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Review

Potential clinical value of circulating chromogranin A in patients with prostate carcinoma

A. Berruti,[1] L. Dogliotti,[1] A. Mosca,[1] G. Gorzegno,[1] E. Bollito,[4] M. Mari,[3] R. Tarabuzzi,[3] M. Poggio,[3] M. Torta,[1,2] D. Fontana[3] & A. Angeli[2]

Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, [1]Oncologia Medica, [2]Medicina Interna, [3]Urologia; [4]Dipartimento di Anatomia Patologica, Azienda Ospedaliera San Luigi, Orbassano (TO), Italy

Summary

Background: Neuroendocrine (NE) differentiation of prostate adenocarcinoma has received increasing attention in recent years as a result of possible implications for prognosis and therapy. The presence of NE tumor subpopulation can be gauged non invasively by measuring circulating levels of secretory products, primarily chromogranin A (CgA).

Methods: This article provides a review on published papers evaluating circulating CgA in prostate cancer patients.

Results: Circulating CgA levels were found to be higher in prostate cancer patients than in patients with benign or premalignant prostatic diseases. In patients with malignancy, they correlated either to the stage of disease or to the condition of hormone refractoriness. CgA levels did not correlate with serum prostate specific antigen (PSA) and were supranormal in the majority of advanced patients with PSA within normality. In hormone refractory cases, elevated CgA was a significant predictor of poor prognosis, independently from serum PSA. CgA values were not substantially affected by either endocrine therapy or chemotherapy. They were found to increase during androgen deprivation in some cases and this trend preceded that of PSA. The administration of a somatostatin analog in hormone refractory cases was able to reduce plasma CgA values consistently.

Conclusions: Present data suggest a potential role of circulating CgA in the management of prostate cancer patients. CgA determination may be useful diagnostically and prognostically and could offer complementary information with respect to PSA. Serial evaluation of circulating CgA could provide information on changes in the NE phenotype expression as a consequence of tumor progression and/or treatment administration.

Key words: chromogranin A, neuroendocrine differentiation, prostate cancer, prostate specific antigen

Introduction

The concept of neuroendocrine (NE) differentiation in prostate carcinoma is very well recognized, but the clinical significance of this phenomenon is still debated [1–4]. As a whole, tumors displaying NE differentiation tend to be more aggressive and resistant to hormone therapy [1–4]. The aggressive behavior, however, cannot be explained by proliferative capacities of NE prostate cancer cells, as they do not show evidence of proliferation [5]. An attractive hypothesis is that neurosecretory products, including bombesin, serotonin, parathyroid hormone-related peptides, calcitonin and calcitonin-related peptides [6, 7], induce proliferation of adjacent exocrine cells by paracrine mechanisms [8].

The detection of NE markers in the blood of patients with prostate cancer constitutes a global indicator of significant NE differentiation, either of the primary tumor or its associate metastases. In addition, these markers can easily provide information on changes in the expression of NE phenotype in the follow-up of patients after treatment. Chromogranin A (CgA) is the quantitatively major secretory granule protein and is commonly used as a marker of NE differentiation [9]. With regard to prostate cancer, it is the most employed marker for the detection of NE features, either at the tissue level or in the general circulation [3, 10, 11].

In this paper, we provide a review of published data on the diagnostic and prognostic significance of circulating CgA in prostate cancer patients, with particular regard to our personal experience.

Cross sectional studies

A number of cross-sectional studies evaluating the circulating levels of plasma CgA in patients with benign and malignant prostate diseases have been published recently [3, 12–21].

Our group measured plasma levels of CgA in a cohort of 354 consecutive patients recruited in our Prostate Cancer Unit from 1995 to 1998 [16]. Study population consisted of 141 patients bearing benign prostate hypertrophy (BPH), 54 intraepithelial neopla-

Table 1. Variation of serum prostate specific antigen (PSA) and plasma Chromogranin A (CgA) according to benign and malignant prostate disease.

			Prostate cancer (AUA stages)				
	BPH	PIN	A, B	C	D1	D2	*P*-value
PSA median (ng/ml) (range)	7.2 (0.1–63.7)	7.9 (0.3–49.7)	11.1 (3.5–130.0)	18.6 (3.9–469.0)	42.2 (0.1–496.0)	59.7 (0.1–3350.0)	<0.0001[a]
Supranormal values (%)	118/141 (83.7%)	44/54 (81.5%)	67/70 (95.7%)	22/24 (91.7%)	20/21 (95.2%)	40/44 (90.9%)	n.s.[b]
CgA median (U/l) (range)	8.0 (1.0–64.5)	10.8 (2.4–185.5)	10.5 (3.0–51.0)	9.9 (2.6–227.0)	12.5 (2.0–140.0)	13.5 (3.0–513.0)	<0.01[a]
Supranormal values (%)	24/141 (17.0%)	14/54 (25.9%)	13/69 (18.8%)	4/24 (16.7%)	7/21 (33.3%)	20/44 (45.5%)	<0.02[b]

Abbreviations: BPH – benign prostate hyperplasia; PIN – prostate intraepithelial neoplasia; AUA – American Urologic Association.
[a] Kruskall–Wallis AOV; [b] Overall chi-square.

sia (PIN) and 159 prostate cancer: 119 with hormone-naive and 40 with hormone-refractory disease [16]. CgA was found to be more frequently elevated in patients with prostate cancer than those with PIN and BPH. In the prostate cancer subset, CgA levels were higher in patients with American Urologic Association (AUA) D2 stage, than those with D1, C and A/B stages (Table 1). A positive correlation between plasma CgA values and prostate cancer stage was also found by Cussenot et al. in a series of 135 patients [19]. The percentage of supranormal CgA plasma values in metastatic patients included in our experience (45%) is consistent with previous studies showing supranormal CgA values in 12 out of 22 (55.5%) [17], in 12 out of 25 (48%) [18], and in 39 out 78 (50%) [13] patients with advanced/metastatic disease. As a whole, the percentage of patients with advanced prostate cancer who had elevated plasma CgA values, is close to the percentage of primary tumor tissues displaying neuroendocrine differentiation (50%) reported by di Sant'Agnese [1].

A comparison of CgA detected immunohistochemically in prostate cancer tissues with the corresponding marker levels in the general circulation was performed in three studies [3, 17, 22]. All these studies concluded that circulating CgA reflects the immunohistochemical findings. Plasma CgA appears a reliable marker in revealing the NE phenotype in metastatic cases, but its diagnostic role may be limited in non metastatic disease, conceivably because the number of NE cells is not enough to raise the circulating levels. On these grounds immunohistochemistry is more sensitive in patients with early stage of disease.

It is noteworthy that elevated plasma CgA levels were reported in the majority of advanced prostate cancer patients with normal prostate specific antigen (PSA) serum levels or serum PSA within the grey zone. Kimura et al. [21] showed supranormal CgA levels in 4 out of 4 cases with normal PSA, included in a series of 33 metastatic cases. Hoosein et al. [23] showed elevated CgA in 6 out of 12 advanced patients with low serum PSA (<7 ng/ml). In our experience, elevated CgA values were found in 5 out of 8 metastatic patients with serum PSA within normality [16].

PSA has become an important tool for detecting prostate carcinoma, however the sensitivity and specificity of this marker are not yet sufficient to make it the perfect screening test for prostate cancer [24]. The measurement of CgA in prostate cancer patients with PSA within normality could increase the diagnostic performance of PSA alone. Moreover, serum PSA is less reliable as a marker of tumor bulk in hormonally treated patients with disseminated disease [23]. In this respect, low PSA associated with progressive metastatic androgen independent prostate cancer, identifies a patient subset with disease characterized by a tendency of visceral metastases, a high proportion of lytic bone metastases and histological features of small cell or poorly differentiated prostate cancer [25]. The patient in this subgroup usually have a poor prognosis but also a great chance to respond to chemotherapy with platinum containing regimens. The histological and clinical patterns described are mainly attributable to the predominance of NE differentiation so that CgA determination could help in the selection of these patients and a serial marker evaluation could provide information on the treatment efficacy.

In case of PSA above the range of normality, the concomitant measurement of CgA, in the absence of renal impairment, uncontrolled hypertension and drug assumption that can interfere with the physiological CgA production, could provide additional information. In our experience, plasma CgA did not correlate with serum PSA [16], suggesting that the extent of NE differentiation does not parallel the overall tumor load. In a group of 24 hormonally treated patients with prostate carcinoma, Abrahamsson et al. [26] demonstrated that both dedifferentiation in tumors and number of NE cells increased with time. If the proportion of NE cells increases with the tumor progression, one would expect the circulating levels of NE markers in patients with

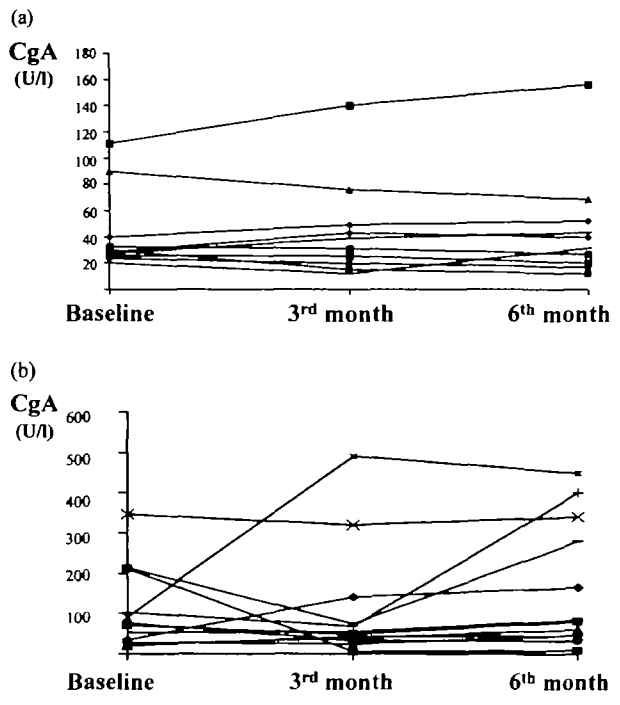

Figure 1. Changes in chromogranin plasma levels in patients who received luteinizing hormone-releasing (a) hormone analogs or (b) chemotherapy.
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progression of prostate carcinoma to increase with time.

A number of studies showed that elevation in circulating CgA values is more frequently observed in the subset of advanced prostate cancer patients with hormone refractory disease, in comparison to the subgroup of advanced cases with hormone naïve disease [17–21]. In our study [16], a trend of greater CgA values, just failing to attain the statistical significance, was found in favor of patients with hormone refractory disease. These data support the notion that the development of androgen independent disease is associated with a clonal propagation of NE cells.

Immunohistochemical studies showed a negative prognostic role of focal NE differentiation in prostate adenocarcinoma. This prognostic implication has been attributed in part to the role of NE features in favoring the disease progression toward an androgen-independent status [8].

The prognostic significance of circulating CgA was explored in our study [16], as well as in that of Cussenot et al. [19]. Both studies, involving 27 and 40 advanced/metastatic cases with hormone refractory disease respectively, reported that elevated CgA plasma levels predict poor survival. These data suggest that the prognostic implications of NE features are maintained even when the disease becomes resistant to hormone manipulation. It is noteworthy that, in our experience, the role of CgA levels in predicting short overall survival [16] was independent from that of PSA.

The poor prognosis associated with NE differentiation in hormone refractory cases is probably related to its manifest correlation with the tumor aggressiveness [27–29]. As recently reported by Bonkoff et al. [30], in fact, NE differentiation in androgen-independent tumors is able to induce proliferation in non endocrine cells surrounding NE cells. This could be linked to the growth factor activity of neurosecretory products [7]. Other possible mechanisms favoring the tumor aggressiveness are the involvement of NE cells in tumor angiogenesis [31], as well as the role of the CgA fragment pancreastatin in favoring the prostate cancer invasiveness [32].

Dynamic evaluations

The effect of systemic antineoplastic treatments on circulating levels of CgA in advanced prostate cancer patients has been explored by our group [16]. As shown in Figure 1, neither endocrine therapy nor chemotherapy were able to substantially affect the marker concentrations [17]. The absence of androgen receptor expression in NE prostate cells could account for the failure of androgen deprivation to modify CgA values, while the scarce, if any, proliferative activity of these cells could explain the limited effect of chemotherapy. In hormonally treated cases our data are similar to those reported by Angelsen et al. [17], who showed, in a cohort of cases followed prospectively during androgen deprivation, that circulating CgA only revealed minor variations within a two year period of time.

Two prospective studies by Reale et al. [13] and Wu et al. [20] pointed out that some cases with circulating CgA within normality before androgen deprivation showed a marker increase during therapy. Interestingly, in both papers CgA elevation during androgen deprivation preceded the PSA increase by some months. These data are consistent with *in vitro* findings [33] showing that androgen deprivation is able to induce the formation of NE tumor residues capable of actively producing NE growth factors and thus favoring the onset of hormone refractory disease. Conceivably, the early appearance of plasma CgA elevation during androgen deprivation would create an opportunity for the early adjustment of therapy, for example, by the addition of somatostatin analogs.

Somatostatin and somatostatin analogs have been repeatedly demonstrated to remarkably reduce products of NE tumors of the gastro-intestinal tract, yet having a modest antiproliferative action [34–36]. They are the treatment of choice for controlling the clinical syndromes associated with NE tumors, such as carcinoid syndrome [35, 36]. The inhibitory effect of somatostatin analogs on NE products could now be easily monitored by serial measurements of CgA values [37, 38].

The putative function of NE cells in stimulating cell proliferation through a paracrine hormone mechanism, provides a rationale for the experimental use of somatostatin analogs, with the aim to counteract the tumor progression [8].

We recently conducted a pilot study in which Lanreotide (a long-acting somatostatin analog) [39] was administered to nine consecutive advanced prostate cancer patients with hormone refractory disease and elevated baseline levels of CgA [39]. CgA consistently decreased in eight of them, and remained unchanged in the remaining one. By contrast, serum PSA did not change in five patients, while it increased in three and decreased in one. These results suggest that somatostatin analogs have antisecretive properties on NE cells, without affecting the exocrine component. Most of the octapeptide somatostatin analogs, such as Octreotide and Lanreotide, bind selectively to somatostatin 2 and 5 receptor subtypes (SSTR2 and SSTR5, respectively) and recent publications showed that SSTR2 types are not expressed by primary prostate cancer [40, 41]. These data seem to be in contrast with our experience, since they suggest that somatostatin analogs may be not effective in inhibiting NE secretion of prostate cancer cells. It should be noted that although SSTR2 subtype was not found in primary prostate cancer specimens, the expression of Octreotide preferring SSTRs has been verified on metastatic hormone-refractory prostate adenocarcinoma [42]. These observations suggest a shift in somatostatin receptor expression from prostate cancer that is potentially hormone sensitive to prostate cancer refractory to hormone manipulation.

Conclusions

Theoretical reasons and preliminary clinical evidences suggest that CgA is a circulating marker potentially useful in the management of prostate cancer patients. With respect to PSA, which is a marker of the exocrine component, it reveals the presence of NE features and this may have diagnostic, prognostic and therapeutic implications.

Circulating CgA could improve the diagnostic sensitivity of PSA and should always be measured in the rare cases of prostate cancer with PSA within normality. Elevated CgA in advanced patients with hormone refractory disease provides prognostic information independently from serum PSA. Finally, circulating CgA levels are not affected, or weakly affected, by either endocrine therapy or chemotherapy, but they significantly decrease after treatment with somatostatin analogs in the patient subset with hormone refractory disease. These data provide a rationale for the use of somatostatin analogs within controlled clinical trials. In this respect, circulating CgA could select a prostate cancer patient population to be addressed to such trials.

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Correspondence to:
Prof. L. Dogliotti
Oncologia Medica
Azienda Ospedaliera San Luigi
Regione Gonzole 10
10043 Orbassano (TO)
Italy
E-mail: luigi.dogliotti@unito.it