Latent Hypothyreosis as a Clinical Biomarker for Therapy Response Under Abiraterone Acetate Therapy

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Abstract. *Background: Abiraterone acetate (AA) is a selective oral inhibitor of Steroid-17α-Hydroxylase, for patients with castration-resistant prostate cancer. Not all patients respond to therapy, however, there are no biomarkers predicting response to AA therapy. The aim of the present study was the identification of a biomarker for patients who are likely to respond to AA therapy. Patients and Methods: We measured thyroid parameters in a collective of 30 patients before and during AA therapy. For statistical analyses, paired and unpaired t-tests were used. Results: During AA therapy, responders developed a significant increase in thyroid stimulating hormone (TSH) compared to non-responders (p=0.03). In the subgroup of responders, 16 out of 21 patients (76.1%) had a significant increase in TSH level (p=0.001), suggesting that TSH increase is predictive of therapy response. Non-responders showed no change in TSH level during AA therapy. Conclusion: Hypothyreosis may serve as a simple predictive biomarker for therapy response under AA therapy.*

Prostate cancer (PCa) is the leading cancer in men in Europe (1, 2). One of the crucial factors in the pathogenesis of PCa is the androgen receptor and its signaling network (3, 4). Therefore androgen deprivation therapy either by surgical or hormonal treatment represents one of the most effective treatment options for advanced PCa. Most patients respond well to hormone therapy, however, resistance often develops, a status defined as castration-resistant prostate cancer (CRPC). New insights into the androgen receptor and its signaling mechanisms in PCa described a hypereactive and aberrantly activated androgen receptor as the driving force of CRPC (3, 5, 6). Thus, new inhibitors of hormone synthesis and new anti-androgens have been developed and introduced into the clinic. Abiraterone acetate (Zytiga®) (AA) is a selective oral inhibitor of the enzyme cytochrome *P CYP17* (17-α hydroxylase and 17,20 lyase) which reduces testosterone to an undetectable range (7, 8). This CYP17 inhibition occurs wherever CYP17 is present, including the testis, adrenal gland, and PCa tissue (8). Because CYP17 inhibition diminishes cortisol synthesis, a glucocorticoid such as prednisone is administered concomitantly with AA. In the absence of glucocorticoid supplementation, adrenocorticotropic hormone (ACTH) rises and drives increasing mineralocorticoid synthesis (9). This can lead to fluid retention, hypertension, and hypokalemia, which are potential adverse events of AA therapy (9). Other adverse events noticed in AA treated patients were hot flushes, anorexia, nausea, abnormal liver function, headache, precipitation of migraine and bronchial asthma (7). Several studies evaluated AA in chemotherapy-naïve and in docetaxel pre-treated patients with CRPC with response rates from 45% to 75% depending on the response criteria. Results of the phase III study in docetaxel pre-treated patients reported longer median overall survival (OS) in patients under AA compared to those on placebo (15.8 months *vs.* 11.2 months). Median radiological progression-free survival (PFS) increased from 3.6 months to 5.6 months in the AA group in comparison to the placebo group (10). In April 2011, AA was finally approved in combination with prednisone for treatment of patients with CRPC who have received prior docetaxel chemotherapy. Evaluation of AA in chemotherapy-naïve patients also demonstrated benefits in both OS and PFS (11). Thus in January 2013, AA was approved for treatment in chemotherapy-naïve patients. Currently, there is no biomarker available predicting therapy response in AA-treated patients. Solely, in phase I and II studies, the presence of the transcriptional regulator ERG re-arrangement has been shown to be associated with a maximal PSA (prostate-specific antigen) decline under AA

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therapy (12).Thus the presence of this fusion is currently discussed as a possible biomarker for predicting response to AA therapy (13, 14). However, ERG is only measurable in tissue and not used as standard marker in most laboratories. Epidemiological studies suggest a tumor-promoting effect of thyroid hormones in the pathogenesis of several tumor entities, including PCa. In pre-clinical studies, thyroid hormones stimulated tumor growth and metastasis, while hypothyreosis reduced tumor growth and metastatic spread (15). Hypothyreosis *per se* modulates paracrine growth factors such as epidermal growth factor (EGF) or insulin like growth factor (IGF). The membrane protein integrin $\alpha_v\beta_3$ contains a cell surface receptor site for thyroid hormone that is linked to the activation of mitogen-activated protein (MAPK) kinase and angiogenesis in tumor cells (16). A prospective study of 87 patients with renal cell cancer found a correlation between sub-clinical hypothyreosis and treatment response to tyrosine kinase inhibitors (sorafentib and sunitinib) (17). Baldazzi *et al*. reported that hypothyroid patients treated with sorafentib or sunitinib experienced longer PFS compared to euthyroid patients (18). In the present study, we identified for the first time latent hypothyreosis occurring after the start of AA treatment as a possible clinical biomarker for therapy response.

Patients and Methods

Between July 2011 and October 2013, 30 patients with CRPC were treated with AA at the Medical University of Innsbruck, Austria. All patients were either pre-treated with docetaxel or had a cardiological or neurological contraindication for chemotherapy. AA was administered according to the therapy protocol including 1,000 mg AA and 10 mg prednisolone/day. Patients were monitored once a month by examination of medical history, especially concerning side-effects under AA therapy, and by blood sample evaluation, including measurement of thyroid parameters thyroid stimulating hormone (TSH), T3 and T4. Additionally patients' systolic and diastolic blood pressure, as well as their weight, were measured and documented daily by patients themselves. Therapy response was recorded by PSA measurements once a month, as well as by computed tomography at three-month intervals. A combination of PSA decline and regressive or stable radiological disease (in comparison to CT scan before therapy) was defined as therapy response.

Statistical analysis. Analysis was performed with Graph Pad Prism Software version 4.0 (Graph Pad Prism Software, La Jolla, CA, USA). Paired and unpaired *t*-tests were used. Data are presented as mean±SEM. A *p*-value of <0.05 was considered significant.

Results

Patient characteristics. We evaluated 30 patients who started AA therapy from July 2011 and October 2013 at the Department of Urology, Medical University of Innsbruck. All patients had histologically-confirmed PCa. The median Gleason score at transrectal ultrasound guided biopsy was 8 (range=5-10). Half of all patients initially underwent radical prostatectomy; the other 50% were initially treated with radiotherapy. The median age of patients was 75 years (range=51-93 years). All patients (100%) were treated with luteinizing hormone releasing hormone (LHRH) analogs. A total of 22/30 (73.3%) of patients received monthly denosumab for bone metastases. Seventeen of the 30 patients (56.6%) had received prior docetaxel chemotherapy ranging from 1 to 10 cycles (median=4.5 cycles); one patient was pre-treated with both docetaxel and mitoxantrone chemotherapy. All patients had Eastern Cooperative Oncology Group (ECOG) status of 0 or 1. None of the patients included in the study had anamnestic hypo- or hyperthyreosis and all had normal thyroid parameters prior to AA therapy.

Table I. *Summary of efficacy of Abiraterone acetate therapy (n=30).*

	n	%
Complete response	1	3.3%
Partial response	20	66.7%
Progressive disease	9	30%

Complete response: Prostate specific antigen (PSA) <0.03 ng/ml, disappearance of all metastases; partial response: PSA decline, stable radiographic findings; progressive disease: no PSA response, radiographic progress.

As shown in Table I, 21 patients responded to AA therapy. One patient had a complete response (PSA <0.03 ng/ml and disappearance of all metastases), while 20 patients developed a partial response under AA therapy, defined as PSA decline and stable radiographic findings.

Latent hypothyreosis after start of AA therapy. Baseline TSH levels before treatment with AA did not differ between responders and non-responders (Figure 1A). However, during AA therapy, responders developed a significant TSH increase compared to non-responders (Figure 1B, $p=0.03$). In the subgroup of responders, 16 out of 21 patients (76.1%) had a significant increase in TSH level (Figure 1D, $p=0.001$), suggesting that TSH increase is predictive of therapy response. Moreover, we found that non-responders showed no change in TSH levels during AA therapy (Figure 1C). Hypothyreosis was transient for one to two months after the start of AA therapy and did not cause any clinical symptoms. T3 and T4 levels were not changed.

Discussion

In recent years, several new therapies for patients with CRPC have fundamentally altered the treatment landscape. PSA measurement has been used so far as a standard parameter for the measurement of treatment efficacy (19, 20). However, it is known that PSA-alone is not a reliable marker for monitoring

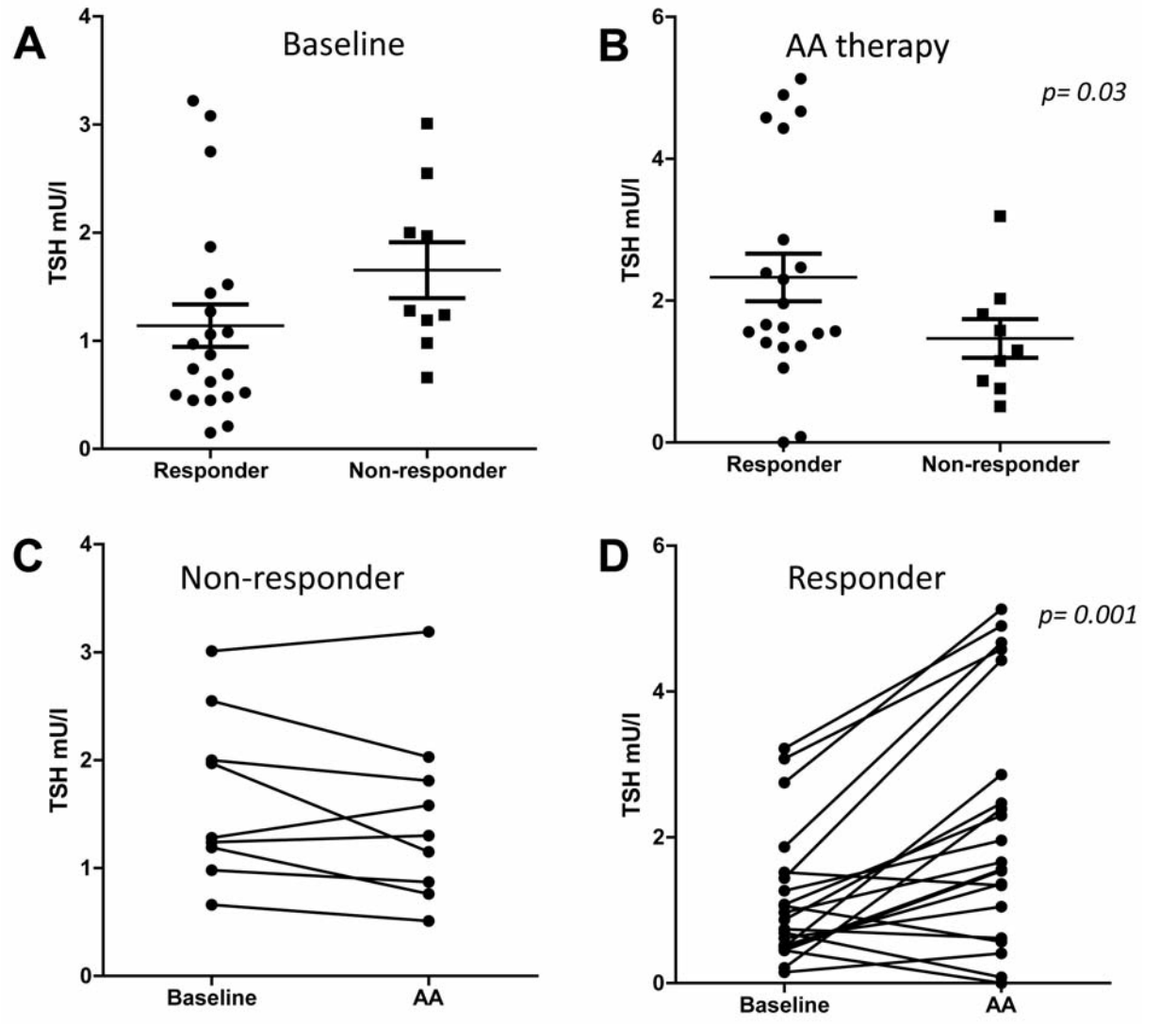

Figure 1. *Baseline TSH levels of responders (n=21) and non responders (n=9) before (A) AA therapy and during (B) AA therapy. TSH levels of patients who did not respond to AA therapy (n=9) (C) and of those who responded to AA therapy (n=21) (D) before and during therapy. Data are shown as the mean±SEM.*

PCa aggressiveness and therapy response. Thus, prognostic biomarkers such as circulating tumor cells, bone turnover markers, lactate dehydrogenase (LDH) or hemoglobin measurement are used as biomarkers in CRPC (14). Admittedly, all biomarkers in clinical use for CRPC have prognostic but not predictive implications. Currently, several studies with the intent of identifying biomarkers for monitoring patients with CRPC, receiving novel drugs targeting the androgen synthesis pathway are ongoing. However, no valid predictive biomarker for selection of these patients exists at present. Our study identified, to our knowledge, for the first time latent hypothyreosis as being a predictive biomarker for response to AA therapy. In summary, we found that 76.1% of patients who responded to AA therapy developed latent hypothyreosis immediately after therapy start. The hypothyreosis was transient for one to two months and did not cause any clinical symptoms. Otherwise all patients who had no response to AA therapy had no changes in thyroid function. These data strongly indicate that a transient hypothyreosis may serve as a clinical marker predicting therapy response to AA therapy. As parameters of thyroid function are measurable in patient's serum, they serve as easily- and quickly-determinable, as well as economic biomarkers for therapy response. In general in clinical oncology, correlations between hypothyreosis and therapy outcome have been observed (16). There is substantial

evidence that thyroid hormones have tumor-promoting effects mainly *via* mitogen-activated protein (MAPK) kinase pathways (21). In rodent models, thyroid hormones stimulated growth and metastasis of tumor transplants, whereas hypothyroidism had opposite effects (15, 22). Prospective studies also assessed the relation between thyroid function and cancer risk. Turkyilmaz *et al*. for example found hyperthyreoidsm might be a risk factor for oesophageal cancer (23). Another prospective study of smokers found that men with elevated TSH and those classified as being in a hypothyroid state were at decreased risk of prostate cancer (24). Possible explanations for hypothyroidism under AA therapy may be the reduction of thyroid volume due to atrophy of follicles, degeneration of follicular epithelial cells and capillary rarefication, or inhibition of iodine uptake (16). Thus, a hypothyroid state appears to be advantageous for patients with cancer. However, it is still unclear whether induction of hypothyreosis in AA-treated patients is a part of its mode of action, or whether it merely represents a pharmacokinetic phenomen. Moreover, it remains unclear whether the degree of TSH increase is relevant to treatment outcome. Induction of hypothyreosis might be a part of the mode of action of AA.

Conclusion

In summary our data strongly indicate that hypothyreosis may serve as a simple biomarker predictive of response under AA therapy. It is tempting to assume that induction of hypothyreosis might be a mechanism through which AA slows tumor growth. Further analyses with a larger patient collective and of a multicenter character are of importance to confirm this finding.

Funding and Conflicts of Interest

No funding or conflicts of interest exist regarding this article.

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