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The importance of the chromogranin A concentration in evaluation of monitoring of treatment effectiveness with the somatostatin analogues in patients with neuroendocrine tumors

Znaczenie stężenia chromograniny A w ocenie monitorowania skuteczności leczenia analogami somatostatyny pacjentów z guzami neuroendokrynnymi

INTRODUCTION

Accurate and early diagnosis of the Neuroendocrine Tumors (NET) is still a fundamental problem in oncology practice. The NETs are rare and its biological distinctiveness and variations in clinical course makes its diagnosis very difficult. Nowadays both: biochemical and immunohistochemical tests may provide additional, valuable diagnostic information in the diagnosis and monitoring of NETs. The introduction of chromogranin A (CgA) to the biochemical diagnostics profile of NET improved significantly the diagnosis and is useful in monitoring of treatment effectiveness with somatostatin analogues. Evaluation of the CgA concentration in serum is considered of limited value at diagnosis of NET; however the importance of this protein is assigned to the treatment monitoring and remission prediction. Recent studies confirmed that the measurement of CgA levels in blood can also be used to diagnose and monitor NETs during treatment [1, 2, 9].

At present the CgA is considered to be non-specific marker of the NET. The CgA is an acidic glycoprotein of the granin family with a molecular weight of 48 kDa. It is expressed in most normal neuroendocrine secretory cell types containing secretory granules, where it is synthesized and released together with peptide hormones and biogenic amines [7, 10, 11, 15, 17, 18]. The rate of its release depends on the degree of the histopathological tumor differentiation [4, 12].

The highest concentrations of the CgA has been demonstrated in patients carcinoid tumors, where the marker level found was a few hundred times of that in healthy subjects [1,8,16]; however

with certain neuroendocrine tumours like SCLC (small-cell lung carcinoma) only weak expression of the CgA was reported [8].

The aim of the study was the retrospective analysis of the CgA concentration in the course of treatment monitoring of patients with clinically diagnosed NETs at Saint John of Dukla Oncological Centre of Lublin Region in the years 2005-2011.

MATERIAL AND METHODS

S t u d y g r o u p. The Chromogranin A concentration was determined in 30 patients diagnosed with NET. In most cases primary localization of NET was identified in the gastrointestinal tract (GEP-NET), and lungs. The patients were treated at Oncology Centre of Lublin Region in Lublin from February 2005 to May 2011. The patients ages ranged from 34 to 80 years (mean 55 ± 15 years). The study group consisted of 18 women (60%) with a mean age of 57 ± 10 and 12 men (40%) with a mean age of 64 ± 10, W/M index=1.5.

All patients included in the study were treated according to current standards of treatment of GEP/NET tumors. They received combination therapy, adjusted individually depending indications, including: surgical treatment, chemotherapy, intravenous somatostatin analogues administration in the regimen every 28 days and/or interferon-alpha therapy. Nature of the treatment depended on the general condition of the patient, severity of cancer, histopathological diagnosis, presence of elevated levels of serum CgA, individual tolerance and efficacy of the treatment. Patients who, despite the use of all treatment options, shown a steady disease progression were further qualified for the symptomatic treatment.

For most of the patients (26 out of 30) the serum CgA determination was performed only 2-3 times in the course of therapy therefore detailed analysis of this marker changes was performed in 4 selected patients with the most frequent determinations.

M a t e r i a l. Peripheral venous blood samples were collected using standard vein puncture technique. The Blood samples were taken at rest, fasting in a sitting position afterwards clotted samples were and centrifuged for 10 min at 2000 rpm/min. Obtained serum samples were separated and aliquoted into eppendorfs and stored at –20°C pending analysis.

M e t h o d s. The CgA plasma determinations were performed with the use of ELISA immunoenzymatic assay of commercially available kit Chromogranin A (DakoCtomation, Denmark). Analyses were done according to the manufacturer's instructions. During the whole course of the study the kits from the same company were used. Analytical sensitivity of the test was 2.0 U/L and imprecision expressed as CV was 8.6%. For statistical analysis of obtained results, Statistica 7.0 StatSoft was used.

RESULTS

In the present study we determined the CgA concentration in the group of patients initially surgically treated with following chemotherapy and/or somatostatin analogues administration.

The serum concentrations of the CgA were elevated in 71.4% patients with disease progression. At patients with stable disease course up to 75% had unchanged levels of this marker. These interesting notices are shown in Table 1.

Table 1. The changes of a CgA concentration in response to the treatment

CgA concentration	An objective clinical response to treatment		
	Regression N=8	Stabilisation N=8	Progression N=14
Stable	50 % (4/8)	75 % (6/8)	21.4 % (3/14)
Increase	-	12.5 % (1/8)	71.4 %(10/14)
Decrease	50 %(4/8)	12.5 % (1/8)	7.2 % (1/14)

Based on the CgA results obtained in this study it is difficult to perform detailed analysis of its concentration changes in the course of the treatment. This is due to the fairly short hospitalization period in the Oncological Centre of Lublin Region. Serum CgA determination was performed only 2-3 times in the course of therapy in most cases therefore out of the group of 30, we carefully selected four patients, as they remained longitudinally under the care of the Oncological Centre of Lublin Region and had most frequent CgA determinations requested. For those selected patients we conducted a thorough analysis of the CgA concentration changes in the course of therapy.

Patient 1 A man diagnosed with highly differentiated NET of ileum with existing liver metastases. In order to remove the intestinal tumor laparotomy was performed with subsequent thermoablation of metastatic lesions localized the liver. Treatment with the Sandostatin was administered afterwards under constant oncologic supervision. The CgA concentration was evaluated at 4^{th}, 8^{th}, 10^{th}, 12^{th}, 14^{th}, 17^{th} and 20^{th} month from the initiation of the treatment with the somatostatin analogues.

Patient 2 A woman diagnosed with highly differentiated NET of cecum with presence of the common clinical signs of carcinoid. For the treatment hemicolectomy and Somatostatin administration was applied. The concentration of CgA was determined at 8^{th}, 12^{th}, 23^{rd},32^{nd}, 38^{th}, 47^{th}, 50^{th}, 53^{rd}, 55^{th} and 57^{th} month of therapy.

Patient 3 A man diagnosed with highly differentiated NET of stomach. After surgery and treatment the CgA determinations were performed at four time points: baseline- initiation of the treatment, and subsequently at 17^{th}, 27^{th} and 32^{nd} month of therapy.

Patient 4 A woman diagnosed with highly differentiated NET in ileum and a high CgA concentration of 635 U/l. After radical surgery and after Sandostatin treatment initiation the CgA concentrations were determined at 8^{th}, 10^{th}, 12^{th}, 13^{th}, 20^{th}, 28^{th}, 32^{nd}, 36^{th}, 47^{th} and 50th month of therapy.

Changes in the CgA concentration dynamics of above selected patients are presented in the figure below (Fig. 1.).

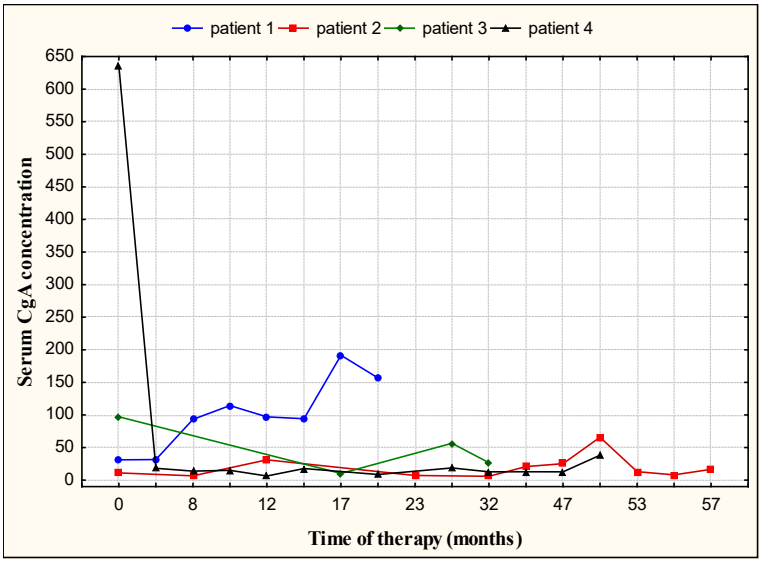

Figure 1. The changes in serum CgA concentration (U/L) over the treatment

DISCUSSION

The state of the art application of CgA at present involves monitoring of the NET treatment effectiveness, regular patients health checks after the therapy termination and early detection of recurrence and/or distant metastases [3,5].

As the result of our study we found progression of the disease in approximately 70% of our patients despite applied chemotherapy and/or somatostatin analogues treatment. Most of the patients in this group had elevated CgA levels. For patients with stable disease course, the CgA concentration was at constant level during treatment, whereas in patients with disease regression, CgA concentration was unchanged or even reduced. Seregni et al. [13] obtained very similar results of their study of 46 patients demonstrating significant usefulness of the CgA concentrations in the assessment of response to treatment with somatostatin analogues or chemotherapy. Stable levels of the CgA were reported in 75% of the patients with partial or complete response to the treatment. On the contrary the patients with disease progression up to 83% had increased concentrations of this marker. Moreover they found out that the CgA is particularly useful in the treatment monitoring of patients with liver metastases, because the concentration of CgA was elevated at 100% of cases. At 69% of the patients with liver metastases and a stable course of disease the CgA levels remained unchanged. Additionally, in the group of 28 patients apart from the CgA levels the authors assessed the levels of NSE (neuron-specific enolase). The concentrations of both markers showed very similar changes and corresponded to the actual clinical condition of the patient.

Results of Stivanello et al. [14] in a group of 24 patients with the NET treated with chemotherapy and/or the somatostatin analogues, show the decline in the CgA concentration found in 12 patients, unchanged levels in 3 patients, whereas the increase in 9 cases. Moreover they demonstrated that the decrease in CgA levels occurred in all patients with partial or complete response to treatment.

Although there is substantial number of available literature about CgA in NET, there are few reports describing the dynamics of CgA changes with time, therapy applied and clinical status. In our study we attempt to analyze the dynamics of CgA concentration changes in 4 patients who underwent repeated determination of this marker in the course of treatment.

Referring to our detailed analysis of the CgA changes during somatostatin analogues treatment we would like to highlight the case of Patient 4 in whom the pre-operative CgA concentration was 635 U/l, while after surgery and Sandostatin treatment implementation, in 4-year follow-up the CgA concentration was relatively stable and ranged within 6.3-32 U/l. Imaging studies confirmed disease regression. Similar profile of CgA concentrations was observed for Patient 2. Over a period of 4 years after surgery and after the hemicolectomy and Sandostatin treatment implementation, the CgA concentrations were respectively 11.1 U/L, 6.63 U/L, 31.1 U/L, 7.1 U/L, 5.9 U/L, 20.8 U/L, 25.3 U/L, 65.8 U/L, 13 U/L, 8 U/L, 17 U/L and the clinical condition of the patient was assessed as stable. Although the CgA concentrations showed different profile for the Patient 3 having the CgA level 97.2 U/L before treatment and 10.3 U/L, 56.5 U/L, 26.6 U/L after stomach resection and Sandostatin treatment. Patient 1**,** who was observed over the 20 months after surgery, presented increasing tendency of the CgA concentrations 31.2 U/l, 31.5 U/L, 93.3 U/L, 114.4 U/L, 97.1 U/L, 94.2 U/L, 191.7 U/L, 156.8 U/L at subsequent time points.

CONCLUSION

The effectiveness of the treatment with somatostatin analogues is highly dependent on the patient commitment and good cooperation with specialists in the field of nuclear medicine in regard to somatostatin receptors analysis, as well as with clinical laboratory performing CgA test. Determination of the CgA in the blood is available; non-invasive test providing additional, valuable information related to the patient response to the treatment.

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ABSTRACT

Neuroendocrine tumors (NET) are a group of relatively rare tumors; biologically distinctive with variations in clinical course what makes its diagnosis very difficult. The introduction of chromogranin A (CgA) to the biochemical diagnostics of NET improved significantly the diagnosis and is useful in monitoring of effectiveness of treatment with somatostatin analogues. At present the CgA is considered to be non-specific marker of the NET. The aim of the study was the retrospective analysis of the CgA concentrations for patients with clinically diagnosed NETs in the course of treatment monitoring at Saint John of Dukla Oncological Centre of Lublin Region, in 2005-2011. We evaluated serum chromogranin A concentrations during treatment with chemotherapy and somatostatin analogues in the group of 30 patients. The serum concentrations of the CgA were elevated in 71.4% patients with disease progression. At patients with stable disease course, up to 75% had unchanged levels of this marker. The effectiveness of the somatostatin analogues treatment is highly dependent on the patient commitment and good cooperation with specialist in the field of nuclear medicine in regard to somatostatin receptors analysis, as well as with clinical laboratory performing CgA test.

Keywords: chromogranin A, neuroendocrine tumors, the somatostatin analogues, monitoring of treatment

STRESZCZENIE

Guzy neuroendokrynne (NET) stanowią grupę nowotworów stosunkowo rzadko występujących, cechujących się odrębnością biologiczną, różnorodnym przebiegiem klinicznym, co sprawia trudności diagnostyczne. Wprowadzenie do diagnostyki biochemicznej guzów neuroendokrynnych oznaczeń stężenia chromograniny A przyniosło poprawę w diagnostyce, a także jest przydatne w kontroli skuteczności leczenia analogami somatostatyny pacjentów z guzami NET. Chromograninę A (CgA) obecnie uważa się za niespecyficzny marker guzów neuroendokrynnych (NET). Celem pracy była retrospektywna ocena znaczenia stężenia CgA w monitorowaniu leczenia pacjentów z rozpoznanymi guzami NET, leczonymi w Centrum Onkologii Ziemi Lubelskiej im. Św. Jana z Dukli w latach 2005-2011. Oceniano wyniki stężenia chromograniny A podczas prowadzonego leczenia chemioterapią i analogami somatostatyny w surowicy krwi u 30 chorych. W grupie pacjentów, u których stwierdzono progresję choroby, stężenie chromograniny A było podwyższone w 71,4% przypadków. U osób ze stabilizacją choroby aż w 75% przypadków zaobserwowano niezmieniony poziom chromograniny A. Skuteczność leczenia analogami somatostatyny w dużym stopniu zależy od dobrej współpracy lekarza prowadzącego pacjenta ze specjalistą z dziedziny medycyny nuklearnej w zakresie badania receptorów somatostatynowych a także z laboratorium wykonującym badania CgA.

Słowa kluczowe: chromogranin A, neuroendocrine tumors, the somatostatin analogues, monitoring of treatment