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Literature Review and study overview

Chromogranin A for therapy monitoring of patients with prostate cancer

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Contents

Serum Chromogranin A-based prognosis in metastatic castration-resistant prostate cancer.

Giridhar, K. V., C. Sanhueza, D. W. Hillman, H. Alkhateeb, R. Carlson, W. Tan, B. A. Costello, F. Quevedo, L. Pagliaro and M. Kohli (2018). Prostate Cancer Prostatic Dis 21(3): 431–437. (Giridhar, Sanhueza et al. 2018)

Rationale

Determination of the prognostic value of serum Chromogranin A (CgA) in patients with metastatic castrate resistant prostate cancer (mCRPC).

Methods

Serum CgA was evaluated in a screening cohort (n=200) and an independent validation cohort (n=72) of men with mCRPC. Men receiving proton pump inhibitors and those with non-castrate levels of testosterone (>50 ng/dl) were excluded.

Laboratory method

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Results

- Elevated CgA was defined as above upper limit of normal (> 93 ng/mL CgA).
- Screening cohort with mCRPC: Median serum CgA was 100.3 ng/mL (interquartile range 67–161.3), the mean was 184.8 ng/mL (standard deviation 396), and 34/200 (17 %) had an elevated CgA (above reference range of 225 ng/mL).
- In 81 men with a Gleason score of ≥ 8, elevated CgA was associated with shorter OS [HR 2.19, 95 %CI: 1.16–3.85, p=0.02). CgA remained associated with overall survival after adjusting for PSA, Gleason score, time from diagnosis to study treatment and radiographic evidence of recurrent prostate cancer.
- Validation cohort with mCRPC: The median CgA was 90 ng/mL (IQ range 55–156), the mean was 174.7 ng/mL (standard deviation 280.2), and 31 (44 %) had a CgA above the reference range (>93 ng/mL). Elevated serum CgA levels were associated with shorter OS (HR 1.91, 95 % CI 1.02–3.67, p 0.043). In the sub-cohort of 36 patients with Gleason scores ≥ 8, the median OS in men with an elevated serum CgA was 6.9 months shorter compared to men with a normal serum CgA (12.0 months vs 18.9, log-rank p=0.043).

Key Conclusions

- Elevated serum CgA was negatively associated with OS in men with mCRPC.
- Serum CgA represents a complementary prognostic biomarker.

Prospective Evaluation of Neuromediator Dynamics in Castration-Resistant Prostate Cancer Patients During Docetaxel.

J. von Hardenberg, M. Schwartz, T. Werner, S. Fuxius, M. Muller, T. Frangenheim, C. Bolenz, C. Weiss and E. Heinrich (2017). Anticancer Res 37(9): 5117–5124. (J, Schwartz et al. 2017)

Rationale

Objective of the study was to evaluate temporal dynamics of CgA and NSE in serum of patients with mCRPC during docetaxel therapy.

Methods

Prospective observational study at six Germany institutions. Patients with histologically-confirmed adenocarcinoma, mCRPC (newly diagnosed or with progression after regimens with Abiraterone and/or Enzalutamide and/or Docetaxel) were included. In total 52 patients were evaluated.

Laboratory method

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Results

- Levels of CgA increased significantly from baseline compared to the 2nd and the 3rd blood withdrawal (p=0.0146 and p=0.0330).
- A total increase ≥100 % of the upper limit of normal (ULN) of CgA was observed in 11 patients.
- A high rise from baseline of CgA was associated with progression free survival (PFS; p=0.0369) and high rise from baseline of CgA trended towards significance with overall survival (OS; p=0.0649).

Key Conclusions

- Early high rise in CgA levels was associated with shorter PFS and trended towards significance with shorter OS
- Early high rise of CgA should be further tested as a preselection tool for multi-core biopsy-sampling of metastases

Influence of abiraterone acetate on neuroendocrine differentiation in chemotherapy-naive metastatic castration-resistant prostate cancer.

Dong, B., L. Fan, Y. Wang, C. Chi, X. Ma, R. Wang, W. Cai, X. Shao, J. Pan, Y. Zhu, X. Shangguan, Z. Xin, J. Hu, S. Xie, X. Kang, L. Zhou and W. Xue (2017). Prostate 77(13): 1373–1380. (Dong, Fan et al. 2017)

Rationale

To determine the influence of abiraterone Acetate (AA) on neuroendocrine differentiation (NED) in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC).

Methods

Analysis of CgA in serum from 115 chemotherapy-naive mCRPC patients with decision for chemotherapy

Results

- Serum CgA levels of 56 patients (= 48.7 %) were above the upper limit of normal (ULN) before chemotherapy.
- The CgA decline and baseline normal CgA groups had much longer PSA PFS (medians: 14.34 vs 10.00 months, p<0.001, and 14.23 vs 10.30 months, p=0.02 respectively) and radiographic PFS (medians: 18.33 vs 11.37 months, p<0.001, and 17.10 vs 12.07 months, p=0.03 respectively).

Key Conclusions

- Circulating CgA seems to be an comprehensive and convenient indicator for revealing and quantifying NED in mCRPC
- Serial CgA might help clinicians guide clinical treatment of mCRPC patients.

Chromogranin A and neuron-specific enolase serum levels as predictors of treatment outcome in patients with metastatic castration-resistant prostate cancer undergoing abiraterone therapy.

Heck, M. M., M. A. Thaler, S. C. Schmid, A. K. Seitz, R. Tauber, H. Kubler, T. Maurer, M. Thalgott, G. Hatzichristodoulou, M. Hoppner, R. Nawroth, P. B. Luppa, J. E. Gschwend and M. Retz (2017). BJU Int 119(1): 30–37. (Heck, Thaler et al. 2017)

Rationale

The impact of elevated neuroendocrine serum markers on treatment outcome in patients with metastatic castration-resistant prostate cancer (mCRPC) undergoing treatment with abiraterone in a post-chemotherapy setting.

Methods

CgA and NSE and were determined in serum drawn before treatment with abiraterone from 45 patients with mCRPC.

Laboratory method

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Results

- Patients were stratified into low- (9 patients), intermediate- (18) or high-risk (18) groups according to elevation of none, one, or both neuroendocrine markers, respectively.
- Cut offs used for stratification: CgA = 85 ng/mL and NSE = 19 ng/mL.
- Risk groups correlated with decreasing median OS (median OS not reached vs 15.3 vs 6.6 months; p<0.001), decreasing median clinical or radiographic PFS (8.3 vs 4.4 vs 2.7 months; p=0.001) and decreasing median PSA-PFS (12.0 vs 3.2 vs 2.7 months; p=0.012).

Key Conclusions

- High CgA and NSE correlated with shorter PSA-PFS, clinical or radiographic PFS, and OS
- High CgA and NSE might indicate elevated risk of developing resistance under abiraterone treatment related to neuroendocrine differentiation

Influence of abiraterone acetate on circulating neuromediators in chemotherapy-naive castration-resistant prostate cancer.

von Hardenberg, J., M. Schwartz, T. Werner, S. Fuxius, M. Muller, C. Bolenz, C. Weiss and E. Heinrich (2016). Prostate 76(7): 613–619. (von Hardenberg, Schwartz et al. 2016)

Rationale

Assessment of serum CgA in patients with chemotherapy-naïve CRPC.
The relation between NED and abiraterone treatment was investigated.

Methods

35 chemotherapy-naive CRPC patients with clinical or radiographic progression of disease (16 priory received Abiraterone Acetate).

Laboratory method

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Results

- Serum CgA values were above the upper limit of normal (ULN) in 20 (57.1 %) patients.
- In univariate analysis, lymph node metastasis (p=0.014), was significantly associated with upregulated circulating CgA levels. On multivariate Cox regression analysis, duration of ADT (p=0.0101) but also proton pump inhibitors (p=0.030) were significantly correlated with CgA levels above the upper limit of normal.

Key Conclusions

- Intake of proton pump inhibitors influences CgA and stop of intake might be considered when analyzing CgA
- Neuromediators were frequently overexpressed after treatment with AA in chemotherapy- naïve CRPC.
- The study gives an insight into the simultaneous expression of neuromediators in chemotherapy-naïve CRPC and underlines the influence of the duration of ADT as key driver of NED.

Chromogranin A predicts outcome in prostate cancer patients treated with abiraterone

Burgio, S. L., V. Conteduca, C. Menna, E. Carretta, L. Rossi, E. Bianchi, B. Kopf, F. Fabbri, D. Amadori and U. De Giorgi (2014).Endocr Relat Cancer 21(3): 487–493. (Burgio, Conteduca et al. 2014)

Rationale

Evaluation of the Chromogranin A (CgA) baseline value as predictor of clinical outcome in patients with metastatic castration-resistant prostate cancer (CRPC) treated with abiraterone 1000 mg abiraterone per day.

Methods

48 consecutive metastatic CRPC patients progressing after docetaxel chemotherapy and decision to start abiraterone treatment.

Results

- CgA levels more than three times the upper normal limit (UNL) predicted an early radiological progressive disease in eight of 11 cases (73 %).
- Patients were stratified into three groups: CgA: <120 ng/ml (group A, n=16), 120 – 360 (group B, n=16), >/=360 ng/ml (group C, n=16). The median progression-free survival (PFS) among the CgA groups A, B, and C was 9.2, 9.2, and 4.8 months respectively, p=0.0459.
- In the multivariate analysis, PSA response rate (nonresponsive vs responsive) and CgA levels were predictors of PFS (p=0.0002 and p=0,0047 respectively).
- CgA was predictive for CT (imaging-based) response at 3 month (complete response, partial response and stable disease vs progressive disease) with an AUC=0.81.

Key Conclusions

- Elevated plasma CgA levels are frequently observed in CRPC patients after docetaxel.
- A plasma CgA level more than three times the UNL predicted PFS and showed a trend vs OS prediction, independently from PSA decline, in CRPC patients treated with abiraterone.

Distribution of high Chromogranin A serum levels in patients with nonmetastatic and metastatic prostate adenocarcinoma.

Sciarra, A., F. Di Silverio, A. M. Autran, S. Salciccia, A. Gentilucci, A. Alfarone and V. Gentile (2009). Urol Int 82(2): 147–151. (Sciarra, Di Silverio et al. 2009)

Rationale

To evaluate the incidence of elevated serum levels of serum Chromogranin A (CgA) (as marker of neuroendocrine activity) in nonmetastatic and metastatic prostate cancer populations.

Methods

264 consecutive men with nonmetastatic prostate adenocarcinoma considered for radical prostatectomy (group 1) and 89 consecutive men with metastatic prostate adenocarcinoma (group 2) represented our population.

Results

- Group 1 (nmPC): CgA levels were in 35.0 % of cases > 60 ng/ml and in 6.4 % of cases > 90 ng/ml.
- Group 2 (mPC): CgA levels were in 100 % of cases > 60 ng/ml and in 69.7 % of cases > 90 ng/ml.
- Odds ratios (OR) for CgA level > 60 and > 90 ng/ml significantly increased from nonmetastatic to metastatic cases (p=0.0001) → OR = 67.510 (23.182–94.90) and = 33.364 (17.110–65.05) respectively.

Key Conclusions

- A significant incidence of elevated serum levels of CgA either in nonmetastatic (using 60 ng/ml as cut-off) or in metastatic (using 90 ng/ml as cut-off) prostate adenocarcinoma cases is decribed

Chromogranin A expression in patients with hormone naive prostate cancer predicts the development of hormone refractory disease.

Berruti, A., A. Mosca, F. Porpiglia, E. Bollito, M. Tucci, F. Vana, C. Cracco, M. Torta, L. Russo, S. Cappia, A. Saini, A. Angeli, M. Papotti, R. M. Scarpa and L. Dogliotti (2007). J Urol 178(3 Pt 1): 838–843; quiz 1129. (Berruti, Mosca et al. 2007)

Rationale

The primary aim was to evaluate the value of tissue CgA to function as a biomarker in predicting the development of hormone refractory disease. Secondary aims were evaluating the prognostic role of CgA immunohistochemical detection, and the predictive and prognostic roles of increased plasma CgA levels at baseline and during androgen deprivation therapy.

Methods

175 patient were included with CgA measured. The study was monocentric and the inclusion criteria for the study were histologically proven adenocarcinoma of the prostate, intermediate to high risk of disease progression according to NCCN guidelines, i.e. T2b stage or more, or Gleason score 7 or more, or serum PSA 10 ng/ml or greater, or eligibility for androgen deprivation therapy.

Results

- Concordance of plasma CgA and tumor tissue CgA status was seen in 105 of 175 patients (60 %) while 52 patients (30 %) had positive immunohistochemistry but negative plasma levels and reverse was observed in 18 (10 %). Increased plasma CgA was observed in 18 of 101 (18 %) with immunohistochemically negative CgA, and in 16 of 65 (25 %) and 6 of 9 (67 %) patients with CgA positive tumors in less than 30 % or 30 % or more cells, respectively (chi-square test for trend p=0.006).
- Serum CgA at baseline (HR 3.0, 95 % CI 1.8–5.2), after 1 year (HR 5.8, 95 % CI 3.1–10.1) and 2 years (HR 3.5, 95 % CI 1.6–7.6) was predictive of hormone refractory risk and confirmed relation of tissue CgA with outcome.

Key Conclusions

- CgA detected in plasma or in tumor biopsies of patients with prostate cancer on androgen deprivation therapy are independent predictive parameters for earlier onset of hormone refractory disease and death.
- The predictive significance of plasma CgA is maintained over time.

Circulating Chromogranin A and hormone refractory prostate cancer chemotherapy.

Cabrespine, A., L. Guy, F. Gachon, H. Cure, P. Chollet and J. O. Bay (2006). J Urol 175(4): 1347–1352. (Cabrespine, Guy et al. 2006)

Rationale

To better evaluate the interest of circulating CgA in terms of prevalence, chemotherapy response and survival in HRPC we analyzed 39 patients who received 2 types of chemotherapy.

Methods

Serum CgA was analyzed in 39 patients treated for hormone refractory prostate cancer (HRPC) with paclitaxel or carboplatin (175 mg/m2 paclitaxel and carboplatin dosed to an area under the on day 1 of every 3-week cycle).

Results

- 45% of patients with HRPC showed increased serum CgA. Local radiotherapy and the duration of hormonal therapy were independent factors that influenced CgA. Three classes of CgA during chemotherapy (25 % ≥ decrease, stability, and 25 % ≥ increase) correlated with measurable disease (complete + partial response vs stability + progression).

Key Conclusions

- The results of the study support the theory that circulating CgA may be predictive of the chemotherapy response in patients with HRPC.
- CgA level variations during treatment offer information complementary to PSA for following the chemotherapy response.

Elevated serum Chromogranin A precedes prostate-specific antigen elevation and predicts failure of androgen deprivation therapy in patients with advanced prostate cancer.

Chuang, C. K., T. L. Wu, K. C. Tsao and S. K. Liao (2003). J Formos Med Assoc 102(7): 480–485. (Chuang, Wu et al. 2003)

Rationale

This study examined whether the neuroendocrine biomarker CgA could be used as prognostic marker in prostate cancer and whether expression of CgA appears earlier than the changes of PSA in the development of HRPC in patients under ADT.

Methods

Patients with locally advanced (n=20) or metastatic (n=70) PC receiving ADT were enrolled. Serum CgA was assessed before ADT and every 3 months during ADT treatment. The median follow-up was 35 months and at least 3 serum samples were obtained during ADT in 78 patients

Results

- 36 (46.2 %)of patients had no PSA re-elevation (< 4 ng/mL) and their CgA remained low (< 84.6 ng/mL). 17 patients (21.8 %) also had low PSA (< 4.0 ng/mL) but had progressively increasing CgA, while 25 patients (32 %) developed HRPC.
- Of the 25 patients with HRPC, 17 showed progressive elevation of serum CgA (> 100 ng/mL). CgA elevations were followed by PSA elevation after a median interval of 10 month. Serum CgA elevations were therefore detected earlier than PSA elevations in 21,8 % of 78 patients.

Key Conclusions

- Elevations of serum CgA preceded elevations of PSA in metastatic prostate cancer patients and/or in patients with high serum PSA who developed hormone resistance
- Elevated CgA predicted the development of HRPC

Acquired neuroendocrine-positivity during maximal androgen blockade in prostate cancer patients

Tarle, M., M. Z. Ahel and K. Kovacic (2002). Anticancer Res 22(4): 2525–2529. (Tarle, Ahel et al. 2002)

Rationale

Aims were to evaluate the influence of maximum androgen blockade on CgA positivity over time.

Methods

Patiens were N=79 referred to maximal androgen blockade and n=24 Stage C-D1 prostate cancer patients without therapy through their own choice and n=20 controls (BPH). Maximal androgen blockade was done with LH-RH analogue and flutamide (750 mg daily dose).

Serum PSA, % FPSA and CgA concentrations were measured at three-month intervals and bone scans were performed 1–2 times during the overall monitoring period. CgA was followed-up for 15 months.

Results

- During the last six months of monitoring, the acquired CgA-positivity was statistically significant in treated patients when compared to the untreated group ($p<0.001$, see Figure 1).
- Bone metastases were found in 38 % of CgA-positive prostate cancer patients (regardless of the therapy status) and in only 6 % of studied patients with a steady normal serum CgA concentration.

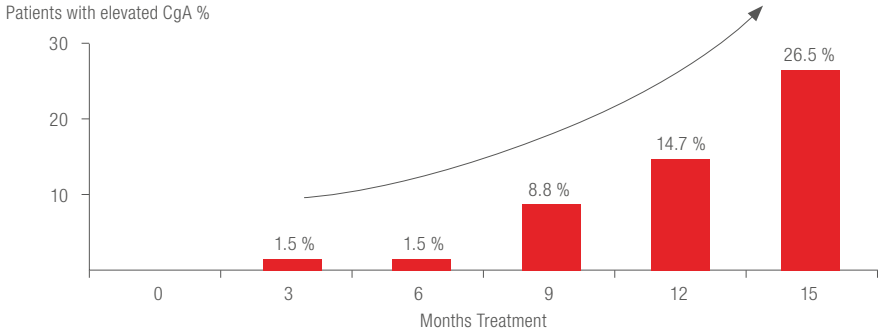

Figure 1: Percentage of patients with acquired CgA positivity in the group with hormonal treatment.

Key Conclusions

- Authors advocate the assessment of serum CgA at 3-months intervals during hormonal therapy

Serum Chromogranin A in monitoring metastatic prostate cancer patients

Tarle, M. (1999). Anticancer Res 19(6C): 5663–5666

Rationale

This study was undertaken to delineate the role of serum CgA concentrations as a possible prognosticator of hormonal and chemo hormonal treatment.

Methods

Serum CgA was evaluated in 24 responders and 14 non responders to maximum androgen blockade (Flutamide 750 mg daily and LH-RH analogs) and chemo hormonal treatment (Estracyt). 12 patients with BPH were included as controls.

Results

- In responders and nonresponders to maximum androgen blockade mean +-SD CgA levels (ng/ml) were 39.5 +-18.3 (7.6–78.4) and 214.8 +-250.3 (9.9–1084.3) respectively.
- In responders (19) and nonresponders (12) to Estracyt, mean CgA +-SD (ng/ml) was 47.6 +/-22.7 (4.4–101.2) and 366.7 +/-291.4 (82.0–925.7) respectively. Osseous metastates were detected in all patients. Cessation of Estracyt therapy in 4 of 14 responders caused sharp elevations of CgA levels.

Key Conclusions

- It is concluded that estracyt may control activity of CgA positive structures.
- The authors advocate serial assessment of serum CgA together with PSA for monitoring patients receiving hormonal therapy

Abbreviations

AA = Abiraterone Acetate
ADT = Androgen Deprivation Therapy
BPH = Benign Prostate Hyperplasia
CgA = Chromogranin A
CRPC = Castration Resistant Prostate Cancer
HRPC = Hormone Refractory Prostate Cancer
LH-RH = Luteinizing Hormone-Releasing Hormone
mCRPC = metastatic Castration Resistant Prostate Cancer
NED = NeuroEndocrine Differentiation
mPC = metastatic Prostate Cancer
nmPC = non-metastatic Prostate Cancer
NSE = Neuron-Specific Enolase
PFS = Progression Free Survival
PSA = Prostate-Specific Antigen
UNL = Upper Normal Limit
OR = Odd Ratio
OS = Overall Survival

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