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DRUGS TO CONTROL HAZARDOUS VIRUSES INCLUDING SOME INVOLVED IN HUMAN MALIGNANCIES

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Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are implicated in human cancers. Drugs controlling these viruses may impede HCV/HIV-induced malignancies.

Using a bacterial construct and mammalian cells, we identified three distinct classes of small molecules with anti-HCV activity. These compounds also inhibited unrelated RNA viruses such as HIV, corona, and Ebola viruses.

NovaDrug's compounds do not display genotoxicity in the mouse micronuclei test nor in the Ames or cell culture mutagenesis assays.

To investigate their mode of action, we used the *in vitro* HIV/peripheral blood cell model, which has useful tools for locating the viral life cycle phase where the drug displays its inhibition. For this study, we tested the ability of the drugs to affect virus cell entry, reverse transcription, genomic integration, translation, and viral release. The results indicated that NovaDrug's compounds operate after virus entry but prior to reverse transcription. As such, they act early in the HIV life cycle.

Representatives of the three drug classes failed to consistently affect the production of 30 different cytokines. Nor did they regularly inhibit the catalytic activity of 359 known protein kinases. An exception was a subgroup of one of the drug classes. This subgroup consistently inhibited the catalytic activity of a protein kinase (PK), termed LK. Moreover, LK specific siRNAs restrained HCV replication, thus implicating LK in HCV life cycle. Studies are ongoing to pinpoint the relevant targets of NovaDrug's antivirals.

Currently, there are a limited number of clinical drugs with a wide range of antiviral activity; NovaDrug's compounds display such a range.

Keywords: human immunodeficiency virus, hepatitis C virus, human malignancies, therapy.

HPV-NEGATIVE CERVICAL CANCER: A DISTINCT TYPE OF THE UTERINE CERVIX WITH POOR PROGNOSIS

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The real-time PCR method was used to study cervical scrapings from 116 patients with stage I–IV primary cervical cancer. Decreased survival and poor prognosis were found in patients with HPV-negative cervical cancer.

Keywords: cervical cancer, human papillomavirus.

Introduction

Nowadays, human papillomavirus (HPV) is considered to be the main causative agent of cervical cancer progression [1][Bosch, 2011 #133][Bosch, 2011 #60]. According to various studies, up to 80–90% of patients diagnosed with cervical cancer (CC) are also carriers of high-risk HPV [2]. A small number of cervical cancers are not caused by HPV or the virus can be eliminated during oncogenesis, i.e. such cancers are HPV-negative. Some researchers claim that such CC subtype may be encountered only due to lab test errors [3]. However, there is another view of the phenomenon. Along with HPV-associated CC, there is HPV-negative tumors, which belong to a more aggressive tumor class and whose oncogenesis essentially differs from that of HPV-associated tumors [4]. The **aim of the study was** to evaluate relapse-free and overall survival for HPV+ and HPV- patients diagnosed with primary CC.

Material and Methods

The research included 116 patients aged from 24 to 79 years and diagnosed with stage I–IV primary CC. The diagnosis was histologically verified; tumors were defined according to the FIGO classification. Complex examination included pelvic examination, colposcopy, cytological and histological tests. Scraping samples from the cervical canal and the outer part of the cervix served as study materials. Detection and genotyping of HPV DNA was carried out via the real-time PCR method using a RotorGene 6000 (Corbett Research, Australia) and Amplisens® reagent sets (Amplisens® HPV HCR-screen; Amplisens® HPV HCR-genotype (Moscow, Russia). The Fisher's ratio test was applied to assess statistical relevance of differences in the qualitative attributes occurrence distribution between the groups. Survival rates were evaluated according to the Kaplan-Meier method.

Results and discussion

The presence of HPV+ CC associated with one or several types of HPV was verified in 84 patients (72.4%), while 32 patients (27.6%) were not diagnosed with HPV. HPV- patients underwent second biopsy, DNA purification, detection and genotyping of HPV DNA in examined samples. Absence of the viruses was verified as a result. The patients were divided into 2 groups depending on the HPV contamination: group 1 – HPV+ patients (n=84) with the average age of 42.1±1.7 years; group 2 – HPV- patients (n=32) with the average age of 45.5±1.6 year old. The groups did not differ in terms of general clinical and pathologic findings: tumor size, lymphatic cancer spread and histotype. Genotyping of HPV+ samples showed that HPV genotype 16 was present in 67.8% of cases. These results were consistent with other recent studies [5, 6]. HPV types 33 and 31 were ranked as the 2nd and 3d most common, respectively (22.6% and 20.2%), whereas some authors reported that HPV 18 was the 2nd most common HPV type [5]. A low viral load (<3 lg HPV DNA/10^5 cells) had 22.6%, who were considered to have low risk of CC [7]. High viral load (>3 lg HPV DNA/10^5 cells) was observed in 77.4% of patients, who were considered at have high risk for CC. Decrease in both the overall and disease-free survival rates was observed in HPV- patients diagnosed with CC. Figure 1 A, B demonstrate disease-free and overall survival of patients with CC: disease-free survival for HPV+ and HPV- patient groups was 102 and 68 months, respectively; overall survival was 52 and 83 months, respectively. The 2-year disease-free survival rate in both groups was 92.0% and 73.0%, respectively. The 2-year overall survival rate in HPV+ and HPV- patients was 86.0% and 65.0%, respectively. Decreased survival may be caused by different oncogenic mechanisms of CC, which may explain the differences in the disease outcome. Harima et al. reported that HPV-cancer is a separate group and this particular subtype responds poorly to radiotherapy [8]. The data on the matter dates back to 2006: HPV viral load in cervical scrapings of patients diagnosed with CC was examined before treatment. The results showed that the hierarchy of CC prognoses depending on its severity was as follows: HPV+ tumors with high viral load, HPV+ tumors with low viral load and the worst prognoses occurred for HPV- tumors [9].

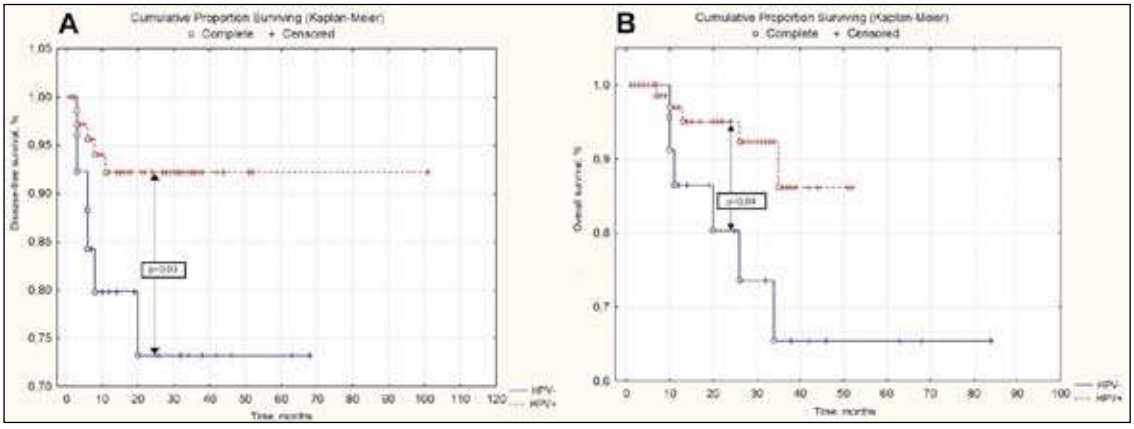

Figure 1. Relapse-free survival (A) and overall survival (B) of patients diagnosed with cervical cancer

Conclusions

The current research has focused on the determinants of infection with oncogenic HPV types, the assessment of prophylactic and therapeutic vaccines, and the development of screening strategies incorporating HPV testing and other methods as adjunct to cytology. These are fundamental stepping stones for the implementation of effective public health programs aimed at the control of cervical cancer.

HPV- cervical tumors are 2.5 times less frequently found than HPV+, but they have significantly worse prognoses. The presence or absence of HPV DNA in a tumor may become a new independent prognostic factor for cervical cancer. HPV- cervical cancer pathogenesis is understudied and requires further and detailed research.

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REFERENCES

1. *Bosch F.X.* Human papillomavirus: science and technologies for the elimination of cervical cancer. Expert opinion on pharmacotherapy. 2011; 12(14): 2189-2204. doi: 10.1517/14656566.2011.596527.
2. *Nazarova N.M., Prilepskaya V.N., Sulamanidze L.A., Mzarelua G.M., Bestaeva N.V.* Papillomavirus infection: prevalence, diagnosis and treatment (literature review). Lechashhij vrach. 2013; 11: 15-19.
3. *Böhmer G., van den Brule A.J., Brummer O., Meijer C.L., Petry K.U.* No confirmed case of human papillomavirus DNA-negative cervical intraepithelial neoplasia grade 3 or invasive primary cancer of the uterine cervix among 511 patients. American journal of obstetrics and gynecology. 2003; 189(1): 118-120.
4. *Komarova L.E.* Current aspects of cytological screening for cancer of the cervix uteri: a review. Tumors of female reproductive system. 2009; 3: 78-83. [in Russian]
5. *Muñoz N., Bosch F.X., de Sanjosé S., Herrero R., Castellsagué X., Shah K.V., Snijders P.J., Meijer C.J.; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group.* Epidemiologic classification of human papillomavirus types associated with cervical cancer. New England J. of Medicine 2003; 348: 518-527. doi: 10.1056/NEJMoa021641.
6. *Kolomiets L.A., Churuksaeva O.N., Shpileva O.V., Urazova L.N., Rodicheva N.S.* Prevalence of various human papillomavirus (HPV) types in patients with cervical intraepithelial neoplasia (cin) and cervical cancer in tomsk region. Siberian Journal of Oncology. 2012; 3: 41-45. [in Russian]
7. *Sasieni P., Castanon A., Cuzick J.* Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. BMJ. 2009 Jul 28; 339: b2968. doi: 10.1136/bmj.b2968.
8. *Harima Y., Sawada S., Nagata K., Sougawa M., Ohnishi T.* Human papilloma virus (HPV) DNA associated with prognosis of cervical cancer after radiotherapy. International J. of Radiation Oncology. 2002; 52: 1345-1351.
9. *Datta N.R., Kumar P., Singh S., Gupta D., Srivastava A., Dhole T.N.* Does pretreatment human papillomavirus (HPV) titers predict radiation response and survival outcomes in cancer cervix? a pilot study. Gynecologic oncology. 2006; 103: 100-105. doi: 10.1016/j.ygyno.2006.01.058.

RELATIONSHIP BETWEEN THE LEVEL DIFFERENT POPULATIONS OF CIRCULATING TUMOR CELLS BEFORE TREATMENT AND EFFEC TO NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH BREAST CANCER

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The relationship between the level of different populations of circulating tumor cells before the treatment (before biopsy) in patients with breast cancer with the effect of neoadjuvant chemotherapy was evaluated. The study showed that patients with a complete and / or partial tumor regression after NACT level CTC with sign EMT in the blood before biopsy was significantly lower than in patients who have no observed response to treatment (stabilization and / or progression) (p= 0.02).

Keywords: heterogeneity of circulating tumor cells; EMT (epithelial-mesenchymal transition), neoadjuvant chemotherapy (NACT), breast cancer.

Introduction

CTCs are a heterogeneous population. Some cells are cancer stem cells, other cells are in an EMT (epithelial-mesenchymal transition) state, and most of the cells do not have EMT and stemness properties [1, 2]. It was shown that neoadjuvant chemotherapy (NACT) on breast cancer does not act on CTCs in the EMT state [3]. The biological properties of circulating tumor cells (CTCs), and their dynamics during neoadjuvant chemotherapy are important, both for disease progression prediction and therapeutic target determination, with the aim of preventing disease progression. It has been observed that significant changes in the quantity of the different subsets of circulating tumor cells in patients' blood were observed after carrying out the 3rd course of NACT. NACT causes significant changes in the quantity of six CTC subsets, with various combinations of stemness and epithelial-mesenchymal transition (EMT) properties [4]. The aim of our study was to