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PECULIARITIES OF PATHOGENESIS OF GASTRIC CANCER FORMED IN THE TREATMENT OF CHRONIC NON -ATROPHIC GASTRITIS BY PROTON PUMP INHIBITORS

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Abstract

The data on the duration of use of proton pump inhibitors, the nature and duration of stress, and the timing of the first clinical and instrumentally confirmed manifestations of gastric cancer in 10 patients with chronic non-atrophic gastritis who were treated with proton pump inhibitors both in the form of monotherapy and the composition of standard regimens of H. pylori therapy. It was found that the duration of taking proton pump inhibitors ranged from 2 days to 2 months, and the duration of stress - from 2 years to 45 years. The first clinical manifestations occurred from the 1st to the 5th month after the end of the treatment, and the deterioration of the patients' condition proceeded quickly, "avalanche-like" within 7-10 days.

Key words: chronic non-atrophic gastritis, proton pump inhibitors, gastric cancer.

Особливості патогенезу раку шлунка, який формується при лікуванні хронічного неатрофічного гастриту інгібіторами протонної помпи

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Резюме

Було проаналізовано дані про тривалість застосування інгібіторів протонної помпи, характер і тривалість стресу, а також терміни перших клінічних та інструментально підтверджених проявів раку шлунка у 10-ти хворих на хронічний неатрофічний гастрит, які проходили лікування із застосуванням інгібіторів протонної помпи як у вигляді монотерапії, так і в складі стандартних схем антигелікобактерної терапії. Було з'ясовано, що тривалість прийому інгібіторів протонної помпи коливалося від 2-х днів до 2-х місяців, а терміни стресу - від 2-х років до 45-ти років. Перші клінічні прояви виникали від 1-го до 5-ти місяців після закінчення лікування, а погіршення стану хворих протікало швидко, «лавиноподібно» протягом 7-10 днів.

Ключові слова: хронічний неатрофічний гастрит, інгібітори протонної помпи, рак шлунка.

Особенности патогенеза рака желудка, формирующегося при лечении хронического неатрофического гастрита ингибиторами протонной помпы

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Резюме

Были проанализированы данные по длительности применения ингибиторов протонной помпы, характера и длительности стресса, а также сроки первых клинических и инструментально подтверждённых проявлений рака желудка у 10-ти больных хроническим неатрофическим гастритом, проходивших лечение с применением ингибиторов протонной помпы как в виде монотерапии, так и в составе стандартных схем антихеликобактерной терапии. Было выяснено, что длительность приёма ингибиторов протонной помпы колебалось от 2-х дней до 2-х месяцев, а сроки стресса - от 2-х лет до 45-ти лет. Первые клинические проявления возникали от 1-го до

5-ти месяцев после окончания лечения, а ухудшения состояния больных протекало быстро, «лавинообразно» в течение 7-10 дней.

Ключевые слова: хронический неатрофический гастрит, ингибиторы протонной помпы, рак желудка.

Introduction. Gastric cancer (GC) remains one of the common forms of gastrointestinal cancer. Annually in the world, according to various sources, from 850 thousand to 1 million new cases of stomach cancer are registered; in Ukraine - more than 10 thousand and more than 8 thousand patients die from this disease [7, 9]. The basis of cancer formation is chronic non-atrophic gastritis (CNG), which accounts for 85% of stomach diseases and which can evolve into chronic atrophic gastritis (more than 80% of people older than 60 years in atrophic gastritis of varying severity are detected in biopsies of the gastric mucosa) [10, 14]. The development of CNG is influenced by various factors: stress, reduced immunity, reduced acidity of gastric juice, poisoning by various substances, environmental factors, etc. [3, 13, 17, 21, 25]. Recently, however, there is evidence that the use of such drugs as proton pump inhibitors (PPI) [5, 15, 16, 20, 22] widely used in the treatment of CNG, increases the risk of developing gastric cancer by 2 times, which requires revision the level of safety of these drugs, as they are freely sold in pharmacies without a prescription [11]. This issue was raised in our publications, where cancer cases that were formed after taking PPI were analyzed [2], however, a more detailed analysis of the features of the development of PPI-induced gastric cancer was not carried out, which was the reason for our research.

Purpose of the study. Determine the pathogenesis of gastric cancer, formed under the influence of proton pump inhibitors in the treatment of patients with chronic non-atrophic gastritis.

Materials and research methods. Based on the clinical department of the problem laboratory for chronic *Helicobacter pylori* at the Petro Mohyla Black Sea National University, we analyzed the data of a comprehensive examination of 10 patients with chronic non-atrophic gastritis, who had gastric cancer after using PPI. The age of patients ranged from 49 to 80 years old (average age was 62.1 ± 3.19 years), there were 3 men (30%) and 7 women (70%).

The study was carried out in compliance with the basic bioethical provisions of the Council of Europe Convention on Human Rights and Biomedicine (dated 04.04.1997), the Helsinki Declaration of the World Medical Association on the Ethical Principles of Scientific

Medical Research with Human Participation (1964-2008), and the MOH Order Of Ukraine No. 690 of September 23, 2009. A written consent was obtained from the patients for the study.

Comprehensive examination included: step-by-step enteric pH - metry on VN Chernobrovyi methodology, esophagogastroduodenoscopy (EGDS) with generally accepted method, double HP's testing: test for urease activity and microscopy of stained by Giemsa smears, material for which was taken during endoscopy of 4 topographical zones: from the middle third of the gastric antrum and body division on the big and small curvature with our developed methodology, which allows you to define and the presence of intracellular "Depot" of HP infection (in the presence of a tumor - departing 1 cm from the edge of the tumor) as well as histological studies of the gastric mucosa, the material for which is taken from the same zone and from the edges of the cancer, using a generally accepted method taking into account recent classifications [1,12,18].

Sequence of inspection: after the anamnesis first patients conducted pH-metry and after-EGDS with biopsy material for testing on HP and histological studies of the stomach mucosa. The study was conducted in the morning, fasting, in 12-14 hours after the last meal. The obtained data were processed statistically using t-student test with the calculation of average values (M) and the estimated probability of deviations (m).

Research results and discussion. When analyzing the anamnesis data, it was found that all patients received for the treatment of CNG with PPI drugs both as monotherapy and as part of the standard treatment regimens prescribed by the Maastricht consensus, from 2 days to 1 month (the average duration of admission was 19.1 ± 2.88 days), and the first clinical manifestations began after 1 to 5 months (average time - 1.7 ± 0.41 months) after the end of the reception of PPI and proceeded in the form of a sharp deterioration of the condition (loss of appetite, pain in the epigastric region, sharp weight loss), what was the reason for coming to the problem laboratory for examination 7-10 days after the onset of deterioration. 1 patient (10%) had already been operated on for cancer of the outgoing part of the stomach (resection of 2/3 of the stomach according to Billroth I) 32 years ago, but after applying an PPI for exacerbation of chronic pancreatitis, after 5 months he developed a gastric stump adenocarcinoma in the region anastomosis.

PPIs, that were taken by patients: pantoprazole ("Nolpaz", "Proxium", " β -Klatinol") - 8 people (80%); Omeprazole ("Omeprazole", "Omez") - 2 people (20%). 2 (20%) patients took the drugs themselves, 8 (80%) - as prescribed by doctors.

When analyzing the psycho-emotional background, it was found that all patients in 100% of cases were subjected to prolonged psycho-emotional stress. Data for the causes of stress are presented in table 1.

Table 1.

Types of psycho-emotional stress to which patients with chronic non-atrophic gastritis were exposed, in which gastric cancer was detected after the use of PPI

Types of psycho-emotional stress	Frequency of identified various types of psycho-emotional stress (n = 10)	
	Number of patients	%
Death of a loved one	1	10%
Death of a loved one + long psycho-emotional work load	1	10%
Stress about the illness of a loved one (care for a bed patient)	1	10%
Stress about the illness of a loved one + long psycho-emotional work load	1	10%
Family stress (family relationships)	2	20%
Family stress (absence of close relatives (grandchildren's children), widow for a long time)	1	10%
Family stress (divorce) + long psycho-emotional work load		
Long psycho-emotional work load	1	10%
Stress about the situation in the country (forced relocation from the ATO zone)	1	10%

Note: n-the number of studies

When analyzing the data on the duration of stress, it was found that patients were stressed from 1.5 months to 45 years (the average duration of stress was 13.41 ± 4.61 years).

The data obtained when conducting pH-metry, are shown in table 2.

Table 2.

Acidity level in patients with chronic non-atrophic gastritis, in which gastric cancer was detected after using PPI

The level of acidity	Frequency of identified different levels of acidity (n = 10)	
	Number of patients	%
Hyperacidity expressed		-
Hyperacidity moderate	-	-
Normacidity	-	-
Hypoacidity moderate	-	-
Hypoacidity expressed	10	100
Anacidity	0	0

Note: n-the number of studies

As can be seen from this table, in all patients the level of gastric juice acidity corresponded to a hypoacidity expressed (pH 3.6 - 6.99), which in no way was an indication for prescribing drugs that suppress acidity, namely, PPI.

Data on the localization of cancer in the stomach and gastric stump are presented in table 3.

Table 3.

Localization of a cancerous tumor in the stomach in patients with chronic non-atrophic gastritis, in whom gastric cancer was detected after using PPI

Anatomical section of the stomach	The frequency of detected cancer (n = 10)	
	Number of patients	%
The distal stomach	1	10
The proximal stomach and the stump of the stomach	9	90

Note: n-the number of studies

When analyzing data on the form of cancer in the distal stomach, a fibrous form of cancer (scirr) was detected in one (10%) patient. When analyzing data on the form of cancer in the proximal stomach, in 7 (70%) adenocarcinoma (tubular and papillary forms) was

detected, in 1 (10%) - signet ring cell adenocarcinoma, in 1 (10%) - squamous a form of cancer.

When analyzing the data of histological studies on the 4 topographical zones in all patients in 100% of cases, the presence of chronic non-atrophic gastritis was confirmed in both the active and inactive stages of varying severity.

When testing for HP, *Helicobacter pylori* infection was detected in 100% of cases with varying degrees of dissemination of the mucous - from (+) to (+++).

The data on the presence of intracellular "depot" of HP infection in the area of the cancer tumor are shown in table 4.

Table 4.

The presence of intracellular "depot" of HP infection in the gastric mucosa near the cancer that arose after the application of PPI

Form of cancer	Detection of intracellular "depot" of HP infection (n = 10)	
	Number of patients	%
Fibrous form of cancer (skirr)	-	0
Squamous a form of cancer	1	10%
Adenocarcinoma (tubular and papillary forms)	7	70%
Signet ring cell adenocarcinoma	1	10%

Note: n-the number of studies

When analyzing the data in this table, it can be seen that in 90% of cases, the HP infection along the edges of the cancer tumor was localized in the cells of the gastric mucosa (the degree of concentration was (++) - (+++)). It is possible that the same picture would have been with a fibrous form of cancer, however, due to the density of the tissues, it was not possible to take a full-fledged biopsy for analysis.

These results are explainable from the point of view of the hormonal shift, the cause of which is the use of IPP, the effect of stress on the level of body immunity and the role of intracellular "depot" of HP infection, which occur both during prolonged stress and when using PPI [23, 24]. When blocking the proton pump of the parietal cell and a sharp decrease in the level of acidity, the response of the organism manifests itself in the form of an increase in the production of the hormone gastrin, hypergastrinemia, as a way of combating the

organism with the resulting hypoacidity [3, 32]. However, such a reaction harbors a certain threat, since gastrin has a pronounced hyperplastic effect, i.e. stimulates the growth and division of cells of the gastric mucosa, as well as the pancreas and colon, which can lead to the formation of cancer in these organs [27, 28, 29, 30, 31]. The emergence of intracellular “depot” of HP infection is the key to the formation of gastric cancer, since, once inside the parietal cell, HP infection begins to actively influence the genetic code of the cell, enhancing the mutation process [3, 4, 19]. The presence of 80% of proximal cancers in patients also has a logical explanation: when using an IPP, HP infection is translocated — the translocation from the antrum to the upper third of the stomach, where the formation of intracellular “depot” of HP occurs in the gastric mucosa and the process of cell mutation increases. Therefore, a decrease in the incidence of distal GC is already noted, while the cancer of the proximal stomach has a steady upward trend, which determines the continuing high incidence and mortality [8].

When the level of immunity is preserved, these changes in the cell composition are under the control of protective forces, however, with prolonged stress, the level of immune protection deteriorates and its ability to prevent the development of cancer becomes extremely weak due to a decrease in the activity of the cellular link of immune protection - cytotoxic T-lymphocytes and natural killer cells which, under favorable conditions, destroy cancer cells by direct contact, as well as reducing antibody production and changes in cytokine production, the use of a small course of PPI is enough for him to start the process of cancer formation [3, 6, 26]. The timing of the clinical and morphological manifestations of gastric cancer after the application of PPI from 1 to 5 months is, in our opinion, the timing of the final depletion of the body's immune system capabilities in the fight against the developing stomach cancer.

Conclusions and prospects for further research.

1. All patients with chronic non-atrophic gastritis on the eve of treatment using PPI were exposed to prolonged psycho-emotional stress, which significantly affected the level of immunity and weakened the body's control over mutated cells of the gastric mucosa.

2. Acceptance of PPI triggers the mechanism of hypergastrinemia, which leads to the acceleration of mucosal cell division and an increase in the number of mutated cells, which neutralized immune systems can no longer cope with.

3. The appearance of clinical symptoms and morphological manifestations of cancer occurs quickly, “avalanche-like” and does not appear immediately, but 1 to 5 months after the

end of the course of PPI, regardless of its duration, in view of the complete depletion of the body's immune system in combating the emerging stomach cancer.

This situation requires the creation of new effective treatment regimens without the use of proton pump inhibitors, which will be the prospects for further research.

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