http://dx.doi.org/10.35630/2199-885X/2020/10/4.3

PERSONALIZED CALCULATOR FOR PREDICTION OF OPIOID-ASSOCIATED PHARMACORESISTANCE IN PATIENTS WITH PANCREASE CANCER

Received 27 August 2020;
Received in revised form 20 September 2020; Accepted 25 September 2020

***Olga Bobrova*[1]✉, *Sergey Zyryanov*[2], *Natalia Shnayder*[1,3], *Marina Petrova*[1]**

[1] *V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk*
[2] *Peoples' Friendship University of Russia, Moscow*
[3] *V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology, St. Petersburg, Russia*

✉ *bop_351971@mail.ru*

ABSTRACT — We studied the complex effect of genetic and non-genetic factors on the formation of opioid-associated resistance using machine learning methods in patients with chronic pain syndrome against the background of pancreatic cancer. Fifty-seven factors for predicting the realization of pharmacoresistance were studied in all examined Caucasian patients. The most significant predictive factors were determined and a software-analytical complex "Algorithm for assessing the significance of clinical and pathogenetic factors for predicting the safety of opioid therapy" was developed.

KEYWORDS — chronic pain syndrome; pancreas cancer; pharmacoresistance, fentanyl TTS; forecasting.

INTRODUCTION

Opioid-associated adverse reactions (HP) are recorded in 49–95% of cases in cancer patients [1]. Pancreas cancer predetermines the obligatory use of strong opioid analgesics in palliative care [2]. A feature of the pain syndrome of pancreatogenic genesis is the development of resistance of opioid analgesics against the background of progression of the underlying disease. In the literature, there are isolated conflicting studies on the study of the complex effect of genetic and nongenetic factors on the implementation of the resistance of opioid analgesics. A personalized comprehensive assessment of predictor factors for the realization of opioid-associated resistance in patients with pancreas cancer will increase the effectiveness and safety of analgesic therapy.

Purpose of the study:

To develop a calculator for personalized risk assessment of opioid-associated drug resistance in patients with pancreas cancer using fentanyl TTS as an example.

MATERIALS AND METHODS

90 patients (Caucasians, residents of the Krasnoyarsk Territory of Eastern Siberia) with pancreas cancer on the background of existing chronic pain syndrome (male to female ratio 1: 1) at the age of 18–75 were examined. The median age of the examined patients was 63 (56–69) years. The intensity of chronic pain syndrome according to the digital rating scale was 6 (6–8) points at the time of inclusion in the study. In 80% of the cases, mixed pain syndrome prevailed, in 20% — no ciceptiveone, respectively. All the patients received fentanyl TTS for pain relief against the background of standard analgesic therapy (ketoprofen 300 mg / day, diazepam 10 mg / day, amitriptyline 25 mg / day).13 geneticfactors(*ABCB1* (rs1045642, rs2032582, rs1128503); *OPRM1* (rs 1799971); *UGT2B7* (rs 7668258, rs12233719, rs7438135); *CYP3A4*1B* (rs2740574); *CYP3A5*3* (rs776746); *CYP3A4*22* (rs35599367); *IL1B* (rs1143627); *PTGS2* (rs5275); *LOC541472* (rs1800795)), 20 clinical and demographicones (gender; age; localization of pancreas cancer; pathogenetic variant of chronic pain 0/6 (0 — start of treatment, 6 — six months of treatment); type of surgical treatment (radical / palliative; physical status on the ECOG scale 0/6; jaundice; cancer-associated weakness syndrome; dyspepsia; comorbidity; ascites; body mass index 0/6; mental status on the MMSE 0/6 scale; life quality indicators on the ESAS 0/6 scale; stage of pancreas cancer, and 24 laboratoryones(glomerular filtration rate 0/6, aspartate aminotransferase 0/6, alanine aminotransferase 0/6, bilirubin 0/6, total protein 0/6, hemoglobin 0/6, leukocytes 0/6, lymphocytes 0/6, platelets 0/6, erythrocytes 0/6, glucose 0/6), amylase 0/6)were analyzed as the studied predictive factors. As part of the accompanying treatment, indices and opioid metabolism inhibitors were excluded as much as possible to reduce the risk of drug interactions. The assessment of the reliability of the development of pharmacoresistance was carried out according to the Naranjo scale and using the algorithms of Karch F.E.,

Lasagna L. [3]. Quality of life was assessed using the Palliative Medicine Symptom Rating Scale (ESAS), and cognitive functions were assessed using the Mental Status Assessment Scale (MMSE). The observation period was 5.95 ± 0.67 months. The following machine methods using the Scikit-learn library (Python) were used as predictive models to determine the likelihood of drug resistance: logistic regression (LR); k — nearest neighbors algorithm for classification problem (KNC); a collective of decision trees by the "random forest" method for the classification problem (RFC); a collective of decision trees by the gradient boosting method for the classification problem (GBC); decision trees for the classification problem (DTC); artificial neural network (multilayer perceptron) for classification problem (MLPC); linear support vector machine for classification problem (LSVC); support vector machine for classification problem (SVC). As a result of machine learning methods using 50 runs in each predictive model, the best quality models were selected using the least number of predictive factors. The model was trained on the entire training data set. The model was checked for quality on a test dataset. The most effective model was taken to be a model that achieves high accuracy with a minimum set of features. Statistical processing of the research results was carried out using the IBM SPSS® Statistics 20.0 software (USA). Differences were considered significant at a significance level of $p < 0.05$.

RESULTS

The most effective model was the support vector machine for the classification problem. For predicting pharmacoresistance, this model used only 4 predictor factors out of 12 possible and was highly reliable ($p = 0.000$). SVC has demonstrated the technological and practical advantage of the algorithms used. The list of important predictors of the implementation of pharmacoresistance includes genetic and non-genetic factors with a certain rank significance (Fig. 1)

The final stage of the study was the development of a software-analytical complex "Algorithm for assessing the significance of clinical and pathogenetic factors for predicting the safety of opioid therapy" in order to support decision-making to ensure the safety of opioid therapy. As a result, the mutual influence of only four predictor factors determined the risk of fentanyl-associated pharmacoresistance realization. (Fig. 2).

DISCUSSION

The frequency indicators of pharmacoresistance of 17 people (18.89%) in this study predetermined the personalized modeling of its implementation based on clinical and genetic factors. The developed model for a comprehensive assessment of the factors of the implementation of pharmacoresistance will allow monitoring the effectiveness and safety of opioid therapy, and will also ensure the availability and timeliness of the use of interventional methods of analgesia when therapy is ineffective. Genetic factors have become the leading predictors in the created integrated model for predicting pharmacoresistance to opioid therapy using fentanyl TTS as an example. Homo- and heterozygotic carriage of one-nucleotide variants (ONV) of the *PTGS2* gene (AA and AG rs5275) and the *IL1B* gene (AA rs1143627) can provide the development of pharmacoresistance due to the implementation of a multicomponent inflammatory mechanism of chronic pain in cancer patients. ONV gene *ABCB1* (GG RS1045642) showed a significant role in progosingpharmacore resistance. ONV gene *ABCB1* (GG rs1045642) showed a significant role in progosing-pharmacoresistance. It is necessary to consider the possibility of extracellular acidosis of the performance space on increasing the functional activity of P-glycoprotein due to hypoxia [4]. The lack of predictive value for laboratory parameters based on the results of machine learning and testing can be explained by the features of the safe pharmacokinetics of the transdermal therapeutic system in comparison with other non-invasive forms of opioids and the mutual influence of the obtained predictors.

CONCLUSION

The results of the study predetermine the obligatory pharmacogenetic study for patients with pancreas cancer. The use of risk stratification in the software-analytical complex for the development of pharmacoresistance predetermines the improvement of the personalized approach to pain relief in patients with pancreatic cancer.

Contributors

Bobrova Olga designed the study and analysed and interpreted data. Sergey Zyryanov and Marina Petrova interpreted and analysed the data. Natalya Schneider, Bobrova Olga, Sergey Zyryanov, Marina Petrova prepared the manuscript for submission.

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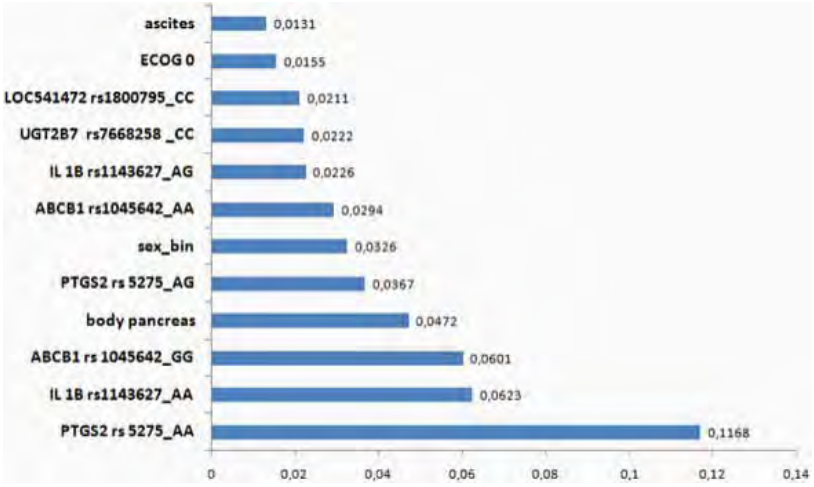

Fig. 1. *The significance of the selected SVC traits for predicting pharmacoresistance in patients with pancreatic cancer during therapy with fentanyl TTS.*
Abbreviations: *TTS — transdermal therapeutic system; ECOG — scale for determining physical status; SVC — support vector machine predictive model for classification problem.*

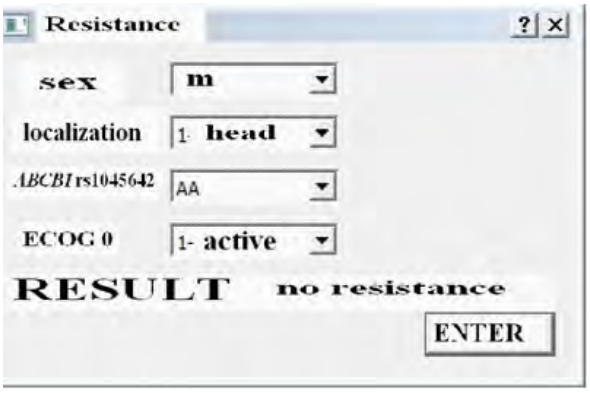

Fig. 2. *Clinical and genetic risk meter for the implementation of fentanyl-associated opioid resistance in patients with pancreatic cancer*

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