CROATIAN INTERNATIONAL PUBLICATIONS

by Ivan Bohaček

ibohacek@hiim.hr

Belev B, Brčić I, Prejac J, Golubić ZA, Vrbanec D, Božikov J, Alerić I, Boban M, Razumović JJ. Role of Ki-67 as a prognostic factor in gastrointestinal stromal tumors. World J Gastroenterol. 2013;19(4):523-7.

Department of Medical Oncology, Clinic of Oncology, Clinical Hospital Center Zagreb, 10000 Zagreb, Croatia.

AIM: To investigate primarily the prognostic value of Ki-67, as well as other parameters, in gastrointestinal stromal tumors (GISTs).

METHODS: Ki-67, c-KIT, platelet-derived growth factor receptor-alpha (PDGFRα), smooth muscle actin (SMA), CD34, S100 were stained for immunohistochemistry which was performed on formalin-fixed, paraffin-embeded sections on representative block from each case. Proliferation index counted by Ki-67 antibody was calculated as a number of positive nuclear reaction over 100 cells. Immunoreactivity for c-KIT and PDGFRα was evaluated semiquantitatively (weak, intermediate, strong) and for c-KIT type of reactivity was analyzed (cytoplasmic, membrane and "dot-like" staining). Immunoreactivity for SMA, CD34 and S100 were was evaluated as positive or negative antigen expression. Pathologic parameters investigated in this study included tumor size, cell type (pure spindle, pured epitheloid mixed spindle and epitheloid), mitotic count, hemorrhage, necrosis, mucosal ulceration. Clinical data included age, gender, primary tumor location and spread of disease. $\chi(2)$ test and Student's t-test were used for comparisons of baseline characteristics. The Cox's proportional hazard model was used for univariable and multivariable analyses. Survival rates were calculated by Kaplan-Meier method and statistical significance was determined by the log-rank test.

RESULTS: According to the stage of disease, there were 36 patients with localized disease, 29 patients with initially localized disease but with its recurrence in the period of follow up, and finally, 35 patients had metastatic disease from the very beginning of disease. Tumor originated most commonly in the stomach (41%), small intestine was the second most common location (36%). The mean size of primary tumors was 6.5 cm. The mean duration of follow-up was 60 mo. Multiple parameters were analyzed for their effect on overall survival, but no one reached statistical significance ($P = 0.06$). Analysis of time to progression/relapse in initially localized disease (univariate analysis), tumor size, mitotic count, Ki-67 and type of d-KIT distribution (cytoplasmic vs membrane/"dot-like") showed statistically significant correlation. In multivariate analysis in the group of patients with localized disease, there were only 2 parameters that have impact on relapse, Ki-67 and SMA ($P < 0.0001$ and $P < 0.034$, respectively). Furthermore, Ki-67 was analyzed in localized disease vs localized with recurrence and metastatic disease. It was shown that there is a strict difference between these 2 groups of patients (median value was 2.5 for localized disease vs 10.0 for recurrent/metastatic disease, $P < 0.0001$). It was also shown that the cut-off value which is still statistically significant in terms of relapse on the level of 6%. The curves for survival on that cut-off level are significantly different ($P < 0.04$, Cox F).

CONCLUSION: Ki-67 presents a significant prognostic factor for GIST recurrence which could be of great importance in evaluating malignant potential of disease.

Duplancic D, Cesarik M, Poljak NK, Radman M, Kovacic V, Radic J, Rogosic V. The influence of selective vitamin D receptor activator paricalcitol on cardiovascular system and cardiorenal protection. Clin Interv Aging. 2013;8:149-56.

Department of Cardiology, School of Medicine in Split, University Hospital Split, Split, Croatia.

The ubiquitous distribution of vitamin D receptors in the human body is responsible for the pleiotropic effects of vitamin D-receptor activation. We discuss the pos-

sible beneficial effects of a selective activator of vitamin D receptor, paricalcitol, on the cardiovascular system in chronic heart failure patients and chronic kidney patients, in light of new trials. Paricalcitol should provide additional clinical benefits over the standard treatment for chronic kidney and heart failure, especially in cases of cardiorenal syndrome.

Bukvic BK, Blekic M, Simpson A, Marinho S, Curtin JA, Hankinson J, Aberle N, Custovic A. Asthma severity, polymorphisms in 20p13 and their interaction with tobacco smoke exposure. Pediatr Allergy Immunol. 2013;24(1):10-8.

General Hospital "Dr Josip Bencevic" Slavonski Brod, University of Osijek, Osijek, Croatia.

BACKGROUND: We investigated the association between genetic variation in chromosomal region 20p13-p12 (ADAM33 and flanking genes ATRN, GFRA4, SIGLEC1 and HSPA12B) and asthma. Amongst asthmatics, we then investigated the association between genetic variants and asthma severity. We evaluated the effect of environmental tobacco smoke (ETS) exposure in the context of genetic variants.

METHODS: In a case-control study, we recruited 423 asthmatic children and 414 non-asthmatic controls (age 5-18 yr). Amongst asthmatics, we measured lung function and extracted data on hospitalisation for asthma exacerbation from medical records. Early-life ETS exposure was assessed by questionnaire. We included 85 single-nucleotide polymorphisms (SNPs) in the analysis.

RESULTS: Seventeen SNPs were significantly associated with asthma; one (rs41534847 in ADAM33) remained significant after correction for multiple testing. Thirty-six SNPs were significantly associated with lung function, of which 15 (six ARTN, three ADAM33, five SIGLEC1 and one HSPA12B) remained significant after correction. We observed a significant interaction between 23 SNPs and early-life ETS exposure in relation to lung function measures. For example, for rs512625 in ADAM33, there was significant interaction with ETS exposure in relation to hospitalisations (p(int) = 0.02) and lung function (p(int) = 0.03); G-allele homozygotes had a 9.15-fold [95% CI 2.28-36.89] higher risk of being hospitalized and had significantly poorer lung function if exposed to ETS, with no effect of ETS exposure amongst A-allele carriers.

CONCLUSION: We demonstrated several novel significant interactions between polymorphisms in 20p13-p12 and early-life ETS exposure with asthma presence and, amongst asthmatics, a significant association with the severity of their disease.

Mišak Z, Hojsak I, Jadrešin O, Kekez AJ, Abdović S, Kolaček S. Diagnosis of coeliac disease in children younger than 2 years. J Pediatr Gastroenterol Nutr. 2013;56(2):201-5.

Referral Centre for Paediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Zagreb, Croatia.

BACKGROUND AND AIM: To diagnose coeliac disease (CD) in children younger than 2 years, the old ESPGHAN criteria based on 3 small bowel biopsies were recommended until recently. The aim of the present study was to investigate the applicability of only 1 small intestinal biopsy plus positive serology for the diagnosis of CD in children younger than 2 years.

METHODS: A prospective cohort study included 81 patients younger than 2 years with symptoms suggestive of CD, who all completed the diagnostic procedure based on 3 small bowel biopsies. According to the finding of the third biopsy, patients were divided into group A-CD confirmed (N=44), and group B-CD not confirmed, after the gluten challenge (N=37).

RESULTS: At the time of the first biopsy, total villous atrophy (Marsh IIIc) was found more often in group A than in group B (77% vs 27%, P<0.01). Also, all of the studied antibodies were more frequently positive in group A than in group B (P<0.01 for all of the tested antibodies). Positive anti-endomysial antibodies and Marsh IIIc finding were the best discriminators between the group A and the group B and considerably contributed to the prediction of CD.

CONCLUSIONS: The second and the third biopsies (before and after the gluten challenge) may also be avoided when diagnosing CD in children younger than 2 years provided that the child, at the time of presentation, has positive anti-endomysial antibodies and Marsh IIIc on the small bowel biopsy. A gluten challenge should be still considered in all other children younger than 2 years.