Serum anti-Müllerian hormone as a marker of ovarian reserve among childhood cancer survivors

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INTRODUCTION

Childhood, adolescent and young adults (CAYA) female patients treated with alkylating agents in childhood for haematological disease are at risk for **ovarian impairment**. Accordingly, the current pivotal challenge in the care of long-term survivors is to screen patients exposed to gonadotoxic treatments in order to precociously identify women with diminished ovarian reserve, to whom provide a reproductive counselling.

Anti-Müllerian Hormone (AMH) has been proposed as a predictor of ovarian reserve in women[1,2], but data about its reliability in the setting of iatrogenic ovarian impairment are lacking.

AIM

We aimed at describing the pattern of residual ovarian function in a cohort of haematological cancer survivors, assessing the **relationship** between the **cumulative dose of alkylating agents** administered (expressed as **Cyclophosphamide Equivalent Dose - CED**) and **Anti-Müllerian Hormone** levels.

METHOD

Inclusion criteria

Adolescents or young women exposed to gonadotoxic treatments for **paediatric lymphoma or leukaemia** between 01.01.92 and 30.06.19 and

- Menarche achieved at least 12 months before
- Off-therapy for more than 12 months

Definitions

Outcome	Menses	FSH (U/L)	AMH-SDS
Premature ovarian insufficiency (POI)	Oligo-amenorrhea	>25	
Diminished ovarian reserve (DOR)	Regular	≤25	<-1.65 (<5th centile)
Normal ovarian reserve (NOR)	Regular	≤25	≥-1.65 (≥5th centile)

Exclusion criteria

- Syndromic conditions involving gonadal impairment
- Polycystic ovarian syndrome
- Haematopoietic stem cell transplantation

Data collection

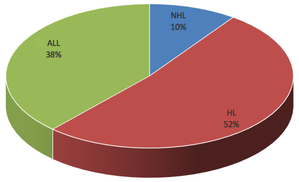
- Clinical: anagraphical, related to treatment, endocrine
- Lab: LH, FSH, oestradiol, **AMH-SDS** (Z score, estimated with reference to the Lie Fong et al reference ranges for age[3])

RESULTS

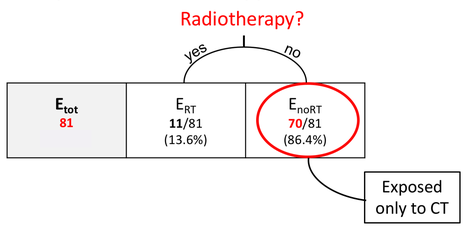
Population enrolled: **81 patients**

- *Underlying disease*

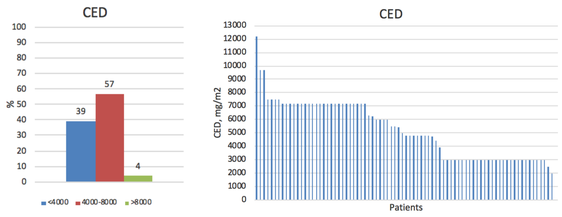
ALL: acute lymphoblastic leukaemia
NHL: non Hodgkin lymphoma
HL: Hodgkin lymphoma



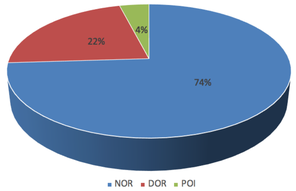
- *Exposure to radiotherapy*



- *Exposure to Cyclophosphamide Equivalent Dose (CED)*



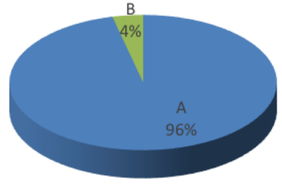
Ovarian function in the study population



AMH-SDS
- Mean: -0.48±1.43
- <1.65: 26%

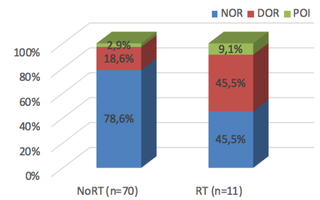
Need for hormonal therapy (HT)

A. Menarche achieved spontaneously and HT never needed
B. Menarche achieved spontaneously, HT started for secondary amenorrhea

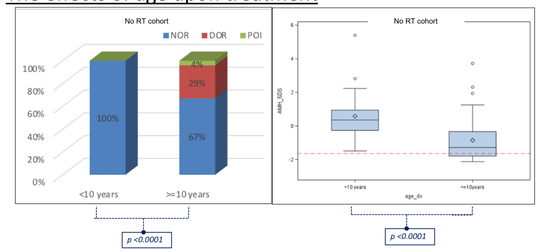


The effects of abdominopelvic RT

	Not irradiated (n=70)	Irradiated (n=11)	P value
Ovarian outcome, N° (%)			**0.0297**
NOR	55 (78.6)	5 (45.5)	
DOR	13 (18.6)	5 (45.5)	
POI	2 (2.9)	1 (9.1)	

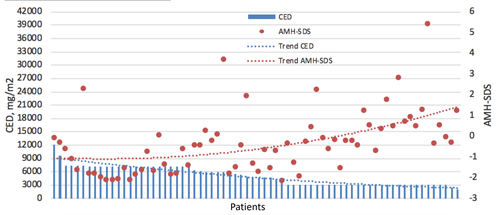


The effects of age upon treatment

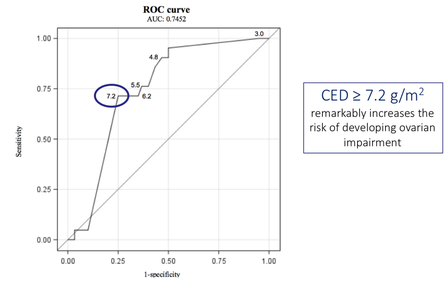


↑ 1 year age ➡ **↓ 0.12 AMH-SDS** (p=0.003)

The effects of CED



↑ 1 g/m2 CED ➡ **↓ 0.14 AMH-SDS** (p= 0.04)



CED ≥ 7.2 g/m^2 remarkably increases the risk of developing ovarian impairment

CONCLUSIONS

- **↑ CED**, above **7.2 g/m^2** ➡ **↓ AMH** ➡ **↑ risk for DOR**
- **Pelvic RT, older age at diagnosis** ➡ **↑ risk for ovarian impairment**

Ovarian assessment for all women treated with alkylating agents and/or radiotherapy is recommended

Age-normalized AMH is a tool for early detection of ovarian impairment

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1. Lunding SA et al. AMH as Predictor of Premature Ovarian Insufficiency: A Longitudinal Study of 120 Turner Syndrome Patients. J Clin Endocrinol Metab. 2015 Jul;100(7):E1030–8.
2. Lunsford AJ et al. Antimüllerian hormone as a measure of reproductive function in female childhood cancer survivors. Fertil Steril. 2014 Jan;101(1):227–31.
3. Lie Fong S et al. Serum Anti-Müllerian Hormone Levels in Healthy Females: A Nomogram Ranging from Infancy to Adulthood. J Clin Endocrinol Metab. 2012 Dec 1;97(12):4650–5.