

Chromogranin A assessment in patients with neuroendocrine neoplasm of the small bowel and carcinoid syndrome treated with somatostatin analogues

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Abstract

Background. Chromogranin A (CgA) is one of the non-specific markers measured in the biochemical diagnostics of neuroendocrine neoplasms (NENs).

Objectives. To analyze the CgA levels of patients with carcinoid syndrome who are being treated with somatostatin analogues (SSAs), depending on the histologic maturity of the neoplasm, the degree of liver involvement and the stage of the disease.

Material and methods. The study group comprised of 41 patients, including 29 women (70.7%) and 12 men (29.3%). All of the patients had undergone surgical removal of the primary site. Hepatic metastases were found in all patients and they all were treated with SSAs. Chromogranin A concentration was determined using the enzyme-linked immunosorbent assay (ELISA).

Results. Among the patients with grade 1 tumors, the mean CgA value was 298.83 ng/mL, whereas in the group with grade 2 tumors, the CgA value was 1498.44 ng/mL, which was a statistically significant difference ($p < 0.001$). In the group of patients with 10% liver involvement, the mean CgA value was 394.44 ng/mL, whereas in the group of patients with 25% liver involvement, this value was 1770.63 ng/mL, demonstrating significantly higher values ($p < 0.001$). Among the patients with a progressing disease, the mean CgA concentration value was 1620.78 ng/mL, whereas in the group of patients with a stable disease, these were considerably lower, amounting to 230.36 ng/mL ($p < 0.001$).

Conclusions. Assessing CgA level in patients with carcinoid syndrome is helpful in the diagnostics and monitoring of treatment because CgA values depend on the tumor grade and the severity of the disease.

Key words: chromogranin A, carcinoid syndrome, somatostatin analogues

Introduction

Neuroendocrine neoplasms (NENs) are characterized by hormonal activity, which is used in diagnosis and monitoring of the treatment. Biochemical markers measured in the blood serum may be specific or non-specific. Non-specific markers include chromogranin A (CgA) and neuron-specific enolase (NSE).¹ Chromogranin A is a highly stable molecule and no special precautions are needed to store the serum or plasma.^{2–4} The highest CgA concentrations have been found in patients with carcinoid syndrome; thus, it is an important marker used in the monitoring and treatment of neuroendocrine cancers and an independent prognostic indicator of survival in patients with NENs. Based on research conducted on patients with carcinoid tumors, it has been determined that CgA concentration may reflect the severity of the disease and correlate with disease progression. Chromogranin A concentrations are considerably higher in the majority of NEN cases, but particularly high values are observed in the classic carcinoid tumor.⁵ Chromogranin A may also be used as a marker in the estimation of a tumor's rate of growth. The time of CgA concentration doubling is of significant prognostic value, that is, the shorter the doubling time the worse the prognosis.^{6,7} Treatment with somatostatin analogues (SSAs) considerably reduces CgA concentrations, particularly with carcinoid tumors, by inhibiting the synthesis and release of CgA from tumor cells. In the case of disease progression during treatment with SSAs, elevated CgA concentration may reflect a lack of control over the tumor secretion activity or its growth.^{8–15} The aim of our study was to assess the concentration of CgA in patients with carcinoid syndrome who were continuously treated with SSAs. The study compared patients according to the degree of histological maturity and the degree of liver involvement by metastases, and depending on whether the disease was stable or progressing. The study had a purely clinical aspect – to assess the prognosis of treatment in patients with varying degrees of disease progression.

Material and methods

The study group comprised 41 patients – 29 women (70.7%) and 12 men (29.3%) – diagnosed with a NEN of the small bowel. The mean age of the men was 60.41 ± 4.90 years, and for the women it was 64.20 ± 10.39 years. All patients had undergone surgical removal of the primary site with histopathological assessment according to the World Health Organization (WHO) 2017 classification. Grade G1 was found in 19 tissue preparations (46.3%) and the remaining 22 preparations were classified as G2 (53.7%). All patients underwent detailed imaging diagnostics (abdominal cavity ultrasonography and computed tomography (CT) of the chest, abdominal cavity, and small pelvis) and supplementary biochemical monitoring (CgA, serotonin and 5-HIAA) in order to assess their clinical progress. In each

case, cardiologic consultation was performed with echocardiography in order to identify any carcinoid heart disease (tricuspid and pulmonary valve lesions were found in 32 cases). All of the patients were found to have hepatic metastases (10% liver involvement in 23 cases and 25% liver involvement in 18 cases). All patients exhibited symptoms of carcinoid syndrome in the form of diarrhea, facial flush, telangiectasia, and myopathic symptoms.

In each case, to qualify the patients for SSA therapy, receptor scintigraphy was performed using ^{99m}Tc -EDDA/HYNIC-TOC. The degree of radiotracer uptake in liver metastases was assessed according to the qualitative scale developed by E. Krenning (degrees 0–4). In the study group, the radiotracer uptake in the liver ranged between grades 3 and 4 on Krenning's scale. In patients with histological maturity (G1), the radiotracer uptake was grade 4, while in the G2 patients, it was grade 3. It is also worth adding that the degree of radiotracer uptake in patients with disease progression in most cases was grade 3. The study group was treated with SSAs from 2014 to 2018 and were administered octreotide LAR at a dose of 30 mg (intramuscularly) or lanreotide autogel at a dose of 120 mg (subcutaneously) every 4 weeks. The CgA levels were measured every 3 months. However, the abdominal CT imaging tests every 6 months in order to obtain an objective assessment of the response to treatment according to RECIST 1.1 criteria. Chromogranin A concentration was determined using enzyme-linked immunosorbent assay (ELISA), using the Cisbio-Bioassays sets (Perkin Elmer, Waltham, USA). The cut-off point for CgA was 100 ng/mL at an analytical sensitivity of 19 ng/mL, in line with the manufacturer's recommendations.

Statistical assessment

An analysis of the quantitative variables was performed by calculating the means, standard deviation (SD), medians, minimum quartiles, and maximum values. The Mann–Whitney test was used to compare the quantitative variables in the 2 groups. Correlation between 2 quantitative variables was analyzed using Pearson's and Spearman's coefficients. A significance level of 0.05 was adopted in the analysis. Thus, all values below 0.05 were interpreted as indicating statistically significant relationships. The analysis was performed in the software R v. 3.3.1 (www.r-project.org).

Results

Assessment of CgA concentration depending on histologic maturity

In the group of patients with G1 tumors ($n = 19$), the mean CgA value was 298.83 ± 99.81 ng/mL, whereas in the G2 group ($n = 22$) the CgA value was 1498.44 ± 459.64 ng/mL; this represents a significant difference between the groups

($p < 0.001$; Table 1). A similar relationship was observed in the analysis of the final CgA concentration values, that is, in the G1 group the mean of the final CgA values was 755.14 ± 218.33 ng/mL, while in the G2 group it was 3486.88 ± 1241.35 ng/mL ($p < 0.001$; Table 2). The CgA doubling time in the G1 group was 39.00 ± 11.13 months, whereas in the G2 group it was considerably shorter, amounting to 18.81 ± 11.64 months. It is worth emphasizing that in the G1 group, the increase in CgA concentration during SSA treatment was significantly lower and more prolonged in comparison to the patients from the G2 group ($p < 0.001$). This resulted in a significant increase in progression-free time.

Assessment of CgA concentration depending on liver involvement

Among the patients with 10% liver involvement ($n = 23$), the mean CgA value was 394.44 ± 120.51 ng/mL, whereas in the group of patients with 25% liver involvement ($n = 18$), this value was 1770.63 ± 404.11 ng/mL, representing a statistically significant difference ($p < 0.001$; Table 3). In the case of the final CgA values in the 1st group, the mean

of the final CgA values was 566.86 ± 285.44 ng/mL, whereas in the 2nd group the values were also higher, with a mean of 4123.44 ± 1874.77 ng/mL ($p < 0.001$; Table 4). It should be also noted that among patients with 10% liver involvement, the CgA doubling time was 37.12 ± 12.99 months, while in the group with 25% liver involvement, it was considerably shorter: 15.16 ± 7.52 months. In the group of patients with 10% liver involvement, the increase in CgA value during SSA treatment was statistically lower than in the group of patients with 25% liver involvement ($p < 0.001$). This had a considerable impact on extending the progression-free time.

Assessment of CgA concentration depending the stage of the disease

Among the patients for whom the disease was found to be progressing during the SSA treatment ($n = 21$), the mean CgA concentration was 1620.78 ± 385.55 ng/mL, whereas in the group of patients with stable disease ($n = 20$), they were considerably lower, amounting to 230.36 ± 106.44 ng/mL ($p < 0.001$; Table 5). The analysis of the final CgA values revealed similar results: the group with a stable disease

Table 1. Mean chromogranin A (CgA) value [ng/mL] depending on grading

Grading	Mean CgA value [ng/mL]								p-value*
	n	mean	SD	median	min	max	Q1	Q3	
G1	19	298.83	99.81	220.80	144.71	836.85	190.81	253.04	$p < 0.001$
G2	22	1498.44	459.64	1452.07	127.86	3801.5	547.50	2243.63	

* Mann–Whitney test; SD – standard deviation.

Table 2. Final chromogranin A (CgA) value [ng/mL] depending on grading

Grading	Final CgA value [ng/mL]								p-value*
	n	mean	SD	median	min	max	Q1	Q3	
G1	19	755.14	218.33	321.34	200.76	2254.74	260.56	366.67	$p < 0.001$
G2	22	3486.88	1241.35	2514.14	65.43	9876.34	1230.38	5612.95	

* Mann–Whitney test; SD – standard deviation.

Table 3. Mean chromogranin A (CgA) value [ng/mL] depending on the degree of liver involvement

Liver involvement degree	Mean CgA value [ng/mL]								p-value*
	n	mean	SD	median	min	max	Q1	Q3	
10%	23	394.44	120.51	219.52	127.86	820.77	176.79	253.04	$p < 0.001$
25%	18	1770.63	404.11	1655.67	198.23	3801.5	745.87	2684.41	

* Mann–Whitney test; SD – standard deviation.

Table 4. Final chromogranin A (CgA) value [ng/mL] depending on the degree of liver involvement

Liver involvement degree	Final CgA value [ng/mL]								p-value*
	n	mean	SD	median	min	max	Q1	Q3	
10%	23	566.86	285.44	321.23	65.43	2793.61	240.43	366.67	$p < 0.001$
25%	18	4123.44	1874.7	3886.72	432.67	9876.34	1788.93	5673.98	

* Mann–Whitney test; SD – standard deviation.

Table 5. Mean chromogranin A (CgA) value [ng/mL] vs stage of disease

Stage of disease	Mean CgA value [ng/mL]								p-value*
	n	mean	SD	median	min	max	Q1	Q3	
PD	21	1620.78	385.55	1465.06	198.23	3801.5	688.82	2264.51	p < 0.001
StD	20	230.36	106.44	196.78	127.86	587.86	172.12	231.52	

* Mann–Whitney test; PD – progressing disease; StD – stable disease; SD – standard deviation.

Table 6. Final chromogranin A (CgA) value [ng/mL] compared to the stage of disease

Stage of disease	Final CgA value [ng/mL]								p-value*
	n	mean	SD	median	min	max	Q1	Q3	
PD	21	3841.95	750.79	2793.61	432.67	9876.34	1677.42	5673.23	p < 0.001
SD	20	328.91	99.33	293.2	65.43	1010.16	236.02	321.79	

* Mann–Whitney test; PD – progressing disease; StD – stable disease; SD – standard deviation.

had a mean level of 328.91 ± 99.33 ng/mL, which was markedly lower than in the group with a progressing disease, where the values were 3841.95 ± 750.79 ng/mL ($p < 0.001$; Table 6). Also, among the patients with disease progression, the CgA doubling time was 15.71 ± 7.28 months, whereas in the group with a stable disease it was considerably shorter: 41.40 ± 8.46 months.

Discussion

Advances in the diagnostics and treatment of NENs has led to increased interest in these rare tumors. Assessment of secretory activity in NENs constitutes an important element in the monitoring and assessment of treatment. Our study assessed CgA values in patients with carcinoid syndrome being treated with SSAs, according to the degree of neoplasm histological maturity, the stage of the disease and the degree of liver involvement from metastatic lesions. In the group of patients with G1 tumors ($n = 19$), both the mean and the final CgA values were significantly lower than in the G2 group ($n = 22$). According to the analysis, the patients with 25% liver involvement had significantly higher CgA concentration, for both mean and final values, than the patients with 10% liver involvement.

Chromogranin A is a major non-specific biochemical marker which can be tested for in the blood as a circulating tumor marker; its level depends on the type of cells and secretory granules. In their meta-analysis, Zatelli et al. presented the levels of CgA in a group of 123 patients diagnosed with a NEN as the major marker in the monitoring of treatment and prognosis. In their conclusions, the authors emphasized that CgA values are proportionate to the size of the primary site and the number of metastases in the liver. The specificity of CgA measurements is estimated to be 90%, while the sensitivity is 68% relative to the severity of the disease.¹⁶ Donica et al., who examined the level of CgA in a group of 41 patients with highly differentiated midgut NENs, reported that the highest CgA concentrations were found in patients with carcinoid

syndrome and numerous metastatic lesions in the liver.¹⁷ Rossi et al., in a study on 91 patients with midgut NENs, demonstrated that a marked increase of CgA precedes by approx. 6 months a disease progression which is detectable with radiography.¹⁸ These studies prove that monitoring biochemical markers constitutes an independent prognostic index of the possible disease progression. Similar observations have been documented by Cheng et al., where an increase in CgA level among 122 patients with NENs was associated with later progression in imaging tests.¹⁹

The observations of Ardill et al. are also noteworthy: they reported that neurokinin A is a more sensitive marker for the monitoring of carcinoid syndrome than CgA or 5-HIAA.²⁰ In a group of 523 patients with a NEN of the small bowel, elevated values of neurokinin A were found in as many as 72.6% of cases.

In the current study, we also performed an analysis of CgA measurements depending on the stage of the disease. Among the patients whose disease was found to be progressing during SSA treatment ($n = 21$), the mean CgA values were statistically significantly higher than in the group with a stable form of the disease. It should also be noted that among patients with disease progression, the CgA doubling time was 15.71 months, whereas in the group with stable disease, it was considerably shorter, amounting to 41.40 months. Similar observations were made by Tang et al., in a study determining the risk factors of disease progression: the doubling time of CgA concentration in patients with midgut NENs is an important prognostic element.²¹ Similar relationships were observed in the assessment of serotonin and 5-HIAA concentrations.²² Raoof et al. presented an assessment of CgA concentration in patients with non-secreting pancreatic NENs as the predictive factor for the decision of whether to treat surgically. Patients with lesions measuring less than 2 cm in the pancreas and with high CgA levels should be treated surgically.^{23,24} Likewise, Rossi et al. reported that levels of CgA circulating in the blood are important in the assessment of disease recrudescence and progression, but considerably less so in differential diagnosis.²⁵

It is currently known that the highest CgA values are found in NENs of the small bowel, large bowel and pancreas. The highest values have been recorded in carcinoid syndrome with numerous liver metastases. In these assays, the test sensitivity was 85.8% and the specificity 98.5%.^{26–28} Oberg and Modlin presented completely new NEN biomarkers in the form of circulating gene transcripts, micro-RNA or the neoplastic cells themselves originating from the tumor. The sensitivity and specificity of these measurements is significantly higher than CgA measurement.^{29–33} Corsello et al. also presented in their study that the CgA 1-76 fragment, known as vasostatin 1 (VS-1), is a more sensitive marker independent of the use of proton pump inhibitors (PPIs).³⁴ Somatostatin analogue treatment reduces CgA concentrations considerably, particularly in patients with carcinoid syndrome, by inhibiting the synthesis and release of CgA from tumor cells and not by reducing tumor mass. In the case of progressing disease during SSA treatment, elevated CgA concentration may reflect a lack of control over the tumor secretion activity or growth.^{35,36} Somatostatin analogues demonstrate an antiproliferative action (cytotoxic or cytostatic), which exerts a direct inhibiting influence on angiogenesis and the induction of apoptosis. Most patients had abnormal fasting blood glucose levels when using SSAs. In rare cases, patients developed non-insulin-dependent diabetes. Gallstones and dyspepsia associated with a suppression of pancreatic exocrine function are common.

The results of the CLARINET study, which concerned the use of lanreotide autogel in NENs, confirmed the antiproliferative effect of SSAs. The study involved 204 patients with NENs of grades 1 and 2 (Ki-67 < 10%), hormonally non-functioning, with the primary site in the pancreas (45%), midgut (36%), hindgut (7%), or unknown (13%); there was >25% liver involvement in 33% of the patients. The two-year treatment with 120 mg of lanreotide autogel every 4 weeks demonstrated no disease progression or death in 62% of the treated patients, compared with 22% of patients administered a placebo.³⁷


Similar results were obtained in the PROMID study, which used octreotide LAR in patients with midgut G1 neoplasm. In the group of patients administered the drug, the median of progression-free survival time (PFS) was 14.3 months, whereas in the placebo group it was 6.2 months. This study found that the use of octreotide LAR at a dosage of 30 mg for 18 months led to a lack of disease progression in 67% of patients.³⁸ Treatment with long-acting SSAs is the treatment of choice in the case of carcinoid syndrome symptoms.


Conclusions

It should be mentioned that despite the fact that CgA is not a perfect biomarker, it remains an important element in the diagnostics and monitoring of treatment of NEN patients.

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