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

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Introduction

- Acute lymphoblastic leukaemia (ALL) is the most frequent cause of childhood cancer, being accountable for more than 25% of paediatric malignancies.
- ALL is classified by the National Cancer Institute as **Standard Risk** (SR), **High Risk** (HR) and **Very High Risk** (VHR).
- Anthracycline cardiotoxicity classification (time after treatment initiation):

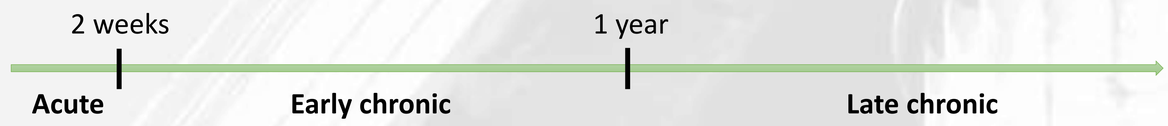

Fig 1. Classification of Cardiotoxicity

- Both the prognosis and survival of these patients are improving, reaching a 5-year survival rate above 90%. However, with this improved survival comes a greater risk of anthracycline-induced cardiac dysfunction and this reinforces the importance of a regular follow-up at a specialized Centre.
- **Goal**: Evaluate and compare functional echocardiographic parameters between **Standard Risk** and **High/Very High Risk** (H/VHR) patient groups and the influence of **age** and **gender** on long-term cardiac function. Acute and subacute toxicities were also evaluated.

Methods

- Observational, analytical, longitudinal, retrospective cohort study in a sample of patients aged 1 to 17 years, diagnosed with ALL between May 2007 and November 2016. The sample was divided into two groups.
- **Echocardiographic evaluation:** An echocardiographic analysis was carried out both before starting chemotherapy as a basal echocardiogram, and during the follow-up period. The parameters used to evaluate left systolic ventricular function were **fraction shortening** (FS) and **ejection fraction** (EF) by the Simpson's biplane method. Right systolic ventricular function was evaluated using the **tricuspid annular plane systolic excursion's** *z-score* (TAPSE).
- **Statistical Analysis:** IBM SPSS Statistics® version 24 with a significance level of 0,05.

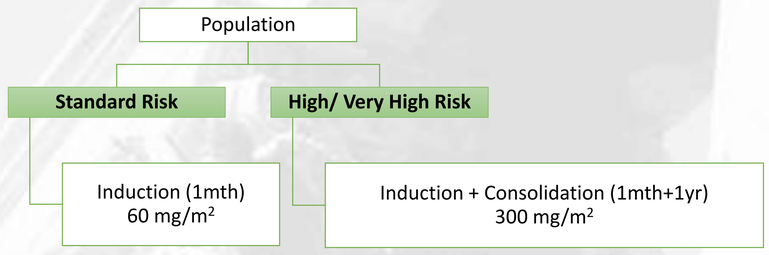

Fig 2. Patient selection

Exclusion factors
1. Early death;
2. Switch of treatment protocol;
3. Philadelphia-positive leukaemia.

Fig 3. Exclusion factors

Table 1. Periods of Echocardiographic Evaluation

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

*The periods were defined to match the classification of cardiotoxicity. This difference is due to the fact that 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).

Results

Table 2. Group Characteristics

	Standard Risk	High/Very High Risk
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
Follow-up (years)	4.9 (0.3 – 10)	3.7 (0.5 – 10)
Anthracycline dose (mg/m²)	60	300
Chemotherapy protocol	DFCI	DFCI

Table 3. Comparison of Echocardiographic Function between **Risk Groups** (Standard vs. High/Very High)

	Standard	High/Very High	*P-value*
FS (Dx)	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
EF (Dx)	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
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

Table 4. Comparison of Echocardiographic Function between **Genders** within the **Standard Risk** Group

	Male	Female	*P-value*
FS (Dx)	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**
EF2	65,24 ± 3,66	68,63 ± 4,23	0,095
EF3	65,68 ± 5,40	62,80 ± 2,86	0,148
TAPSE2	0,95 ± 1,75	1,31 ± 1,35	0,426
TAPSE3	**1,96** ± 1,56	**-0,08** ± 1,45	**0,010**

Table 5. Comparison of Echocardiographic Function between **Genders** within the **High/Very High Risk** Group

	Male	Female	*P-value*
FS (Dx)	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
EF1	61,39 ± 6,10	63,90 ± 3,33	0,278
EF2	64,83 ± 3,14	61,56 ± 8,24	0,370
TAPSE (Dx)	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 6. Comparison of Echocardiographic Function between **Age at Diagnosis** within the **High/Very High Risk** Group*

	1-9 yrs.	10-17 yrs.	*P-value*
FS (Dx)	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
EF1	61,67 ± 1,87	62,35 ± 6,48	0,099
EF2	63,07 ± 6,41	63,61 ± 5,95	0,493
TAPSE (Dx)	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

* Not performed for the Standard Risk group because an age of diagnosis of 10+ years can't be classified as Standard Risk.

Discussion

- TAPSE during 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.
- FS and TAPSE during the late follow-up period (**FS3** and **TAPSE3**) were both **lower** in **female** patients within the **SR** group, suggesting that **chronic biventricular systolic dysfunction** would be more likely to happen in this group.
- No statistically significant differences were found between genders within the H/VHR group.
- TAPSE during treatment and one year after its conclusion (**TAPSE1**) in **H/VHR** group showed **lower** values in **older** subjects, possibly meaning that there might be a higher probability of **acute/ early chronic right ventricular dysfunction** in these patients.
- 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.