Study of the molecular alterations in pediatric patients with Rhabdomyosarcoma and their associations with clinical and histopathological characteristics

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INTRODUCTION

Rhabdomyosarcoma(RMS) is the most common soft tissue sarcoma in children and adolescents. There are two main histological subtypes: embryonal (ERMS) and alveolar (ARMS), with distinct clinical and biological features. The molecular signature of ARMS is the *PAX-FOXO1* gene fusion subtypes: t(2;13)(q35;q14)/*PAX3-FOXO1* in 60% of patients and t(1;13)(p36;q14)/*PAX7-FOXO1* in 20% of the patients. The histopathological and molecular classification of patients with RMS have been studied for prognostic and therapeutic decisions. However, other molecular alterations are being studied as important to prognosis. The aim of this study is to analyse the cytomolecular alterations in *FOXO1* gene, the presence of somatic and germline mutations in *TP53*, the expression of *EZH2* gene and to relate these findings with the clinical, pathological and outcome in patients with RMS.

METHODS

A retrospective study of 126 patients with RMS admitted in the Pediatric Oncology Department at INCA / HCI , from January 2003 to December 2017 will be analysed. So far, we have studied 45 patients with RMS, relating the clinical and pathological data with cytomolecular study of *FOXO1* gene performed by FISH method in the tumor paraffin samples.

RESULTS

The median age at diagnosis was 7 years. There were 19 females and 26 males. The histopathologic subtypes were ERMS: n=23 (51.1%), ARMS: n=20 (44,4%), mixed RMS: n = 1 (2.2%) and spindle cell RMS: n = 1(2.2%). Patients were stratified at diagnosis as high risk in 20/45 (44,4%) patients and metastatic in 8/45(17.7%) patients. Sixteen out of 20 ARMS patients were analyzed using FISH for *FOXO1* gene. *FOXO1* gene translocation was present in 11/16 patients, in 3/11 there was concomitant amplification of *FOXO1* gene and in one patient we observed only *FOXO1* amplification. In 4/16 patients no cytomolecular alterations were detected. Next steps: to complete the cohoort study, with patient chart review and to perform and complete the molecular studies in patients with RMS.

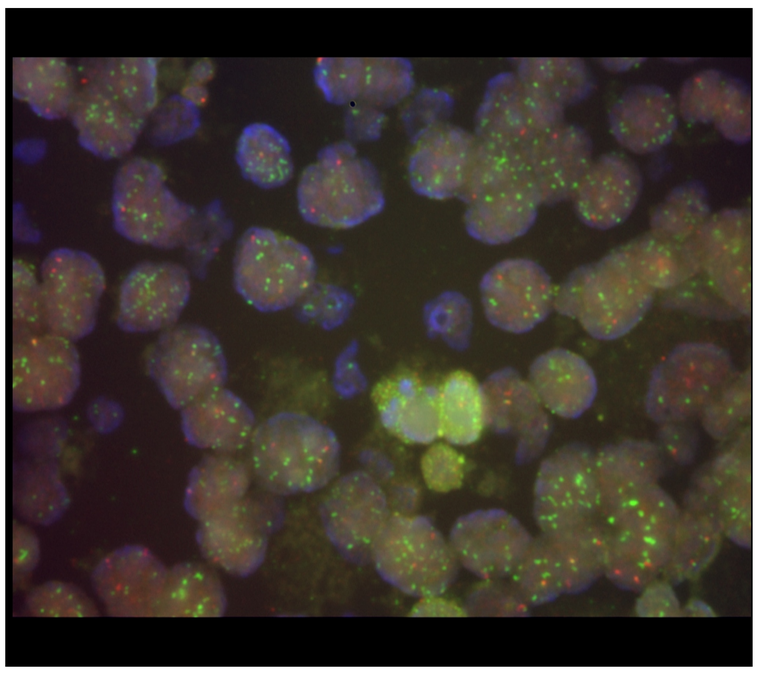

Figure 1. Detection of *FOXO1* translocation and amplification by FISH in rhabdmyosarcoma

Table 1. Clinicopathologic and molecular features of Rhabdomyosarcoma patients (2003 - 2017)

Characteristics	No of patients (%)
Total No.	**45 (100)**
Age,y	
<1	6 (13,3%)
1-9	20 (44,4%)
>10	19 (42,2%)
Sex	
Male	26 (57,7%)
Female	19 (42,2%)
Stage	
1	3 (6,6%)
2	0 (0%)
3	34 (75,5%)
4	8 (17,7%)
Primary site	
Favorable	14 (31,1%)
Unfavorable	31 (68,8%)
Tumor invasiveness	
T1	12 (26,6%)
T2	33 (73,3%)
Lymph node involvement	
N0	28 (62,2%)
N1	12 (26,6%)
Unknown	5 (11,1%)
Tumor size, cm	
< 5 cm	32 (71,1%)
>5 cm	12 (26,6%)
unknown	1 (2,2%)
Risk group	
Low risk	1 (2,2%)
standard risk	9 (20%)
high risk	20 (44,4%)
very high risk	7 (15,5%)
metastatic group	8 (17,7%)
Histopathology type	
Embryonal	20 (44,4%)
Alveolar	23 (51,1%)
Spindle cells	1 (2,2%)
Mixed	1 (2,2%)
Molecular characteristics	
FOXO1 positive	8 (17,7%)
FOXO1 negative	4 (8,8%)
amplification/translocation	3 (6,6%)
amplification only	1 (2,2%)
not done	29 (64,4%)

CONCLUSION

The use of different laboratory techniques such as histology, immunohistochemistry and molecular cytogenetics are fundamental for the diagnosis, prognosis and for better understanding the development and clinical evolution of pediatric RMS.

Keywords: pediatric Rhabdomyosarcoma, molecular alterations, clinical and histopathological features.

Supported by: INCA-Ministry of Health.

Projeto Gráfico: Área de Edição e Produção de Materiais Técnico-Científicos / INCA