Average and Standard Deviation of TAPSE in a North American population (28)

Age	Average (cm)	Standard Deviation
1 month	0,91	0,11
3 months	1,14	0,14
6 months	1,31	0,15
12 months	1,44	0,16
1 years	1,55	0,15
2 years	1,65	0,14
3 years	1,74	0,13
4 years	1,82	0,13
5 years	1,87	0,13
6 years	1,9	0,14
7 years	1,94	0,15
8 years	1,97	0,15
9 years	2,01	0,14
10 years	2,05	0,13
11 years	2,1	0,14
12 years	2,14	0,15
13 years	2,2	0,17
14 years	2,26	0,19
15 years	2,33	0,20
16 years	2,39	0,20
17 years	2,45	0,20
18 years	2,47	0,21

Table 9 - FS (%) in each "Oncological Risk" group

	SR	H/VHR	*p-value*
FS before treatment	39,71 ± 4,96	37,79 ± 4,64	0,226
FS1	36,35 ± 3,76	34,73 ± 3,98	0,242
FS2	36,07 ± 3,41	35,27 ± 3,86	0,366
FS3	35,72 ± 3,61	33,40 ± 2,51	0,100

Table 10 – EF (%) in each "Oncological Risk" group

	SR	H/VHR	*p-value*
EF before treatment	70,00 ± 2,83	66,20 ± 7,50	0,286
EF1	66,75 ± 4,99	62,14 ± 5,46	0,139
EF2	66,60 ± 4,06	63,43 ± 5,95	0,110
EF3	64,72 ± 4,80	63,50 ± 3,49	0,394

Table 11 – EF (%) between genders in the SR group

	Male	Female	*p-value*
EF2	65,24 ± 3,66	68,63 ± 4,23	0,095
EF3	65,68 ± 5,40	62,80 ± 2,86	0,148

Table 12 – FS (%) between genders in the H/VHR group

	Male	Female	*p-value*
FS before treatment	38,11 ± 4,99	37,20 ± 4,44	0,312
FS1	34,12 ± 4,13	35,94 ± 3,55	0,220
FS2	36,23 ± 3,23	33,87 ± 4,43	0,210
FS3	36,00 ± 1,41	31,67 ± 0,58	0,100

Table 13 – EF (%) between genders in the H/VHR group

	Male	Female	*p-value*
EF1	61,39 ± 6,10	63,90 ± 3,33	0,278
EF2	64,83 ± 3,14	61,56 ± 8,24	0,370

Table 14 – TAPSE (z-score) between genders in the H/VHR group

	Male	Female	*p-value*
TAPSE before treatment	2,60 ± 3,01	3,02 ± 1,37	0,381
TAPSE1	-0,66 ± 1,32	-0,65 ± 0,99	0,320
TAPSE2	0,74 ± 1,83	0,50 ± 1,49	0,391

Table 15 – FS (%) between age at diagnosis in the H/VHR group

	1 – 9y	10 – 17y	*p-value*
FS before treatment	40,00 ± 4,58	36,56 ± 4,45	0,111
FS1	34,91 ± 2,99	34,65 ± 4,34	0,421
FS2	36,26 ± 4,87	34,80 ± 3,38	0,320
FS3	34,50 ± 3,54	32,67 ± 2,08	0,300

Table 16 – EF (%) between age at diagnosis in the H/VHR group

	1 – 9y	10 – 17y	*p-value*
EF1	61,67 ± 1,87	62,35 ± 6,48	0,099
EF2	63,07 ± 6,41	63,61 ± 5,95	0,493