ROLE OF THE ANAPLASTIC LYMPHOMA KINASE INHIBITOR CRIZOTINIB IN THE MANAGEMENT OF NEUROBLASTOMA

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ULOGA KRIZOTINIBA INHIBITORA ANAPLASTIČNE LIMFOMSKE KINAZE U TERAPIJI NEUROBLASTOMA

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ABSTRACT

Neuroblastoma (NB) is a common extra-cranial solid malignancy of childhood. NB displays several clinical and biological features as well as many indeterminate aspects. Studies attempting to determine a prognostic factor in NB have been performed for a long time. Recent studies have focused on the anaplastic lymphoma kinase (ALK) gene. ALK mutations are one of the most prevalent and important biological disorders in NB. The presence of ALK mutations contributes to a more malignant character in NB. However, there is a limited number of studies on the clinical relevance of the expression of ALK or of its mutations. The elucidation of gene expression analyses in ALK can guide in the identification of risk groups and selection of treatment protocols. There is a need for further studies, as it is important to define patients eligible for use of ALK inhibitors.

Keywords: *neuroblastoma, ALK inhibitors, therapy, children*

SAŽETAK

Neuroblastom (NB) je najčešći ekstrakranijalni solidni tumor u detinjstvu. NB se karakteriše različitim kliničkim i biohemijskim osobinama kao i različitim medjusobnim pojedinostima. Već duže vreme, studije pokušavaju da pronađu verodostojan prognostički faktor NB-a. Pored toga, prethodne studije su se zasnivale na ispitivanju gena za anaplastičnu limfoblastnu kinazu (ALK). ALK mutacije su jedan od najčešćih i najvažnijih poremećaja u NB. Upravo prisustvo ALK mutacije doprinosi malignom karakteru NB-a. Ipak, još uvek je nedovoljno studija koje su se bavile ekspresijom ALK mutacija. Rasvetljavanje genske ekspresije ALK može pomoći u identifikaciji rizičnih grupa i protokola lečenja. Nedvosmisleno postoji potreba za budućim istraživanjima kako bi se i definisao profil pacijenta na terapiji ALK ihibitora.

Ključne reči: *neuroblastom, ALK inhibitori, terapija, deca*

Neuroblastoma (NB) is a common extra-cranial solid malignancy of childhood. NB displays several clinical and biological features as well as many indeterminate aspects. NB may be associated with spontaneous regression, benign transformation or aggressive course due to alterations in biological behaviour, making it difficult to predict prognosis and to manage the disease (1-4). Studies attempting to determine a prognostic factor in NB have been performed for a long time. Recent studies have focused on the anaplastic lymphoma kinase (ALK) gene. Activating ALK mutations or amplifications have been detected in the majority of familial NBs and approximately 10% of sporadic cases. The ALK mutations are seen at similar rates in patients with early and advanced NB (2, 4). In studies on the association of the ALK gene with NB, it was shown that the ALK gene is highly expressed and that the amplification in the ALK gene increases kinase activation of ALK. Based on these results, it has been proposed that the ALK gene could be a prognostic factor for NB. In NB, the relationship between ALK protein expression and clinical course, as well as the effect of ALK on prognosis, are controversial, with contradicting results in several studies (1, 3-6). In a meta-analysis on 709 cases of NB, Brouwer et al. investigated the prevalence of ALK mutations and their relationship with clinical param-

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eters. Those authors detected ALT mutations in 6.9% of cases with similar frequency in early and advanced tumours. They proposed that cases with ALK mutations have poorer prognosis, although no significant correlation was detected between ALK mutations and tumour stage (2).

ALK is a tyrosine kinase receptor belonging to the insulin receptor superfamily. Mutant or amplified ALK induces cell growth and viability through activation of the JAK-STAT, PI3K-AKT or Ras-MAPK pathways. Normally, the ALK gene is expressed by the developing nervous system. Its expression is very low and limited in adults. Despite considerable variation in results, it was reported that ALK expression was detected in 39% of cases with NB (2-6). It is thought that tumours with ALK mutations, either germline or somatic, are responsive to treatments targeting the activity of this kinase. There are ongoing attempts to develop ALK kinase inhibitors for use in such patients. In addition, tyrosine kinase inhibitors such as crizotinib, which act via ALK, are considered to be future alternative therapies in several cancers, mainly NB (1, 4). Crizotinib used in the treatment of NB inhibits the tyrosine kinase activity of the ALK and c-Met genes. This molecule binds to the tyrosine kinase of ALK by competing with adenosine triphosphate (1, 3, 5). Dujikers et al. proposed that immunohistochemical ALK assays in tissue will be a simple test for risk stratification in patients with NB and ganglioneuroblastoma in the future (6). In recent studies, the NB cases shown to have high ALK expression by immunohistochemical techniques were sensitive to ALK inhibition even in the absence of ALT mutation (5-7). Cases with the R1275Q mutation were sensitive to crizotinib, while those with F1174L mutations were relatively resistant (4).

In conclusion, ALK mutations are one of the most prevalent and important biological disorders in NB. The presence of ALK mutations contributes to more a malignant character in NB. However, there is a limited number of studies on the clinical relevance of ALK mutations and ALK expression. The elucidation of gene expression analyses in ALK can guide in identification of risk groups and selection of treatment protocols. There is a need for further studies, as these are important to define patients eligible for use of ALK inhibitors.

REFERENCES:

1. Alshareef A, Gupta N, Zhang HF, Wu C, Haque M, Lai R. High expression of β-catenin contributes to the crizotinib resistant phenotype in the stem-like-cell population in neuroblastoma. Sci Rep. 2017 Dec 4;7(1):16863. doi: 10.1038/s41598-017-17319-9.
2. De Brouwer S, De Preter K, Kumps C, Zabrocki P, Porcu M, Westerhout EM, Lakeman A, Vandesompele J, et al. Meta-analysis of neuroblastomas reveals a skewed ALK mutation spectrum in tumors with MYCN amplification. Clin Cancer Res. 2010;16(17):4353-62.
3. Tucker ER, Tall JR, Danielson LS, Gowan S, Jamin Y, Robinson SP, Banerji U, Chesler L. Immunoassays for the quantification of ALK and phosphorylated ALK support the evaluation of on-target ALK inhibitors in neuroblastoma. Mol Oncol. 2017 Aug;11(8):996-1006. doi: 10.1002/1878-0261.12069. Epub 2017 May 31.
4. Carpenter EL, Mossé YP. Targeting ALK in neuroblastoma—preclinical and clinical advancements. Nat Rev Clin Oncol. 2012 May 15;9(7):391-9. doi: 10.1038/nrclinonc.2012.72.
5. Moore NF, Azarova AM, Bhatnagar N, Ross KN, Drake LE, Frumm S, Liu QS, Christie AL, Sanda T, Chesler L, Kung AL, Gray NS, Stegmaier K, George RE. Molecular rationale for the use of PI3K/AKT/mTOR pathway inhibitors in combination with crizotinib in ALK-mutated neuroblastoma.Oncotarget. 2014 Sep 30;5(18):8737-49.
6. Duijkers FA, Gaal J, Meijerink JP, Admiraal P, Pieters R, de Krijger RR, van Noesel MM. High anaplastic lymphoma kinase immunohistochemical staining in neuroblastoma and ganglioneuroblastoma is an independent predictor of poor outcome. Am J Pathol. 2012;180(3):1223-3
7. Murga-Zamalloa C, Lim MS.ALK-driven tumors and targeted therapy: focus on crizotinib. Pharmgenomics Pers Med. 2014 Mar 20;7:87-94. doi: 10.2147/PGPM.S37504. eCollection 2014.