

Chromogranin A as a valid marker in oncology: Clinical application or false hopes?

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Abstract

Chromogranin A, due to its primary expression throughout the neuroendocrine system, is a widely accepted biomarker for the assessment of neuro-endocrine tumors. It has been traditionally used in the management of patients with tumors of gastro-enteropancreatic origin. Lately, it has also been implicated in various conditions and diseases, both benign and malignant. However, the paucity of data of adequate strength, as well as its relation with common physiologic conditions and its interaction with commonly prescribed medications, limit its clinical use in only a narrow spectrum. Herein, we present a thorough review to the most frequent conditions where its levels are affected, focusing specifically on its potential use as a prognostic and predictive biomarker in oncology.

Key words: Cancer; Neuroendocrine tumors; Prognosis; Chromogranin A; Biomarker

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Core tip: In the era of targeted therapy, there is an unmet need for the development of more sensitive, specific and reliable biomarkers for early diagnosis, prognosis and detection of early recurrence to tumors which comprise an extremely heterogeneous group.

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INTRODUCTION

The Granins comprise a family of proteins whose most well known members are chromogranin A (CgA), chromogranin B (CgB) and secretogranin II, with their most common characteristic being their acidic profile. They are produced as pre-proteins in the ribosomes and subsequently they undergo post-translational modifications in the endoplasmic reticulum and in the Golgi apparatus^[1]. It has been shown that they are co-stored with peptides and amines in the granules of endocrine cells. They can also be found in a number of other cells, including immune cells, epithelial cells and peripheral neurons^[2]. Other proteins that are also included in the granin family are secretogranin III, the HSL-19 antigen (secretogranin IV), the neuroendocrine secretory protein 7B2 (secretogranin V), NESP55 (secretogranin VI) and nerve growth factor-inducible protein VGF (secretogranin VII)^[3].

Granins are composed of single-polypeptide chains of approximately 180 to 700 amino acids, with CgA being a 49 kDa protein produced mainly by endocrine and neuroendocrine cells^[1,4,5]. It was first discovered in the chromaffin granules of the adrenal medulla, where it is stored along with the resident hormones, like calcitonin, and then secreted with them^[5]. The CgA gene, located on chromosome 14, is probably a single copy gene rather than a member of a dispersed, multigene family^[6].

Since the discovery of CgA and its pathologically high levels in patients with neuroendocrine tumors, it has been correlated with a number of other conditions, both benign and malignant (Tables 1 and 2). Its sensitivity and specificity in each one of these conditions differ significantly, depending on various factors, limiting its use as an effective prognostic and/or predictive marker in a narrow spectrum of conditions. This review summarizes the most frequent conditions where CgA levels are affected, focusing specifically on its function as a biomarker in oncology.

CgA may be secreted in the blood in its full length or in fragments after cleavage. These fragment peptides include Catestatin, Chromacin, Pancreastatin, Parastatin, Vasostatin I, Vasostatin II and WE-14^[1]. Although CgA and its peptides definite functions have not been fully understood, it is believed that they are important factors for the formation and regulation of dense-core granules, heart function, catecholamines and parathyroid hormone secretion, carbohydrate and lipid metabolism, immune properties and reproduction^[7].

CGA IN NON-MALIGNANT DISEASES AND CONDITIONS

CgA has been correlated with a wide range of non-malignant systemic diseases, including hypertension, heart and hepatic failure (Table 1)^[1,8]. It is produced by the human myocardium and exerts negative inotropic effect, so in chronic heart failure it is significantly elevated and its levels can parallel the severity of cardiac dysfunction and

could be used as an independent predictor of mortality^[8]. Furthermore, basal plasma CgA levels correlate with sympathetic tone and increased adrenal sympathetic nerve activity. Subsequently, CgA levels are usually elevated in hypertension^[8].

Furthermore, it can be raised in renal insufficiency, as a result of decreased plasma clearance. It has also been implicated in inflammatory and autoimmune conditions, like Rheumatoid arthritis^[9,10]. Furthermore, PPIs, which are some of the most commonly prescribed drugs, may cause a secondary increase in CgA levels due to increased gastrin production^[11]. Another common condition that is associated with elevated levels of CgA, is chronic atrophic gastritis (Table 1)^[12]. Summarizing, in non malignant diseases and conditions, CgA values may reach values of hundreds (ng/mL), but it is very uncommon to reach levels of several thousands that could be consistent with cancer diagnosis.

CGA IN MALIGNANT DISEASES

Bronchopulmonary neuroendocrine tumors

In small cell lung carcinomas (SCLC) the mean CgA plasma levels are higher than those found in normal controls or in patients with chronic obstructive pulmonary disease, lung adenocarcinoma and large-cell lung carcinoma. The levels of CgA are associated with the extent of the disease, but the levels of NSE have been proven to be more accurate in that regard^[13-16]. Bronchopulmonary neuroendocrine tumors (BP-NETs) comprise approximately 20% of all lung cancers and represent a spectrum of tumors arising from neuroendocrine cells of the BP-epithelium. Although they share structural, morphological, immunohistochemical, and ultrastructural features, they are separated into 4 subgroups: Typical carcinoid tumour (TC), atypical carcinoid tumour (AC), large-cell neuroendocrine carcinoma (LC-NEC), and SCLC^[17]. The diagnosis is based on the recognition of neuroendocrine morphology, such as organoid pattern, and on the immunohistochemical demonstration of specific neuroendocrine markers, like chromogranin, synaptophysin, and neural cell adhesion molecule (NCAM), also known as CD 56. To confirm the neuroendocrine origin of the tumour cells, at least one of those markers must be positive^[18]. Although they can produce a variety of peptides and hormones, like gastrin-releasing peptide (bombesin) and 5-hydroxytryptophan, bronchial NETs only occasionally secrete bioactive products that can easily be measured. As a result, elevated plasma or urinary hormone levels are only rarely detected. Serum levels of CgA are lower in bronchial NETs than those observed in NETs of other sites, and they overlap with those seen in patients who have non-malignant conditions associated with increased CgA levels^[17].

Breast cancer

In breast cancer CgA was discovered both in epithelial cells of normal mammary gland as well as in breast cancer. However, it does not seem to offer any additional

Table 1 Non cancerous causes of chromogranin A elevation

Disease			
Cardiovascular	Endocrine	Gastrointestinal	Inflammatory
Acute coronary syndrome	Hyperparathyroidism	Chronic atrophic gastritis	Chronic bronchitis
Arterial hypertension	Hyperthyroidism	Chronic hepatitis	Chronic obstructive pulmonary disease
Cardiac insufficiency	Hypercortisolism	Inflammatory/irritable bowel syndrome	Giant cell arthritis
		Liver cirrhosis	Rheumatoid arthritis
		Pancreatitis	Systemic inflammatory response syndrome
Drugs			
Corticoids	H2 receptor antagonist	Proton pump inhibitor	
Status			
Exercise	Ingestion of a meal	Pregnancy	
Factors having potential influence on sample			
Fibrin presence	Haemolysis	Imposing effect: Autoantibodies presence (RF-IgM, Avidine, Heterofile)	Late afternoon/night > morning
Lipaemia	Plasma > serum	-	

Table 2 Frequent cancer-related causes of increased chromogranin A

Cancer	Neuroendocrine tumors
Breast	Colorectal
Colon	Gastric
Hepatocellular	Medullary thyroid
Ovarian	Neuroblastoma
Pancreatic	Pancreatic
Prostate	Paraganglioma
	Pheochromocytoma
	Pituitary
	Small cell lung
	Small intestinal

information about the presence, the extent and the histology of breast cancer when compared to the more established Ca 15-3. Furthermore, serum CgA was not sensitive enough to identify the rarely encountered subtype of breast cancer with neuroendocrine differentiation^[19].

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a rare, aggressive, cutaneous malignancy with neuroendocrine differentiation, that predominantly affects older adults with light skin complexion. MCC has a propensity for local recurrence and regional lymph node metastases. On immunohistochemistry, the tumour cells show features of both epithelial and neuroendocrine origin, including the expression of CgA. CgA blood levels are used by many physicians as a predictive marker for the response of the tumour to chemotherapy, though it has never been shown to correlate with progression-free survival, disease specific survival, or disease recurrence^[20].

Gastroenteropancreatic neuroendocrine tumors

Chromogranins were early discovered to be elevated in the plasma of patients with neuroendocrine tumors^[21,22]. They arise from neuroendocrine cells that occur throughout the length of the entire gut, and about two-thirds of them are of gastrointestinal or pancreatic origin (GEP-NETs)^[23]. Their relevance in the diagnosis, prognosis, clinical evaluation

after cytoreductive surgery, and subsequent follow-up of patients with those types of tumors, has been studied for more than 20 years^[21].

Although GEP-NETs excrete a number of peptides specific to the neuroendocrine cell of origin, CgA is the most frequently studied biomarker for their diagnosis and subsequent follow-up^[24-26]. Not all GEP-NETs produce CgA, but for those that do, elevated circulating levels of CgA could be related with tumour burden as well as recurrence, and are considered a marker of poor prognosis and reduced survival in both ileal and pancreatic NETs^[27,28]. For example, in patients with midgut carcinoids the 5-year OS was estimated to be 22% with CgA levels > 75 nmol/L, while it was raised to 63% with levels lower than this value. The decrease of CgA levels has also been used as a marker of response to treatment in clinical trials, where biochemical response is defined as a $\geq 50\%$ reduction of CgA^[29].

The highest levels of CgA are observed in patients with functioning ileal NET and carcinoid syndrome, followed by those with liver metastases. Metastatic disease in the lymph nodes does not seem to cause a significant increase in the levels of CgA^[27,29]. However, its value in predicting liver metastases, as compared to morphological tumour changes as measured by CT or MRI, is limited, with a sensitivity and specificity of 71% and 50% respectively^[30]. On the contrary, it should be noted that its elevation, even in values of several thousands (ng/mL), could be not related with deterioration of clinical status.

The overall sensitivity of CgA in the diagnosis of neuroendocrine tumors is around 60%-80% and depends on the primary site, on the degree of differentiation and on the status of the disease^[31]. This marker has a low sensitivity regarding its use in distinguishing the different types of NETs. It should be noted also, that the specificity and sensitivity of the assay for CgA measurement differ between the available commercial kits^[32].

Moreover, the use of CgA as a diagnostic biomarker in GEP-NETs has certain limitations. Firstly, although CgA could be useful in predicting tumor relapse or progression, with rapidly increasing levels correlating

Table 3 Chromogranin A diagnostic accuracy in neuroendocrine tumor studies

Type (no pts)	CgA cut-off	Sensitivity (%)	Specificity (%)	Ref.
NET (128)	100 µg/L	59	68	[57]
NET (127)	34.7 u/L	67.9	85.7	[35]
NET (80)	17 u/L	56.3	100	[58]
NET (63)	34 u/L	55	94	[59]
GEP/NET (61)	20 u/L	92	83	[50]
	100 u/L	47	99	
GEP/NET (124)	130 µg/L	62.9	98.4	[16]
GEP/NET (202)	53 ng/mL	71.3	77.8	[60]
NET (120)	98 ng/mL	79	NA	[61]
GEP/NET (119)	2.8 nmol/L	92.9	100	[62]

no: Number; pts: Patients; NA: Non available; CgA: Chromogranin A; NET: Neuroendocrine tumor; GEP: Gastroenteropancreatic.

with shorter survival, it should be noted that CgA levels are also affected by the secretory activity of a functioning tumor. This has particular importance in patients treated with somatostatin analogues (SSAs), where the drop in CgA levels may reflect the inhibition of the secretory activity of the tumour rather than a true anti-tumour effect^[33].

Midgut carcinoids have often been misdiagnosed as irritable bowel syndrome or inflammatory bowel disease, where CgA may also be increased, due to the common manifestation of watery diarrheas^[34].

CgA along with NSE have been retrospectively studied as prognostic biomarkers in GEP-NETs^[35]. In a phase II study of Everolimus in GEP-NETs it has been demonstrated that higher baseline levels of CgA were associated with shorter PFS, while the patients with the shortest PFS had elevated concentrations of both CgA and NSE at baseline. In that same study, CgA and NSE responses were defined as a 50% or greater reduction from baseline or normalization, and early CgA and NSE responses were defined as a 30% or greater decrease from baseline or normalization after 4 wk of treatment. For both those markers, an early decrease predicted for clinical benefit, which, in the case of CgA, meant both longer PFS (13.3 mo vs 7.5 mo; HR = 0.25; $P < 0.001$) and longer OS (24.9 mo vs 12.7 mo; HR = 0.4; $P = 0.01$)^[36].

Those results have been confirmed in a relevant analysis of the phase III RADIANT-2 clinical trial, where it was shown that early decrease of CgA levels by Everolimus can be used as a surrogate marker of PFS in this setting^[37]. To our knowledge, no such data exist for patients with GEP-NETs treated with Sunitinib.

There is no doubt that due to the existing data, CgA role in NET diagnosis is strongly limited and debated. Therefore, it could not be recommended and applied in our daily clinical practice. Moreover, it could be used primarily but with caution, in NETs as a marker of therapy response.

Prostate cancer

CgA is excreted by the neuroendocrine cells that are

dispersed throughout the prostatic gland. Neuroendocrine cells can be found in the normal prostate as well as in benign prostate hyperplasia and in primary or metastatic prostatic adenocarcinoma^[38]. In addition to CgA, neuroendocrine cells produce a variety of biogenic amines, such as NSE, calcitonin and somatostatin. According to their degree of differentiation, prostatic malignant neuroendocrine cells may continue to produce those amines, though they differ in their morphology from their normal counterparts^[39].

Although not specific for prostate cancer, there is evidence that high levels of serum CgA are a marker of advanced disease, associated both with high tumor grade and later stage^[40]. High levels also characterize the shift from a disease responding to androgen deprivation therapies (ADT) to an androgen-independent, aggressive malignancy^[41,42]. Pathophysiologically, this is to be expected, since an increase in circulating CgA and NSE reflect tissue neuroendocrine differentiation. There is evidence that the degree of neuroendocrine differentiation increases with prostate cancer progression, and it has been suggested that it constitutes a major mechanism of resistance to ADT^[38]. Neuroendocrine cells do not express androgen receptors, consequently they are not regulated by androgens^[43].

There is also evidence that serum CgA, either alone or combined with serum PSA, may predict poor prognosis in castration-resistant prostate cancer following endocrine therapy^[44-46]. Moreover, circulating neuroendocrine peptides have been linked with angiogenesis and invasive potential^[39,47]. However, serum concentration of CgA and tissue IHC expression do not show robust correlation and CgA does not seem to positively correlate with treatment response to cytotoxic chemotherapy in metastatic prostate cancer with neuroendocrine differentiation^[48].

Multiple Endocrine Neoplasia type 1 syndrome

Multiple Endocrine Neoplasia type 1 (MEN 1) is a rare hereditary autosomal dominant endocrine cancer syndrome, that is characterized by the development of tumors, both benign and malignant, in multiple endocrine organs. The tumors most often appear in the parathyroid glands, in the endocrine cells dispersed throughout the gastroenteropancreatic (GEP) tract and in the anterior pituitary, though other endocrine and non-endocrine tumors have also been reported, namely adrenocortical and thyroid tumors, visceral and cutaneous lipomas, meningiomas, facial angiofibromas and collagenomas, and thymic, gastric, and bronchial carcinoids^[49].

Several studies have assessed the role of CgA in demonstrating the presence of a GEP-NET in MEN 1 syndrome. It has been confirmed that abnormally elevated CgA levels are highly suggestive of both sporadic and MEN 1-related GEP-NETs. The highest levels are observed in metastatic disease, especially when the metastases are located in the liver, and in functioning tumors, especially in gastrinomas^[50]. In MEN 1 patients without biochemical or imaging evidence of GEP tumors, the data are scanty and conflicting. Some studies have reported increased CgA

levels in 11%-33% of patients with pituitary adenomas, both secreting and non-functioning^[51]. In addition, conflicting data have been published regarding the relationship between CgA levels and hyperparathyroidism, either primary or in the context of MEN 1 syndrome^[52]. However, it appears that the generalised hyperplasia of the endocrine system, that occurs in MEN 1 syndrome, tends to lead to at least mildly elevated levels of circulating CgA, while markedly raised levels may indicate the presence of a GEP-NET^[50].

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) represents the most frequent complication and a major cause of death in patients with cirrhosis of any aetiology^[53]. The most widely used biomarker for diagnosis and follow-up is AFP^[54]. CgA has been found elevated in patients with liver cirrhosis and in those with HCC^[55,56]. However, its use as a diagnostic biomarker for the presence of HCC in the context of cirrhosis should be discouraged, since the levels of CgA have not been found to differ significantly between these two conditions^[54]. The prognostic meaning of CgA in HCC has yet to be elucidated.

DISCUSSION

The extent of the physiological functions of CgA indicates its potential role as a biomarker in a wide spectrum of benign and malignant diseases (Tables 1 and 2). However, certain factors limit its usefulness in only a few. There is a lack of prospective studies that aim to evaluate its validity in the diagnosis and prognosis of specific conditions.

Although limitations exist, CgA is the most studied biomarker for GEP-NETs' diagnosis and management. Clinicians should be aware of the variation of measurements by numerous physiologic and pathologic conditions, its limited predictive value and the modest sensitivity (Table 3)^[57-62]. Moreover, data support that baseline CgA levels and changes during treatment are prognostic. Even, its specificity could be heavily affected by several benign conditions, also intrinsic features of the disease could be related with the high variability of CgA values^[63]. Diagnostic accuracy of CgA for GEP-NETs appear to be higher for well vs poorly differentiated tumors, functioning vs non-functioning, metastatic vs locoregional disease. There is no doubt that it is more reliable when used to evaluate response to therapy or disease progression than early diagnosis or recurrence.

It should be underlined that there are many assays and commercial kits available for CgA levels evaluation, thus very strict quality assurance and standardization should be used. In addition, CgA evaluation is more convenient than U5-HIAA, which requires a 24-h urine collection and 3 d before the collection a dietary abstinence from tryptophan/serotonin-rich foods.

Finally, in cancers where a biomarker is already in use, such as AFP in hepatocellular carcinoma or Ca 15-3 in

breast cancer, CgA has not been proven to be of greater diagnostic and/or prognostic value than the currently used biomarker. It also provides an indication for the presence of a strong component of neuroendocrine differentiation within an adenocarcinoma. That also applies to cases of prostatic adenocarcinoma that develop resistance to androgen deprivation therapy during the progression of the disease, as a result of the gradual shift of the tumor cells towards a neuroendocrine phenotype. The early recognition of that phenomenon may lead to an earlier change in the treatment strategy, which, in turn, may prove to provide clinical benefit. Moreover, it should be used with caution and only in comparison with other methods of determining the course of the disease, such as radiologic and histological evaluation, simply because there are not enough data to support its use as a single, stand-alone marker.

CONCLUSION

Due to the fact that NET symptoms could be vague, or even the disease course may be asymptomatic, diagnosis could be delayed for many years. There is an unmet need for the development of more sensitive, specific and reliable biomarkers for early diagnosis, prognosis and detection of early recurrence to these tumors which comprise an extremely heterogeneous group. Multianalyte assays focusing on novel analytes, such as microRNA, gene transcripts, and circulating tumor cells could be an interesting area for further research given the fact that is unlikely any single marker to be effective.

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