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PERSONALIZED CHOICE OF OPIOID THERAPY IN A PATIENT WITH CHRONIC PAIN SYNDROME ON THE BACKGROUND OF PANCREAS CANCER: CLINICAL CASE REPORT

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ABSTRACT — The paper presents a successful experience of personalized choice of opioid therapy when taking into account genetic and nongenetic factors in a patient with chronic pain syndrome on the background of pancreas cancer.

KEYWORDS — opioids, case study, pancreas cancer, chronic pain syndrome, personalized medicine.

A 65-year-old patient A. complains of weakness, increased fatigue, persistent pain in the upper abdomen 2 p. by VRS with intensification when changing the position of the body up to 3 p.; yellowness of the skin; reduction of the duration of night sleep to 4–5 hours.

Medical history:

The patient notes the appearance of jaundice within two weeks. According to the examination results, the patient was diagnosed with malignant neoplasm of the head of the pancreas 4 tbsp T3NxM1 (C25.9). Obstructive jaundice. After additional examination, the patient underwent external drainage to decompress the biliary tract.

After 3 weeks, a trial laparotomy with biopsy of the lymph nodes of the abdominal cavity was performed in order to clarify the staging and verification of the process. Abdominal carcinomatosis, ascites, chronic pain syndrome 3p on a verbal rating scale were added to the structure of the existing diagnosis.

By the decision of the medical commission, the patient was assigned palliative status, taking into account the fourth clinical group, and it was recommended to carry out systemic chemotherapy on an outpatient basis.

Anamnesis of life:

For five years he has been suffering from type II diabetes mellitus, non-insulin dependent. Ten-year history of hypertension 3st., risk 4., ischemic heart disease 2 functional class. The patient suffers from a duodenal ulcer with rare exacerbations (H. p. -). He is constantly taking antihypertensive, hypoglycemic drugs.

Objective status:

The patient's condition is satisfactory. Yellowness of the sclera and skin. There was no peripheral edema. The number of respiratory movements per minute is 19, breathing is hard, the absence of wheezing. The heart sounds are muffled, the rhythm is correct, the emphasis of the second tone is on the aorta, the number of heartbeats is 84 per minute. Blood pressure is 145/89 mm Hg. The tongue is coated with white bloom. The abdomen is soft. Percussion sizes of the liver are not increased.

The spleen is not enlarged by palpation. A slight soreness in the right mesogastrium is determined. Symptom XII ribs are negative on both sides. Of the features of the local status: on the right in the intercostal space is drainage, liquid discharge of yellow up to 800 ml per day. The stool is liquid with foam impurities. The results of laboratory and functional studies are shown in Table 1.

Against the background of systemic chemotherapy with capecitabine 2000–2500 mg/m^2/ a day, orally from day 1 to day 14 every 3 weeks ECOG status 3 points, BMI 24.16 kg/m^2, chronic pain intensity 3 points on a verbal rating scale and 7/10 points on a digital rating scale were observed. The patient was prescribed oral morphine sulfate in a daily dose of 90 mg in two doses on an outpatient basis, ketoprofen 100 mg intramuscularly at 22.00 and 100 mg rectally at 8.00 and 15.00, amitriptyline 12.5 mg at 23.00.

Table 1. *Laboratory and functional indicators*

Markers	Determined values	Reference values
Total protein,g/l	56,7	64–83
Potassium,mmol/l	3,15	3,5–5,1
Amylase,E/l	27	28–100
Creatinine,mkmol/l	56	44–80
ALT,E/l	22,3	5–33
AST,E/l	35,2	5–32
Glucose, mmol/l	7,10	4,11–5,89
Urea, mol/l	2,30	2,76–8,07
Total bilirubin, μmol/l	14,5	5–17
ESR, mm/hour	22	2–18
CA 19, ED/ml	988,81	0–27
GFR, ml/min/1.73 m^2	89	≥ 60 ml / min - a sign of preserved renal function
Child-Pugh scale score, points	5	Class A — 5–6 Class B — 7–9 Class C — 10–15
BMI, kg/m^2	34	18,5–24,99
ECOG, points	2	1–4
MMSE, points	28	28–30 points — no impairment of cognitive functions
ESAS, points	3	
DN 4, points	3	≥4 points — a sign of neuropathic pain

Abbreviations: *ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI — body mass index; GFR — glomerular filtration rate; ESR — erythrocyte sedimentation rate; CA19 — tumor marker; DN4 (Douleur Neuropathiqueen 4 questions) — a questionnaire to identify the neuropathic component of pain; ECOG (Eastern Cooperative Oncology Group) — physical status assessment scale; ESAS (Edmonton Symptom Assessment System) — Edmonton Symptom Assessment Scale; MMSE is a short scale for assessing mental status.*

After 3 weeks of therapy with a gradual increase in the patient, the development of morphine-associated constipation and an increase in the intensity of chronic pain syndrome up to 4b on a verbal rating scale and 8–9b on a digital rating scale were recorded.

Prescribing trimebutin in a daily dose of 400 mg and lactulose 60 ml a day did not give the desired result. The assessment of the reliability of the relationship between morphine sulfate and the development of constipation on the Naranjo scale was 9 points (definitely), a notification about the development of an adverse reaction was filled out.

A detailed analysis of comorbidity pharmacotherapy did not reveal constipation risk factors.

On the recommendation of a clinical pharmacologist, the patient underwent pharmacogenetic testing for carriage of SNV rs2032582 and rs1045642 of the *ABCB1* gene, rs1800795 of the *LOC541472* gene.

The analysis of the possibility of a personalized choice of opioid therapy is realized thanks to the created software-analytical complex "Evolutionary algorithm for the automated formation of decision support models for predicting the safety of opioid therapy" (authors Lipinsky L.V., Polyakova A.S., Melnikova O.D., Bobrova O. P., Schneider N.A., Zyryanov S.K., Petrova M.M., Russia, Krasnoyarsk).

The basis for the creation of this algorithm was the clinical, laboratory and genetic factors of patients - residents of Eastern Siberia with chronic pain syndrome against the background of pancreas cancer.

As part of the development of models for predicting the safety of opioid therapy, nine different machine learning methods were used with the resulting selection of the best quality model.

The best quality model was characterized by the use of at least fifty runs used by fifty-seven traits of patients with pancreas cancer.

An example of the selection of significant predictor factors for the implementation of constipation in patients with pancreas cancer based on the results of machine learning is presented in Table 2.

Table 2. *Comparative significance of the signs of the prognostic model of constipation "Decision trees for the classification problem" in the group of patients with pancreas cancer by the example of morphine sulfate*

Sign	Significance
AST0	0,296
Ascites	0,0013
Pancreas head	0,0022
Stage _bin	0,02
CC rs1800795 gene *LOC541472*	0,0008
GG rs2032582 gene *ABCB1*	0,007
AA rs1045642 gene *ABCB1*	0,0013

Abbreviations: *AST0- aspartate aminotransferase; Pancreas – pancreas.*

According to the results of genetic testing, this patient turned out to be a carrier of the homozygous genotype GG of the single nucleotide variant rs2032582 of the *ABCB1* gene, CC of the single nucleotide variant of rs1800795 of the *LOC541472* gene and AA of the single nucleotide variant of rs1045642 of the *ABCB1* gene.

And also the fourth stage of the process, the localization of cancer in the head of the pancreas, the presence of ascites and the level of aspartate aminotransferase with a cut-off point of more than 31.5 U/L confirmed the significance of a mutually aggravating prognostic effect for the obligatory realization of morphine-associated constipation. The patient also did not have prognostic factors for predicting the realization of morphine- and fentanyl-associated neurotoxicity and pharmacoresistance according to the results of the automated testing. It should be borne in mind that modeling using machine learning methods predetermines the mutually influencing associative nature of significant prognosis factors, in contrast to the monocomponent influence of each factor separately in a particular patient. Thus, taking into account the hepato-renal functional reserve of the patient, nutritional status, obtained predictive results, clinical data, structure and volume of concomitant therapy for analgesia as part of the combined treatment, fentanyl TTS was prescribed taking into account the conversion rate. The choice of the drug is explained by the lack of noroxycodone and pure oxycodone in Russia. This choice of opioid therapy was also predetermined by the difficulties in providing oxycodone/naloxone in the Krasnoyarsk region. Further monitoring of the patient's condition showed a decrease in the intensity of chronic pain to 1b on a verbal rating scale at rest and 2b during movement using 100 μkg fentanyl TTS (the dose was titrated in increments of 25 μkg once every 72 hours for 14 days) with no constipation.

This example clearly demonstrates the possibility of a comprehensive assessment of the combination of various most significant predictive factors for the implementation of this adverse reaction.

Thus, the use of an optimal set of seven prognostic factors (clinical — genetic and laboratory) for the selection of a priori personalized non-invasive opioid therapy made it possible to increase the efficiency and safety of the treatment in a palliative patient.

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