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Novel diagnostic approach based on telomere dysfunction linked high chromosomal unstable neuroblastic tumors and patients with indolent disease course.

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Background: Telomere dysfunction (TD) and high chromosomal instability are related factors which have been associated with poor prognosis in cancer. Currently, analysis of TD caused by telomerase activation or by alternative lengthening of telomeres (ALT) is a novel and promising therapeutic approach in cancer. In neuroblastoma (NB), the most frequent extracranial solid childhood cancer, genetic mechanisms and molecular basis underlying the heterogeneity in clinical courses are poorly understood. To gain insight into the genetic etiology of NB, different telomeric patterns have been recently defined taking into account histological and genomic features, and could be used in future for therapeutic stratification.

Aim: To determine the patterns of TD in a subset of NB with high chromosomal instability, defined by the presence of multiple genetic amplifications with or without chromothripsis.

Material and Methods: TD were studied in a cohort of 16 high chromosomal unstable primary NB. Thirteen patients were classified into the high-risk NB (HR-NB) group according the INRG parameters, mainly because their tumor genetics. Only 3 patients were older than 5 years old. All samples were included in a tissue microarray and analyzed by interphase quantitative fluorescent in situ hybridization (IQ-FISH) using a telomeric probe (FITC-labeled telomeric PNA probe, Dako). For each biopsy, at least 200 nuclei were quantified from digital fluorescence microscopy images with the Telometer software (Image J). Standard deviation (SD) mean of the fluorescence ratio (total telomeric intensity/total DAPI intensity), area and number of signals per nucleus were calculated in pixel units for each biopsy. IQ-FISH tumor results were associated with biological and clinical data of the patients.

Results: Dichotomization and subsequent comparison between IQ-FISH parameters resulted in two distinct and well-defined tumor groups: (A) including nine out of sixteen NB with mean values of intensity, area and number of signals per nucleus over the median and (B) with the remaining NB (7/16) with values under the median in, at least, one of these parameters. Seven cases of group A (77.8%) showed SD values of intensity over the median, in contrast with three cases in group B (42.8%). Regarding the association with other tumor genetic features, we found MYCN amplification in 66.7% and 100% of the cases belonging to group A and B, respectively; 11q deletion was only present in 33.3% of group A cases. The average age at diagnosis was 43m and 20m associated with group A and B tumor\'s patients, respectively. Only five patients had stage 4 tumors, three of them were included in group A. Half of patients relapsed, 75% of them with tumors belonging to group A and related to exitus, 56.3% of patients died, 77.8% of them had also tumors linked to group A. Event-free survival (EFS) of all patient cohort was 37m, however the relapse time of group A decreased to 15m and increased to 64m in group B. Overall survival (OS) of all patient cohort was 44m, however the mean time decreased to 21m in patients with tumors included in group A whereas increased to 73m in those of group B. To sum up, patients with indolent disease course had tumors with long telomeres and presence of ALT mechanism faced with the evidence of i) high intensity and area of telomere sign, ii) high SD intensity values that suggests important heterogeneity cell clones and therefore a possible presence of ALT mechanism of telomere elongation in some clones, iii) reduced EFS and OS although both groups had tumors with high chromosomal instability and equal percentage of patient tumors stage 4.

Conclusion: Our study shows an important link between telomere dysfunction and clinical features of HR-NB patients with high chromosomal unstable tumors. Further studies in large cohorts of HR-NB with indolent courses would clarify the prognostic impact of the routinely use of this novel diagnostic approach.

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