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TARGETED PREVENTION OF THE PROSTATE CANCER: FOCUS ON THE CHEMOPREVENTION AGENT AND GROUP OF PATIENTS

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The study has been carried out with participation of 24 male patients, who, due to high PSA level and suspicious data previously underwent polyfocal biopsy of the prostate gland. Pathological examination of prostate biopsy samples detected no prostate cancer, high-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation focuses. All the patients were divided into two groups. The main group comprised 14 men, who during 12 months had been taken 2 capsules of nutraceuticals containing 200 mg of indole-3-carbinol (I3C) and 45 mg of epigallocatechin-3-gallate (EGCG) in the mealtime (daily dose of 400 mg I3C and 90 mg EGCG). Patients of the comparison group (10 people) were under observation. Patients of both groups followed behavioral and dietary recommendations throughout the year (recommendations EAU 2016). The LUTS index according to IPSS after 1 year of research decreased by 38.7% in the main group patients, while there were no changes in the comparison group. The total of PSA level significantly decreased by 46.2% only in patients of the main group. The data obtained in the research indicate a significant decrease in the level of PSA and LUTS with long-term use of the combination of I3C and EGCG. The previous research, conducted with the use of multivariate analysis in the molecular genetic diagnosis of preclinical stages of prostate cancer, identified a subcluster of patients with histologically confirmed BPH and the molecular genetic characteristics (as the presence and level of methylation of the promoter zone of the genes GSTP1, APC, RARb), completely relevant to PCa. Patients with histologically confirmed BPH and the molecular genetic characteristics (as the presence and level of methylation of the promoter zone of the genes GSTP1, APC, RARb), completely relevant to PCa, can be ideal focus group for targeted prevention of the development of prostate cancer with various drugs, including nutraceuticals based on I3C and EGCG.

Key words: Targeted prevention; prostate cancer; benign prostatic hyperplasia; prostate specific antigen; indole-3-carbinol; epigallocatechin-3-gallate.

The study is a fragment of the research project "The role of molecular genetic, metabolic and enzym-endocrine disorders in the pathogenesis and clinical course of diseases of the genitourinary system and their impact on perioperative tactics, the nature of treatment and rehabilitation of patients", state registration No. 0111U010174.

Prostate cancer (PCa) is one of the most frequently diagnosed malignant neoplasms in men. The risk of PCa development directly depends on the age, family medical history, ethnicity, hormonal status, nutrition and lifestyle [4]. Due to the slow growth, hormone-dependent regulation, staged carcinogenesis, well-studied molecular genetic mechanisms of tumor growth, PCa is an ideal target for the application of various chemoprevention methods [8, 9, 12]. Various chemical compounds, agents and drugs have been proposed for this scope [2, 3, 7]. However, for example, the results of the well-known REDUCE study, turned out to be not entirely unambiguous [1]. Until now, there has been no definitive answer to the question: who, when and how is likely to undergo effective chemoprevention of prostate cancer. Given the slow tumor growth, its staging, early stages of PCa carcinogenesis, prevention of its development is most relevant at the stage of preneoplastic prostate changes. The strategy of monitoring patients with verified PCa biopsy or such preneoplastic changes in prostatic tissue as high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) is determined by various recommendations. Algorithm of managing patients with histologically confirmed benign prostatic hyperplasia (BPH), high level of prostate-specific antigen (PSA) (not caused by concomitant prostatitis) and absence of histological markers of early stages of carcinogenesis, still remains unclear [5]. Recently, there has been increasing evidence of suppressive action of indole-3-carbinol (I3C) and epigallocatechin-3-gallate (EGCG) on molecular mechanisms, which block tumor transformation and progression. The experimental data showed such effects of I3C as anticarcinogenic effect, inhibition of cell growth and induction of cell cycle and inhibition of signaling pathways in tumor cells [10]. In the meantime, EGCG has anti-inflammatory, anti-angiogenic, pro-apoptotic effects, inhibits DNA methyltransferases, participating in the epigenetic regulation of genes that suppress growth and fission of tumor cells. The clinically conditioned study of synergism of the preventive capabilities of I3C and EGCG at the early stages of carcinogenesis of PCa is relevant at present.

The purpose of the study was to evaluate the feasibility and effectiveness of the combination of I3C and EGCG in the therapeutic monitoring of patients with histologically verified BPH and high PSA level. This study was performed as a prospective, open, non-randomized, controlled in parallel groups from November 2016 to November 2017.

Materials and methods. Study design: our work was conducted as a prospective, open, non-randomized, controlled in parallel groups study in patients with histologically verified prostate biopsy of

BPH, with a concomitant high PSA level. The effect of the combination of I3C and EGCG on the dynamics of symptoms and clinical features of patients with non-neurogenic lower urinary tract dysfunction (main group) was compared with the implementation of only general recommendations (comparison group). Patients of both groups were prescribed general preventive measures for the consumption of fluid, balanced diet, lifestyle (according to the recommendation of the European Association of Urology (EAU) for non-neurogenic dysfunction of the lower urinary tract in men, 2016) during the year [11]. Patients of the main group additionally took 2 capsules of nutraceutical, containing 200 mg of indole-3-carbinol (I3C) and 45 mg of epigallocatechin-3-gallate (EGCG) («Epigalin», ProPharma Plant LLC, Ukraine) in daily dose of 400 mg of I3C and 90 mg of EGCG during the year, once during meals. The study was performed in accordance with the Declaration of Helsinki and the harmonized tripartite Regulations on Good Clinical Practice of ICH (CPMP / ICH / 135/95).

Study population**.** Twenty-four patients aged 52 to 68 years who had previously undergone a 12-point polyfocal biopsy of the prostate gland in connection with suspicious data for prostate cancer were examined. Such suspicious data included: an increase in the level of total PSA above 3.5 ng / ml (from 5.8 to 14.7 ng / ml), suspicion data of digital rectal examination (DRE) and transrectal ultrasound of the prostate (TRUS). Randomly (envelope method), all subjects were divided into 2 groups: the main group (14 men) and the comparison group (10 men).

Inclusion criteria:

- presence of symptoms of the lower urinary tract;
- increase in the level of total PSA;
- performed earlier polyfocal prostate biopsy;
- the presence of foci of benign prostatic hyperplasia according to a previous histological report;
- the patient's ability to adequately and motivated cooperation in the research process.

Exclusion criteria:

- history of previous surgical interventions in the lower urinary tract;
- the presence of leukocytes exceeding the threshold values in Meares and Stamey test;
- the presence of foci of prostate cancer according to a previous histological report;
- the presence of foci of the high-grade prostatic intraepithelial neoplasia of the prostate gland according to a previous histological report;
- the presence of foci of small-acinar atypical proliferation of the prostate gland according to a previous histological report;

Research methodology. Patients of both groups underwent general clinical tests of blood and urine; write down the International Symptom Score for Prostate Cancer (IPSS) Scale, in scores; conducted DRE; TRUS of the prostate with the determination of the volume of residual urine was performed by the Simens Acuson device; Uroflowmetry (with the determination of the maximum urine rate) was performed by "Potok-K" device; the determination of the level of total PSA was performed by an immunochemical method with electrochemoluminescent detection by a Cobas 6000 (Roshe Diagnostics) device. Evaluation of the results was carried out when included in the study and after one year. Statistical processing of the results of the study was carried out using the program STATISTICA 7.0. for Windows.

Results of the study and their discussion. In the patients of the main group, the baseline and control indices were as follows: according to the IPSS Scale 14.2 ± 1.3 and 8.7 ± 0.9 points ($p<0.05$); volume of the prostate 54.5 ± 4.9 and 56.3 ± 5.0 cm3 ($p<0.1$); the volume of residual urine was 20.8 ± 1.6 and 22.0 ± 1.9 ml ($p<0.1$); the maximum rate of urination was 15.6 ± 1.1 and 15.0 ± 1.3 cm / s ($p<0.1$); total PSA 9.3 ± 0.9 and 5.0 ± 0.4 ng / ml ($p<0.05$), respectively. (tab. 1).

Table 1

Indices of dynamic monitoring of patients of the main group

Index	Baseline	Control
IPSS Scale, points	14.2±1.3	8.7±0.9*
Volume of the prostate, cm^3	54.5±4.9	56.3±5.0
Volume of residual urine, cm^3	20.8±1.6	22.0±1.9
Maximum rate of urination, cm/s	15.6±1.1	15.0±1.3
Total PSA, ng/ml	9.3±0.9	5.0±0.4*

* $p<0.05$

In the patients of the comparison group, the baseline and control indices were as follows: according to the IPSS score of 12.1 ± 1.5 and 13.7 ± 1.9 points ($p<0.1$); volume of the prostate 51.8 ± 4.2 and 53.4 ± 4.8 cm3 ($p<0.1$); the volume of residual urine is 25.7 ± 2.1 and 28.4 ± 2.5 ml ($p<0.1$); the maximum rate

of urination is 13.4 ± 1.5 and 12.9 ± 1.4 cm / s ($p<0.1$); total PSA of 8.7 ± 0.5 and 9.2 ± 0.7 ng / ml ($p<0.1$), respectively (tab. 2).

The severity of lower urinary tract symptoms (LUTS) according to the IPSS scale after 1 year of research decreased by 38.7% in the main group patients, while there were no changes in the comparison group. The volume of the prostate gland, the volume of residual urine, the maximum rate of urination in patients of both groups did not change significantly. The level of total PSA significantly decreased by 46.2% only in the main group patients. PSA is an organ-specific marker and is produced by both normal and tumor cells of the prostate excretory ducts. Besides using PSA for the primary diagnosis of prostate diseases, it is a reliable laboratory indicator that contributes to determination of distant metastasis and is also used as a criterion for the effectiveness of prostate cancer treatment and disease prognosis. The data obtained in the research indicate a significant decrease in the level of PSA with long-term use of the combination of I3C and EGCG. It is likely to happen due to various mechanisms of antitumor effect of these components, carried out through regulation of the cell cycle of fission, cell proliferation, apoptosis, oncogenesis, transcription and cellular signal transduction.

Table 2

Indices of dynamic monitoring of the comparison group

Index	Baseline	Control
IPSS Scale, points	12.1±1.5	13.7±1.9
Volume of the prostate, cm3	51.8±4.2	53.4±4.8
Volume of residual urine, cm3	25.7±2.1	28.4±2.5
Maximum rate of urination, cm/s	13.4±1.5	12.9±1.4
Total PSA, ng / ml	8.7±0.5	9.2±0.7

$p<0.1$

The previous research, conducted with the use of multivariate analysis in the molecular genetic diagnosis of preclinical stages of prostate cancer, identified a subcluster of patients with histologically confirmed BPH and the molecular genetic characteristics (as the presence and level of methylation of the promoter zone of the genes GSTP1, APC, RARb), completely relevant to PCa [16]. These patients can be ideal candidates for targeted prevention of the development of prostate cancer with various drugs.

Conclusion

Patients with histologically confirmed BPH and the molecular genetic characteristics (the presence and level of methylation of the promoter zone of the genes GSTP1, APC, RARb), completely relevant to PCa, can form an ideal focus group for the targeted prevention of PCa by various drugs. The active strategies of therapeutic monitoring for these patients are pathogenetically justified, including the use of nutraceuticals based on I3C and EGCG.

It is advisable to continue the research with the aim to determine the biochemical, histological, molecular-genetic criteria for selecting candidates and to determine the most effective and safe means for the targeted prevention of PCa.

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Реферати

ЦІЛЬОВА ПРОФІЛАКТИКА РАКУ ПРОСТАТИ: АКЦЕНТУВАННЯ НА ХІМІОПРОФІЛАКТИЦІ ТА ГРУПІ ПАЦІЄНТІВ

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Проведено дослідження 24 чоловіків, яким була виконана поліфокальна біопсія передміхурової залози. За даними гістологічного дослідження біоптатів передміхурової залози РПЗ, фокусів простатичної інтраепітеліальної неоплазії високого ступеня або мелкоацінарной атипові проліфірації передміхурової залози виявлено не було. Пацієнти були розділені на дві групи: основна група (14 чоловіків) протягом 1 року одноразово під час їжі вживала 2 капсули нутрицевтика, що містить 200 мг індол-3-карбінолу (I3C) і 45 мг епігаллокатехін-3-галлата (EGCG) (добова доза 400 мг I3C і 90 мг EGCG) та група порівняння (10 осіб), що перебувала під наглядом. Хворі обох груп протягом року дотримувалися поведінкових та дієтичних рекомендацій (рекомендації ЄАУ 2016). Ступінь вираженості СНСШ за даними Шкали IPSS через один рік дослідження була на 38,7% нижче у хворих основної групи, в групі порівняння змін не виявлено. Рівень загального ПСА достовірно знизився на 46,2% тільки у пацієнтів основної групи. Отримані дані свідчать про значне зниження рівня ПСА і вираженості СНСШ при тривалому застосуванні комбінації I3C і EGCG. Раніше нами виявлено субкластер хворих (за даними молекулярно-генетичної діагностики доклінічних стадій РПЗ з використанням багатовимірного аналізу) з гістологічно підтвердженою ДГПЗ і молекулярно-генетичними характеристиками отриманих біоптатів (за наявністю і рівнем метилювання промоторной зони генів GSTP1, APC, RARb) повністю відповідними РПЗ. Пацієнти з гістологічно підтвердженою доброякісною гіперплазією передміхурової залози та молекулярно-генетичними характеристиками (наявністю і рівнем метилювання промоторной зони генів GSTP1, APC, RARb), повністю відповідними РПЗ, є ідеальною фокус-групою для таргентной превенції РПЗ різними лікарськими засобами, в тому числі з використанням нутрицевтиков на основі I3C і EGCG.

Ключові слова: таргентна превенція, рак передміхурової залози, доброякісна гіперплазія передміхурової залози, простато-специфічний антиген, індол-3-карбинол, эпігаллокатехин-3-галлат

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ЦЕЛЕВАЯ ПРОФИЛАКТИКА РАКА ПРОСТАТЫ: АКЦЕНТИРОВАНИЕ НА ХИМИОПРОФИЛАКТИЧЕСКОМ ПРЕПАРАТЕ И ГРУППЕ ПАЦИЕНТОВ

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Проведено исследование 24 мужчин, которым была выполнена полифокальная биопсия предстательной железы. По данным гистологического исследования биоптатов предстательной железы РПЖ, фокусов простатической интраэпителиальной неоплазии высокой степени или мелкоацинарной атипической пролифирации предстательной железы выявлено не было. Пациенты были разделены на две группы: основная группа (14 мужчин) которые в течении 1 года однократно во время еды принимали 2 капсулы нутрицевтика, содержащего 200 мг индол-3-карбинола (I3C) и 45 мг эпигаллокатехин-3-галлата (EGCG) (суточная доза 400 мг I3C и 90 мг EGCG), пациенты группы сравнения (10 человек) находились под наблюдением. Больные обеих групп в течении года придерживались поведенческих и диетических рекомендаций (рекомендации ЕАУ 2016). Степень выраженности СНМП по данным Шкалы IPSS через один год исследования была на 38,7 % ниже у больных основной группы, в группе сравнения изменений не выявлено. Уровень общего ПСА достоверно снизился на 46,2 % только у пациентов основной группы. Полученные данные свидетельствуют о значительном снижении уровня ПСА и выраженности СНМП при длительном применении комбинации I3C и EGCG. Ранее нами выявлен субкластер больных (по данным молекулярно-генетической диагностики доклинических стадий РПЖ с использованием многомерного анализа) с гистологически подтвержденной, по данным биопсии предстательной железы, ДГПЖ и молекулярно-генетическими характеристиками полученных биоптатов (по наличию и уровню метилирования промоторной зоны генов GSTP1, APC, RARb) полностью соответствующими РПЖ. Пациенты с гистологически подтвержденной доброкачественной гиперплазией предстательной железы и молекулярно-генетическими характеристиками (наличием и уровнем метилирования промоторной зоны генов GSTP1, APC, RARb), полностью соответствующими РПЖ, являются идеальной фокус-группой для таргентной превенции РПЖ различными лекарственными средствами, в том числе с использованием нутрицевтиков на основе I3C и EGCG.

Ключевые слова: таргентная превенция, рак предстательной железы, доброкачественная гиперплазия предстательной железы, простато-специфический антиген, индол-3-карбинол, эпигаллокатехин-3-галлат

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