FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA

CARDIOTOXICITY ASSOCIATED WITH PEDIATRIC HODGKIN LYMPHOMA TREATMENT

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ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE CARDIOLOGIA PEDIÁTRICA

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Abreviations:

TAPSE - Tricuspid Annular Plane Systolic Excursion

Fej – Ejection Fraction

SF – Shortening Fraction

IC – Cardiac insufficiency

CHUC - Centro Hospitalar e Universitário de Coimbra

LD-IFRT – Low Dose Involved Field Radiation

EURONET- Chemotherapy protocol recommended by a trial group used after 2015 in CHUC for Pediatric Hodgkin Lymphoma

CCG 5942- Chemotherapy protocol recommended by Children´s Cancer Group used before 2015 in CHUC for Pediatric Hodgkin Lymphoma

OEPA - Chemotherapy combination that is often used with radiation therapy to treat a certain type of childhood Hodgkin lymphoma. It includes the drugs vincristine sulfate, etoposide, prednisone, and doxorubicin hydrochloride.

Abstract

Introduction:

Cardiotoxicity is one of the possible consequences of treating Hodgkin's lymphoma. This assumes a very important role in the patients' outcomes, since, increasingly, they have a higher survival rate, better quality of life and inherently longer survival. This is due to the improvement in the treatment of this pathology.

Material and methods:

Clinical information was collected from 103 patients about their age at diagnosis, sex, cardiovascular risk factors (arterial hypertension, diabetes, previous family disease, obesity, dyslipidaemia), anthracycline dose to which they were subjected and the use of mediastinal radiotherapy.

According to this information, echocardiograms of these patients were analysed at five different times, baseline (time of diagnosis), 6 months, 1 year, 2 years, 3 years, and 5 years after the end of the chemotherapy protocol to which they were subjected (EURONET or CCG 5942).

Results: Statistically significant results were obtained between TAPSE values measured 2 years after treatment with both dose ($p=0.01$) and sex ($p=0.024$). We obtained lower TAPSE values for females and for higher doses. Inverse relationships were also observed between the TAPSE value measured 6 months after treatment. The LV systolic function 5 years after treatment was inversed relationed with the age of the patients.

Discussion: It was observed that there may be a relationship between the TAPSE 3 values and the anthracycline dose to which the patient was submitted, and we found lower TAPSE values in the group with the highest dose, in this case of 220 mg/m2.

In this relationship, lower mean TAPSE values were found in females compared to males, which could mean a greater predisposition for females to develop this cardiac toxicity. As observed in the relation with anthracycline dose, it only refers to chronic toxicity, therefore from 2 years after the end of treatment.

It should also be noted that there seems to be an inverse relation between age and TAPSE1, that is, for older patients, TAPSE 1 values would be lower, indicating greater cardiotoxicity. We also noted direct relation between SF5 and age, meaning that for older patients, SF5 was higher, meaning that cardiotoxicity was greater at younger ages.

Conclusion:

The incidence of cardiotoxicity after treatment for Hodgkin's lymphoma was 8% in the studied population.

One of the conclusions we can take from this study is that it appears that cardiac toxic cardiac toxicity begins to reflect on right heart function in a chronic phase, more than 2 years after treatment.

Other conclusions we can draw are that younger age, female sex and higher cumulative dose could be risk factors for cardiotoxicity due to anthracyclines.

Keywords:

“Cardiotoxicity”; “Paediatric Hodgkin lymphoma”; “Ventricular disfunction”; “Anthracyclines”; “Cardio-oncology”; “Ecocardiography”

Introduction

Classic Hodgkin lymphoma (CHL) is a malignancy involving lymph nodes and the lymphatic system and is generally characterized by the presence of large binucleate cells, (Hodgkin Reed-Sternberg [HRS] cells) in a background of benign inflammatory cells. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older.

Chemotherapy protocols for the treatment of this pathology have evolved over the years, and those used in the patients in this article are the CCG 5942 protocol used until 2015, and the Euronet protocol, after 2015.

For patients before 2015, CCG 5942 was the chosen protocol and favourable risk and intermediate risk patients received 4 and 6 monthly cycles of cyclophosphamide, vincristine, prednisone, procarbazine, doxorubicin, bleomycin, and vinblastine (COPP/ABV) respectively. High risk patients received 6 cycles of treatment: 2 cycles of COPP/ABV, 2 cycles of high-dose cytarabine with etoposide, and 2 cycles of cyclophosphamide, vincristine, doxorubicin, methylprednisolone and prednisone. Patients were evaluated at completion of chemotherapy; all patients who achieved a complete response were eligible for randomization to receive either LD-IFRT or no further therapy. Patients who did not achieve a complete response to chemotherapy were non-randomly assigned to receive LD-IFRT. A total dose of 21 Gy was given in 12 fractions to all lymph node regions containing radiologically abnormal lymph nodes at the time of diagnosis.

This meant that patients before 2015 either received 140 mg/m^2 if it was a low-risk patient, 210 mg/m^2 for an intermediate risk or 220 mg/m^2 for an high risk.

For patients diagnosed after 2015 with stage IA, IIA, and IB CHL (with or without bulky disease) treatment was according to EuroNet-PHL-C1.

After initial cycles of chemotherapy, patients with adequate response may avoid RT and move to routine follow up. Patients with inadequate response receive ISRT (to all sites and boost to sites of inadequate response per EuroNet-PHL-C1.

For the regimen based on EuroNet-PHL-C1, after 2 initial cycles of OEPA, patients with adequate response are treated with 2 cycles of COPDAC (cyclophosphamide, vincristine sulfate, prednisone, and dacarbazine).

Patients with stage IIB, IIIA, IIIB, and IV followed EuroNet-PHL-C1 protocol.

For treatment based on EuroNet-PHL-C1, after 2 initial cycles of OEPA, patients with adequate response are treated with 4 cycles of COPDAC. Patients with inadequate response are treated with 4 cycles of COPDAC and ISRT to all sites and boost to sites of inadequate response. In both cases, based on an end of therapy PET assessment, patients were either followed up or considered for biopsy to confirm persistent active disease.

This meant that after 2015 patients were submitted to either 140 mg/m^2 or 160 mg/m^2 of anthracycline dose.

Cardiotoxicity is one of the possible consequences of treating Hodgkin's lymphoma. This assumes a very important role in the lives of patients since, increasingly, they have a higher survival rate, better quality of life and, inherently, longer survival. This is due to the improvement in the treatment of this pathology. (1) However, success in fighting this entity also provides a greater probability of deleterious cardiovascular alterations, such as: electrocardiographic alterations, left ventricular dysfunction subclinical or with heart failure. These changes have been increasingly reported. (two)

Additionally, these changes take on even greater dimension when we talk about individuals with pathology in pediatric age due to their greater susceptibility to this iatrogenic cardiac dysfunction. That said, the number of studies that investigated these changes in this specific population is still small and, as such, the need for research in this area is evident. (3)

Anthracycline-related cardiomyopathy is one of the most relevant patterns of cardiotoxicity regarding cancer therapy. There is evidence that left ventricular systolic dysfunction is directly related to the use of cumulative doses of anthracyclines. The cumulative total dose is the main risk factor for the occurrence of congestive heart failure related to the use of anthracyclines. However, there is no safe dose at the cardiotoxic level, which must always be balanced with its degree of anticancer efficacy.

Currently, it is estimated that more than 50% of cancer patients are treated with radiotherapy. Along with the development of new chemotherapeutic agents, radiotherapy has revolutionized the prognosis of individuals with various types of cancer. However, late cardiovascular effects are often detected after the use of this therapeutic method. Most clinical information obtained on cardiotoxicity from chest irradiation is based on studies of individuals with breast cancer or Hodgkin's lymphoma who developed symptomatic disease during treatment or monitoring.

All risk factors for cardiotoxicity resulting from Hodgkin's lymphoma therapy are closely related to early and late cardiotoxicity, and not to acute cardiotoxicity, according to the scientific literature on this topic.

The major risk factors for cardiotoxicity are younger age, female sex, high dose of anthracyclines, mediastinal radiotherapy, arterial hypertension, coronary heart disease and electrolyte disturbances.

To reduce cardiotoxicity, the dose of anthracyclines can be limited, the use of structural analogues of anthracyclines or, mainly, cardioprotective pharmacological agents can be promoted. (5)

This study aims to analyse the occurrence of these harmful effects and the impact of factors such as patient characteristics, as well as to analyse prevention measures and early diagnosis in their evolution.

Material and methods

This is an observational, retrospective, analytical cohort study in which patients at the Pediatric Hospital of the Centro Hospitalar e Universitário de Coimbra diagnosed with Hodgkin's Lymphoma were studied over a period of 23 years, from 1998 to 2021.

Patients aged between 4 and 18 years who attended a pediatric cardiology or cardio-oncology consultation were included.

Clinical files containing clinical information on patients as well as results of complementary diagnostic tests, namely echocardiograms, were analysed.

Authorization for this consultation and for carrying out the study was requested from the CHUC ethics committee.

The bibliographic search was carried out by consulting the PubMed public database.

Schedule:

Throughout 2021, the study was planned, and the approval of the CHUC ethics committee was also requested. In October 2021, approval was obtained, and the subsequent research began, as well as the effective analysis of clinical processes and complementary diagnostic tests.

Throughout this year 2022, the statistical analysis was carried out as well as data analysis.

Statistical analysis

Clinical information was collected from 103 patients about their age at diagnosis, sex, cardiovascular risk factors (hypertension, diabetes mellitus, previous family disease, obesity, dyslipidemia), anthracycline dose they were subjected to and the use of mediastinal radiotherapy.

According to this information, echocardiograms of these patients were analysed at five different times, 6 months, 1 year, 2 years, 3 years, and 5 years after the end of the chemotherapy protocol to which they were subjected (EURONET or CCG 5942).

From the analysis of the echocardiograms, it was possible to obtain 3 parameters that are related to cardiac functionality, allowing to determine the degree of affectation of the same, namely the *Tricuspid Annular Plane Systolic Excursion* (TAPSE), the *ejection fraction (FEVE)* and *the shortening fraction of the Left ventricle (FS).*

Values of $p < 0.05$ were considered statistically significant.

We compared parameters corresponding to cardiac functionality as a function of the clinical information.

Patients were divided according to the cumulative dose of anthracyclines to which they were submitted into 5 categories, 140, 160, 210, 220 and 270 mg/m2. With this division it was possible to use the Kruskal Wallis test, as we have more than 2 categories in this variable.

As for Age, being a continuous ordinal variable with a non-normal distribution, it was compared using the Spearman coefficient.

Both in Sex and in Radiotherapy, as they are nominal variables with only 2 categories, they were analysed using non-parametric tests, namely Mann Whitney.

The parameters “Ejection fraction” and “Shortening fraction” were evaluated in percentage, so they are indicative of the entire population. However, due to TAPSE variations according to age group, it was necessary to transform each measured value into Z-score, considering the normal value for each age group. The attached table was used for this.

Patients who had relapsed Hodgkin's lymphoma or who died prematurely were excluded from the study.

The program used for statistical analysis was the “Statistical Package for the Social Science” (SPSS) software, version 27.

Ethical Conflicts

The CHUC ethics committee granted the researchers authorization to access the clinical data of all patients, with no conflicts of interest to be recorded.

Results

Data from 103 patients diagnosed with Hodgkin's lymphoma and treated with variable cumulative doses of anthracyclines (from 140 mg/m2 to 270 mg/m2) were analysed, with a mean age of diagnosis of 12.23 +/- 3.60 years, minimum value of 4 and a maximum of 18 years.

From the initial sample (N=103) patients with early death (N=5) were excluded.

Of the analysed sample, 45.9% of the patients were male, and 19.5% underwent mediastinal radiotherapy.

The mean age at diagnosis was similar in both sex: Within the male group, 12.19 +/- 3.61 years, while for females it was 12.20 +/- 3.60 years.

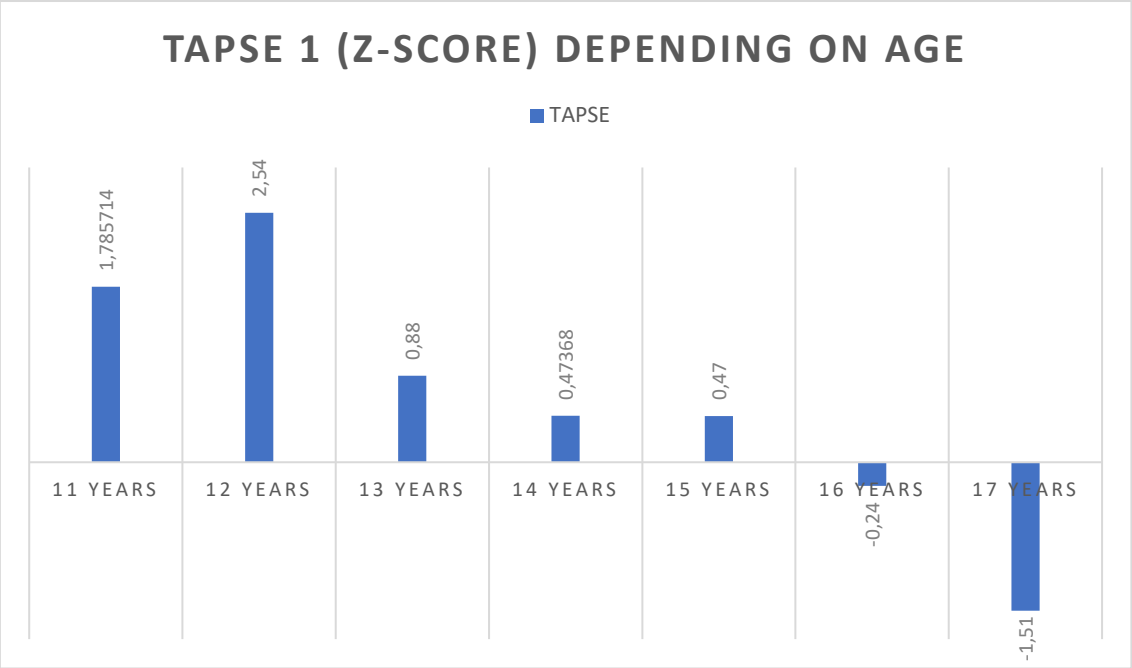
A reduced number of patients with previous cardiovascular risk factors were found, with obesity (N=3) and dyslipidaemia (N=1).

Comparison between the first measurement of echocardiographic values, 6 months after diagnosis (TAPSE 1, Fej 1 and SF1) and the different variables being studied

	TAPSE 1	**Fej 1**	**SF 1**
AGE	Spearman's Coefficient: -0.686	Spearman's Coefficient: -0.116	Spearman's Coefficient : -0.088

We can observe through the Spearman correlation coefficient that the relationship between the variables Fej1, SF1 and the age of the patients is weak since the absolute values of these coefficients are less than 0.4 in absolute value.

The value of the correlation coefficient between the variable TAPSE 1 and age is greater than 0.4, which indicates an inverse relationship between the two.



Graphic 1

We can observe the inverse relation proved in the statistical test, as age increases, we observe a decrease in the value of TAPSE 1, showing that for patients with older age there may be a greater risk of right ventricular dysfunction. It is important to note that we only have representation of age groups over 11 years old, given the age distribution of this pathology.

It should also be noted that this measurement was always performed 6 months after diagnosis, so any type of toxicity proved here would always be an acute or subacute cardiotoxicity.

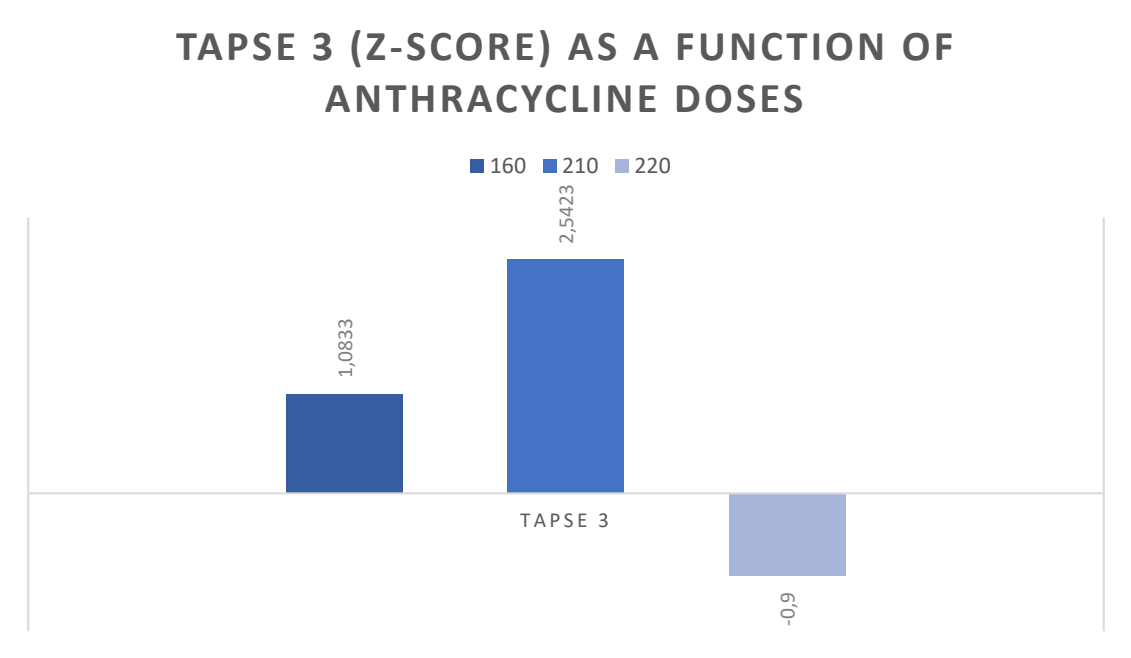
Regarding the variation of TAPSE 1 with the remaining variables under study, no statistically significant relations were observed.

Comparison of the third measurement of echocardiographic values, 2 years after diagnosis (TAPSE 3, Fej3, SF3) and the variables mentioned in the study

	TAPSE 3	FEj3	SF3
RADIO	Significance =0.925	Significance =0.396	Significance =0.26
DOSE	Significance =0.010	Significance =0.278	Significance =0.607
SEX	Significance =0.024	Significance =0.792	Significance =0.969

We can observe a value of p<0.05 (=0.010) in the relation between TAPSE 3 and Anthracycline Dose, which proves a statistically significant relation between these variables. As such, the mean and standard deviation of the variable TAPSE 3 in the different doses were evaluated, and it was found that for a dose of 220 mg/m2, we have -0.9029 +/- 0.584, which is the highest dose in this group and the highest value corresponded to a dose of 210 mg/m2, with 2.5423 +/- 1.

Below, the values observed in this comparison are shown.

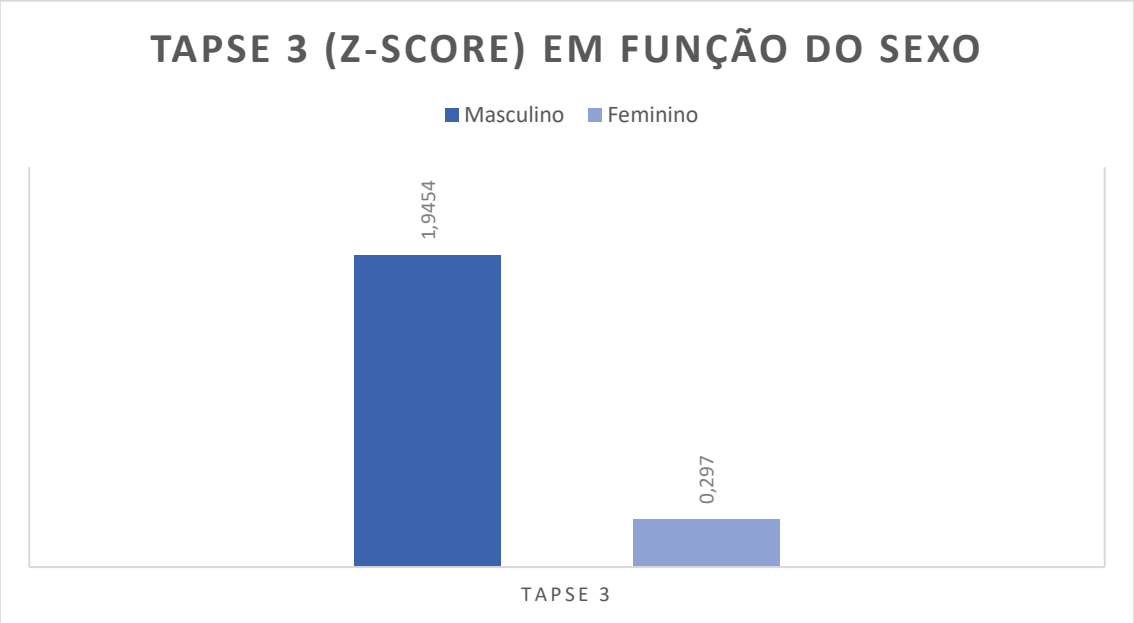


Graphic 2

We can observe lower values of TAPSE 3 for a higher dose of 220 mg/m2, which supports the hypothesis that a higher dose will mean greater cardiac toxicity.

It is important to mention that the mean value of TAPSE 3 for patients submitted to a dose of 210 mg/m2 could be falsely estimated due to the low amount of data referring to this dose. However, even when comparing the lower (160 mg/m2) and higher (220 mg/m2) TAPSE's, the difference is evident.

In the relation between the same TAPSE 3 and Gender, a p value of 0.024 was obtained, also indicating a statistically significant relationship between them. In this case, an average of 1.9454 +/- 1.5138 for males was evaluated, which is higher than the value for females of 0.2968 +/- 1.5096.



Graphic 3

We can see that for females, a value of TAPSE 3 was found much lower than for males, which may mean that females are more susceptible to cardiac toxicity.

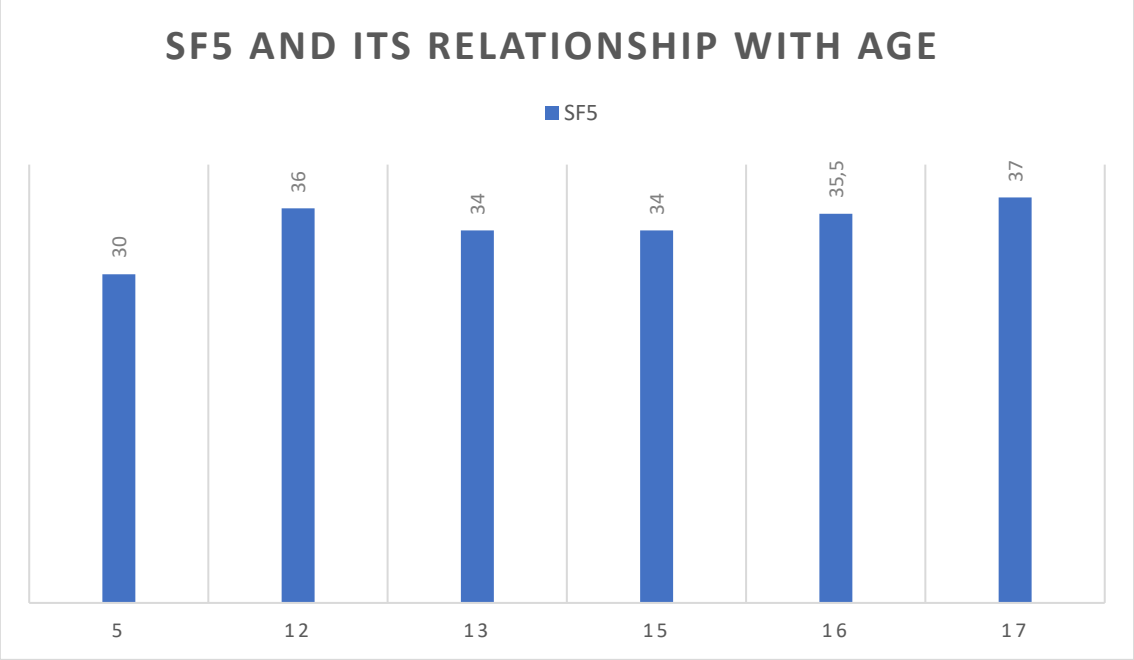
In the remaining variables measured 2 years after diagnosis, no statistically significant relations were observed.

Comparison of the fifth measurement of echocardiographic values, 5 years after diagnosis (TAPSE 5, Fej5, SF5) and the variables mentioned in the study

	TAPSE 5	FEj 5	SF5
AGE	Spearman's Coefficient: 0.068	Spearman's Coefficient:0.152	Spearman's Coefficient:0.576

We have a direct relationship between Fenc5 and age as the Spearman coefficient is 0.576

The values of Spearman's coefficient for comparing the values of age and the variables TAPSE 5 and SF 5 are less than 0.4, which shows that there is no statistically significant relation.



Graphic 4

From the graphic we can see a slight increase in SF5, demonstrating that in the case of chronic cardiotoxicity, younger age may in fact be a risk factor, as advanced by the current scientific literature.

Discussion

The incidence of cardiotoxicity after treatment for Hodgkin's lymphoma was 8%. At the diagnosis they were between 12 and 17 years old.

One of these patients has moderate LV dysfunction and other two have mild LV dysfunction one year after treatment. All patients with LV dysfunction started cardioprotective therapy with Lisinopril, two recovered function and one evolved into severe LV dysfunction five years after treatment. Two of them had undergone radiotherapy, namely the patient with sustained ventricular dysfunction. They also had anthracycline cumulative dose greater than 210 mg/m2. It is important to note that given the small number of these dysfunctional events (3 out of 103), the final conclusions should be carefully evaluated.

Regarding right ventricular dysfunction, through the TAPSE analysis, the incidence of Z-score values below -2 was 6%. Two patients presented this dysfunction 6 months after treatment, three one year after treatment and another, 3 years after. All patients who showed RV dysfunction started cardioprotective therapy, 4 recovered function and 2 have no data after the dysfunction. One of these 6 patients had undergone radiotherapy. Regarding the TAPSE values in the group who underwent radiotherapy, the values were lower 6 months after treatment. However, in the remaining measurement times, the group that was not submitted to Radiotherapy had lower values. This fact can be explained by the smaller amount of data after the first measurement time, but any relationship between these variables must be analysed with caution since no statistically significant relationship was obtained between the two.

There may be a relationship between the TAPSE 3 values and the anthracycline dose the patient took, and we found lower TAPSE values in the group with the highest dose of 220 mg/m2.

This finding may mean that patients submitted to higher doses of anthracyclines will suffer from greater risk of right ventricular dysfunction. It may also mean that cardiac toxicity begins to reflect on right heart function in a chronic phase, more than 2 years after treatment.

Lower mean TAPSE values were found in females, which demonstrate a greater predisposition for females to develop this cardiac toxicity. As observed with the anthracycline dose, it only refers to chronic toxicity, two years after the end of treatment. This finding agrees with other articles that address the possibility that female sex is a risk factor for cardiotoxicity resulting from anthracycline therapy. (3)

It should also be noted that there seems to be an inverse relationship between age and TAPSE1, that is, for older patients, TAPSE 1 values are lower, indicating greater cardiotoxicity in the early chronic toxicity.

On the other hand, there seems to be a direct relationship between age and Fenc5, which is measured 5 years after treatment, but in this case this higher toxicity at younger ages will be chronic.

The conclusions drawn from this study are in line with some resolutions of other studies related to this topic, in which it was concluded that younger age, female sex and higher cumulative dose could be risk factors for cardiotoxicity due to anthracyclines.

However, it was not possible to verify relationships with the use of radiotherapy, which may be due to the low percentage of patients in the sample who underwent this therapy.

Also, due to the small sample of patients with cardiovascular risk factors, it was not possible to make valid comparisons, to understand a possible worse prognosis.

It is important to note that many of the patients studied had a reduced number of echocardiograms, as they were not followed up in cardio oncology consultations.

Cardio oncology consultations only started in 2015, that is, only patients diagnosed after that date have records of consultations performed with echocardiograms performed at the desired times.

As such, I emphasize the importance of this consultation in the follow-up of these patients to control the effects addressed in the study of this therapy

The importance of cardiotoxicity has increased over the years as the therapy of neoplastic diseases becomes more effective. This is because the number of patients undergoing anthracyclines and radiotherapy who survive and with a considerable survival is becoming greater.

As such, it is very relevant to understand the real cardiotoxic effects of this therapy and what variables can influence its manifestation.

More studies like this are needed so that we can analyse patients at higher risk so they can be followed in a more controlled way to reduce these harmful effects.

It would be important to understand whether, with a higher number of patients undergoing mediastinal radiotherapy, we could obtain statistically significant relationships in any of the variables, since, as mentioned in other articles, this exposure is a risk factor for greater cardiotoxicity.

The low incidence of cardiotoxicity in this group should be look at carefully because it can be result of the low amount of data of some patients.

Some of the results of this study are contrary to articles on this topic, namely the greater early chronic cardiotoxicity for younger ages. However, it can be explained by the low representation of age groups below 11 years old, due to the age distribution of this pathology.

It should also be noted that because it is a retrospective study, based on often incomplete records, its limitations are great.

As such, especially in measurements made years after treatment, it will be necessary to carefully evaluate the conclusions obtained.

Conclusion

The incidence of cardiotoxicity after treatment for Hodgkin's lymphoma was 8% in the studied population.

One of the conclusions we can take from this study is that it appears that cardiac toxic cardiac toxicity begins to reflect on right heart function in a chronic phase, more than 2 years after treatment.

The same happened with the toxicity reflected on left heart function.

Other conclusions we can draw are that younger age, female sex and higher cumulative dose could be risk factors for cardiotoxicity due to anthracyclines.

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Ao Prof. Dr. António Pires por aceitar colaborar neste projeto e pelo acompanhamento.

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(1-9)

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Attachments

Table with variation of TAPSE value according to age group of a North American population

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

Ethics committee approval

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

CHUC CENTRO HOSPITALAR E UNIVERSITÁRIO DE COIMBRA

Comissão de Ética para a Saúde

Visto/ À U.I.D.
para difusão
3/12/21
Dr. Nuno Deveza
Diretor Clínico
C.H.U.C. - EPE

Exmo. Senhor
Dr. Nuno Deveza
Digmº Diretor Clínico do CHUC

SUA REFERÊNCIA	SUA COMUNICAÇÃO DE	NOSSA REFERÊNCIA	DATA
		Nº 409/CES	02-12-2021
		Proc.Nº **OBS.SF.134-2021**	

PI OBS.SF.134-2021 *"CARDIOTOXICIDADE ASSOCIADA AO TRATAMENTO DE LINFOMA DE HODGKIN PEDIÁTRICO"*
Entrada na UID: 08-07-2021
Entrada na CES: 03-11-2021
Investigador/a/es: João António de Almeida Mendes - Mestrado Integrado em Medicina
Coordenador/a/es: Andreia Sofia Santos Francisco
Co-Investigador/a/es:
Promotor: Não se aplica
Serviço de Realização: Cardiologia pediátrica do Hospital Pediátrico do CHUC

Cumpre informar Vossa Ex.ª que a CES - Comissão de Ética para a Saúde do Centro Hospitalar e Universitário de Coimbra, reunida em 17 de Novembro de 2021, após reapreciação do projeto de investigação supra identificado, emitiu o seguinte parecer:

"A Comissão considera que se encontram respeitados os requisitos éticos adequados à realização do estudo, pelo que emite parecer favorável à sua realização. Contudo, a Comissão de Ética solicita: 1) que o formulário específico da Comissão de Ética seja integralmente preenchido; 2) que sejam corrigidas as discrepâncias relativas à proteção concedida aos dados colhidos (irreversivelmente anonimizados ou codificados); 3) que a versão final dos documentos a corrigir seja enviada, com as alterações efetuadas devidamente assinaladas, para encerramento do processo administrativo".

Mais informa que a CES do CHUC deverá ser semestralmente atualizada em relação ao desenvolvimento dos estudos favoravelmente analisados e informada da data da conclusão dos mesmos, que deverá ser acompanhada de relatório final.

Com os melhores cumprimentos,

A Comissão de Ética para a Saúde do CHUC, E.P.E.

Margarida Silvestre

Prof. Doutora Margarida Silvestre
Presidente

CES do CHUC: Prof. Doutora Margarida Silvestre, Enfª Adélio Tinoco Mendes, Dra. Cláudia Santos, Dra. Isabel Gomes, Dra. Isabel Ventura, Rev. Pe. Doutor Nuno dos Santos, Dr. Pedro Lopes, Doutora Teresa Lapa, Dra. Teresa Monteiro

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