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DEVELOPMENT OF SECONDARY ANAEMIA IN PATIENTS WITH DIFFERENTIATED THYROID CANCER TREATED WITH RADIOTHERAPY

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Abstract

Relevance. Thyroid cancer is one of the most prevalent endocrine cancers, which makes the study of issues related to its variants and complications arising during treatment relevant. Secondary anaemia may occur in patients with differentiated thyroid cancer treated with radiotherapy.

Aim of this study was to analyse the potential of using hypocalcaemia as a predictor of onset of secondary anaemia after radiotherapy in differentiated thyroid cancer patients.

Materials and methods. The study covered a cohort of 120 differentiated thyroid cancer patients treated using conventional methods (including surgery, radiotherapy and hormone therapy). The occurrence and development of complications in the form of secondary anaemia were analysed.

Results. Blood calcium under 2.2 mmol/L in thyroid cancer patients prior to radiotherapy represents a risk factor for the occurrence of secondary anaemia. Calcium deficiency must be monitored and treated in order to avoid this complication.

Conclusions. Onset of secondary anaemia is correlated to hypocalcaemia in thyroid cancer patients with hypoparathyroidism. Blood calcium must be monitored prior to radiotherapy during treatment of thyroid cancer.

Key words: Differentiated Thyroid Cancer, radiotherapy, secondary anaemia.

Резюме

РАЗВИТИЕ ВТОРИЧНЫХ АНЕМИЙ У БОЛЬНЫХ ДИФФЕРЕНЦИРОВАННЫМ РАКОМ ЩИТОВИДНОЙ ЖЕЛЕЗЫ НА ФОНЕ РАДИОЙОДТЕРАПИИ

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Актуальность. Рак щитовидной железы является одним из наиболее распространенных эндокринных раков, что делает актуальным изучение вопросов, связанных с вариантами его течения и осложнениями, возникающими в процессе лечения.

Цель. Обосновать предикторную ценность гипокальциемии в возникновении вторичных анемий при проведении радиойодтерапии у больных дифференцированным раком щитовидной железы.

Материалы и методы. Изучались вопросы появления и развития непосредственных осложнений радиойодтерапии в виде вторичных анемий на катamnестических данных 120 пациентов с диагностированным раком щитовидной железы, которые проходили лечение по стандартной схеме, включающей радикальное хирургическое лечение, радиойодтерапию и гормонотерапию.

Результаты. Показано, что снижение уровня Са в крови ниже 2,2 ммоль/л у пациентов с раком щитовидной железы перед проведением радиойодтерапии является фактором риска развития вторичных анемий и требует соответствующей превентивной подготовки пациента для предотвращения их появления.

Выводы. В результате проведенного исследования изучена зависимость между возникновением вторичной анемии у пациентов с гипокальциемией на фоне гипопаратиреоза и обоснована необходимость контроля уровня кальция крови перед проведением радиойодтерапии в процессе специального лечения рака щитовидной железы.

Ключевые слова. Дифференцированный рак щитовидной железы, радиойодтерапия, вторичные анемии.

Түйіндеме

РАДИОЙОДТЕРАПИЯ ФОНЫНДА ҚАЛҚАНША БЕЗІНІҢ ДИФФЕРЕНЦИАЛДЫ ОБЫРЫМЕН НАУҚАСТАРДАҒЫ ҚАЙТАЛАМА АНЕМИЯСЫНЫҢ ДАМУЫ

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Өзектілігі. Қалқанша безінің обыры ең көп таралған эндокриндік обырдардың бірі болып табылады, бұл емдеу процесінде пайда болатын оның ағымы мен асқынуларға байланысты мәселелерді зерттеу өзекті етеді.

Мақсаты. Қалқанша безінің дифференциалды обырымен ауыратын науқастарда радиойодтерапия өткізу кезінде қайталама анемия пайда болуында гипокальциемияның негізгі құндылығын негіздеу.

Материалдар және әдістер. Катamnестикалық деректерде қайталама анемия түріндегі радиойодтерапияның тікелей асқынуларының пайда болуы және дамуы, радикалды хирургиялық ем, радиойодтерапия және гормонотерапия кіретін стандартты схема бойынша емделген қалқанша безінің диагноз қойылған обыры бар 120 пациент зерттелді.

Нәтижелер. Қалқанша безінің обыры бар емделушілерде қандағы Са деңгейінің 2,2 ммоль/л-ден төмендеуі радиойодтерапия жүргізер алдында қайталама анемиялардың даму қаупінің факторы болып табылатыны және олардың пайда болуының алдын алу үшін пациенттің тиісті превентивті дайындығын талап ететіндігі көрсетілген.

Қорытындылар. Жүргізілген зерттеу нәтижесінде гипопаратиреоз аясында гипокальциемиясы бар емделушілерде қайталама анемияның пайда болуы арасында тәуелділік зерттелді және қалқанша безінің обырын арнайы емдеу процесінде радиойодтерапия жүргізер алдында қан кальций деңгейін бақылау қажеттілігі негізделді.

Түйінді сөздер. Қалқанша безінің дифференциалды обыры, радиойодтерапия, қайталама анемиялар.

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Introduction

Thyroid cancer is one of the most common endocrine cancers. In the USA, thyroid cancer represents 1.0-1.5% of newly diagnosed cancers every year. Over the past three decades, the prevalence of thyroid cancer has been increasing across all continents except for Africa. In Africa itself, the absence of this trend could be due to insufficient diagnosis. Recent data suggest that thyroid cancer is the fifth most frequent cancer in women. In Italy, it is the second most frequent cancer in women under 45 years of age. Only in a few countries (notably, in Norway and Sweden) is thyroid cancer becoming less frequent, currently affecting 3 out of 100,000 people [14].

The frequency of this pathology asks for analysis of variations of its course and complications arising during therapy.

The standard of care for thyroid cancer is surgery, radiotherapy and hormone therapy.

One of the possible complications arising upon radiotherapy thyroid cancer treatment is secondary anaemia.

The Research Work protocol (ref. №5 from 15.05.2018) established within the SE «Institute of Medical Radiology named after S.P. Grigoriev» of the National Academy of Medical Sciences of Ukraine (hereafter referred to as the Institute) investigates the impact of anti-inflammatory therapy on the development of adverse effects of thyroid cancer treatment. The results show that, in thyroid cancer patients having undergone radiotherapy, hypocalcaemia under 2.2mmol/L represents a predictive factor of clinical outcome. However, in-depth analysis of the literature covering complications of thyroid cancer therapy showed no studies of the causality between said complications. Hence, an investigation of their pathophysiology is called for [2-4, 7, 9, 12, 13, 20-23, 25, 27, 29].

The aim of this project is to investigate hypocalcaemia as a predictive marker of secondary anaemia, a possible complication of radiotherapy of differentiated thyroid cancer.

Materials and methods:

The study was performed in the Institute's radiology department between 2013 and 2017. Retrospective analysis of the clinical history of patients diagnosed with thyroid cancer was undertaken. 238 clinical histories were selected at random from the paper archives of the Institute, in order to investigate unfavourable outcomes of surgery and radionuclide therapy.

In order to investigate the complications arising over the course of treatment, the following data were compiled within a database: sex, age at diagnosis, stage of primary disease, histological structure of the tumour, comorbidities, adverse habits, gynaecological history, duration of past treatments with certain drugs, treatment strategy, dose of radioiodine therapy (RIT), surgical complications (vocal cord paresis, laryngeal stenosis and hypoparathyroidism (HPT)), radiotherapy complications (anaemia, leukopenia, thrombocytopenia, gastritis, cystitis, pneumonitis, acute laryngitis and arrhythmia), inflammatory markers, blood calcium over time, and quality of life at various stages of anti-inflammatory treatment. Randomisation of the trial was performed using computerised random numbers. The investigation was a retrospective case-control study.

Diagnosis was determined based on the International Classification of Diseases (v. X) and existing documents: Order of Ministry of Health of Ukraine No. 554 dated 17.09.2007 "On approval of protocols for providing medical care in the speciality "Oncology", "Protocols for providing medical care in patients with malignant tumors", SE «Institute of Medical Radiology named after S.P. Grigoriev» of the National Academy of Medical Sciences of Ukraine", 2011. Complications of RIT - namely sialadenitis, gastritis, cystitis, pneumonitis, acute laryngeal inflammation and arrhythmia - were diagnosed according to local methodological recommendations.

Analysis of complications associated with treatment was performed using the Common Terminology Criteria for Adverse Events v. 3.0 (CTCAE), Publication Date: 12 December, 2003.

In order to study secondary anaemia as a treatment complication, a cohort of 120 patients were investigated. They were selected under the condition of normal haemoglobin levels upon discharge from the surgical wing and admittance to radionuclide therapy in the Institute, 3-6 weeks after surgery.

Anaemia was diagnosed according to the World Health Organisation criteria, with a cut-off at 120g/L in women and 130g/L in men.

At the time of radiotherapy, haemoglobin in the selected patients was 129 (125-134) g/L.

The cohort contained 104 women (86.7%) and 16 men (13.3%) aged 18-79.

The majority of patients (50.8% or 61 individuals) were diagnosed with stage I disease. 27.5% (33 individuals) were diagnosed at stage II, 14.2% (17 individuals) were diagnosed at stage III, and 7.5% (9 individuals) were diagnosed at stage IV.

The dose of radiation was 3,385 (3,330-5,365) MBq. An average of two courses of radiotherapy was undergone by each patient.

Statistical analysis was performed using open source package STATISTICA (License Number: 139-956-866). The variables were not normally distributed (Kolmogorov-Smirnov criteria), therefore non-parametric analyses (Mann-Whitney tests) were performed. Comparisons of the frequencies of occurrence was performed using Pearson's chi-squared criteria. Differences with $p < 0.05$ were considered significant.

Results:

The initial phase of our investigation showed that, in our cohort of 120 patients, anaemia as an early complication of radiotherapy was observed in $15.8 \pm 3.3\%$ of patients (19 individuals) [1]. The total dose of radiation received by each patient was 4,255 (3,330-5,365) MBq. No statistically significant differences were observed between the characteristics of radiotherapy undergone by patients who developed secondary anaemia and those who did not.

The onset of secondary anaemia was shown to be inducible by post-operative HPT ($p < 0.01$, chi-squared Pearson test). Indeed, 15 ($30 \pm 6.5\%$) of the 50 patients with HPT developed anaemia. On the other hand, only four ($5.7 \pm 2.8\%$) of the 70 patients without HPT developed anaemia. The results are presented in Figure 1.

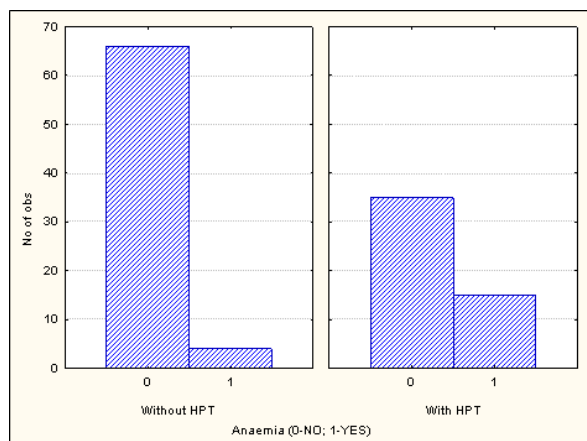


Figure 1. Histograms representing the number of anaemic and non-anaemic patients with or without post-operative HPT.

Defining the risk as the probability of occurrence of an unfavourable event, we were able to assess the risk of development of anaemia in patients with HPT (15/50) and in patients without HPT (4/70). The ratio of the former over the latter represents 5.25, implying that HPT increases the risk of onset of secondary anaemia over five-fold.

The relation between onset of secondary anaemia as an early treatment complication, and reduced blood calcium prior to RAIT, was also statistically significant ($p < 0.01$, Mann-Whitney test).

Patients who developed anaemia over the course of treatment presented a median calcium level under 2.05 mmol/L prior to radiotherapy. Patients that were non-anaemic after radiotherapy presented a median calcium level of 2.4 mmol/L beforehand (Figure 2).

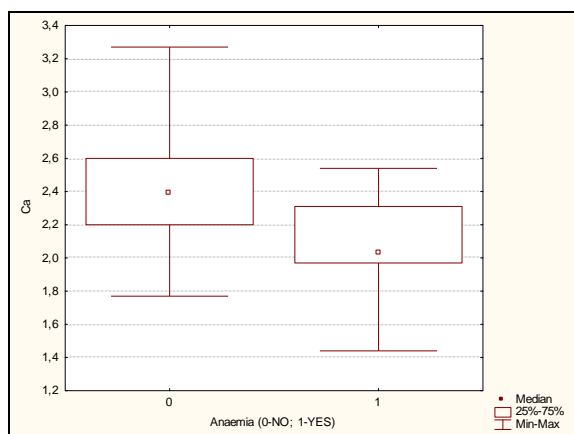


Figure 2. Box and whisker plot of blood calcium level before radiotherapy in patients with (1) or without (0) secondary anaemia.

The value of the first quartile of blood calcium in non-anaemic patients was 2.2 mmol/L (Figure 2). We therefore hypothesise that a value under this cut-off constitutes a marker increased risk of onset of secondary anaemia after radiotherapy. It is therefore necessary to further explore this correlation in order to adequately prepare thyroid cancer patients for radiotherapy, in order to prevent this complication.

Discussion:

To investigate the connections between hypoparathyroidism, hypocalcaemia and secondary

anaemia, an extensive review of the literature was performed. NCBI website PubMed and Europe PubMed Central were utilised, as well as the websites ClinicalTrials.gov and German Medical Science, ZB MED catalogues of the German National Library of Medicine, and publications of the International Institute of Anticancer Research (IIAR). The IIAR journals that were used were ANTICANCER RESEARCH, IN VIVO and CANCER GENOMICS & PROTEOMICS. BMC Genomics journals (Thyroid Research, Applied Cancer Research, BMC Endocrine), Springer Science+Business Media journals, open access publications from Medicine®, publications from the online library eLIBRARY.RU and search platform of the Vernadsky National Library of Ukraine were also reviewed.

After an extensive review of the literature, we became convinced that no studies redundant with our observations have ever been published. Indeed, only studies of post-operative hypoparathyroidism and hypocalcaemia have yet been performed to our knowledge.

According to the authors of [8], hypoparathyroidism occurs as a consequence of damage to, and/ or de-vascularisation of the parathyroid glands. As a result, secretion of parathyroid hormone (PTH), mobilisation of bone calcium, reabsorption of calcium from the distal convoluted tube and stimulation of renal 1α -hydroxylase, are compromised. This induces hypocalcaemia. Hypocalcaemia can be symptomatic or asymptomatic, and develops within days after surgery. The standard of care is treatment with vitamin D analogues and calcium supplements.

Acute hypocalcaemia occurs in 50 - 68% of patients who undergo complete thyroidectomy. 3% of patients suffer from chronic hypocalcaemia. Acute hypocalcaemia refers to a decrease of blood calcium over 6-12 months. Otherwise, the hypocalcaemia is classified as chronic. We note that the majority of hypocalcaemia cases are asymptomatic [6, 10, 11, 17-19, 24, 26].

The authors of [25, 28] observe correlations between thyroid dysfunction and anaemia. However, their observations go no further and analysis of causality is not performed.

Further analysis of the literature on animal studies drew our attention to the work of A.D. Perris, J.F. Whitfield (1968 - 1971) [16]. The authors demonstrate a correlation between mitotic activity in the bone marrow and blood calcium in rats. They observe a decrease in mitotic activity in the bone marrow and blood calcium, upon resection of the parathyroid glands. In turn, injection of PTH extract increased both parameters. These observations expose a direct impact of calcium on haematopoiesis, and an indirect relation between haematopoiesis and the hormones regulating blood calcium.

In, Perris A.D., Whitfield J.F., Rixon R.H. [15] also demonstrate renewed mitotic activity in the rat bone marrow after radiation. Injection of PTH extract mobilised bone calcium into the bloodstream.

These investigations were followed by the works of Rixon R.H., Whitfield J.F. [20], which demonstrate the role of Ca^{2+} and PTH in stimulating haematopoiesis. Parathyroid gland resection in rats was rapidly followed by a significant decrease in mitotic activity in the bone marrow. Erythrocyte ^{59}Fe levels and also reticulocyte production were reduced

thereafter. These symptoms were relieved upon treatment with calcium chloride or PTH. Moreover, this study demonstrates a role of PTH in normalisation of haematological parameters after extensive blood loss.

The authors demonstrate the independence of calcium homeostasis from other pathways in rats. Indeed, calcium or PTH treatment alone were sufficient to restore mitotic activity within the bone marrow after nephrectomy (which prevented synthesis of erythropoietin).

As a final piece of evidence in this field, we recognise the work of A.G. *Gianoukakis*, M.J. *Leigh*, (1979) [5]. Here, the authors investigate the role of PTH and calcium as regulators of lymphoid cells and erythrocytes. They demonstrate that the metabolic index in rats after parathyroidectomy and thyroparathyroidectomy was modified by decreased cell proliferation within the bone marrow, and not by a decrease in the duration of mitosis. These processes were accompanied by a progressive decrease in the population of nucleated cells to 40% of their initial number. The shift in numbers concerned exclusively the erythrocytes and lymphoid populations. The myeloid population remained stable. Interestingly, the haematopoietic cell populations of animals being fed with a calcium-supplementing diet did not undergo any change. This suggests that, at steady state, calcium plays a key role in controlling haematopoietic cell proliferation.

This evidence suggests that secondary anaemia is directly related to insufficient blood calcium and hypoparathyroidism. Given the frequency of asymptomatic hypocalcaemia and post-operative hypoparathyroidism, it seems essential to determine blood calcium levels and remedy deficiencies in thyroid cancer patients prior to radiotherapy.

No difference in radionuclide therapy parameters was observed between the patients who did or did not develop anaemia. Hypoparathyroidism was shown to represent a risk factor, increasing the probability of onset of secondary anaemia by over a factor of five. Moreover, we have demonstrated a correlation between onset of anaemia and blood calcium prior to treatment. Blood calcium under 2.2 mmol/L in thyroid cancer patients undergoing radiotherapy represents a risk for onset of secondary anaemia.

These results suggest a putative relation between the above-mentioned mechanisms -demonstrated on animal models-, and the observations made on patients -presented in this paper-. These results demonstrate the relevance of blood calcium as a marker of risk of secondary anaemia in thyroid cancer patients treated with radiotherapy. They argue the need for timely prophylactic treatment of these patients.

Conclusions:

These results suggest an association between hypocalcaemia, and onset of secondary anaemia in thyroid cancer patients with hypoparathyroidism.

Given the probability of asymptomatic hypocalcaemia and post-operative hypoparathyroidism, these observations call for monitoring and therapeutic correction of blood calcium prior to radiotherapy of thyroid cancer.

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