

Measurement of bone turnover in prostate cancer patients receiving intermittent androgen suppression therapy

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Purpose: Reports on clinical measurements of bone mineral density (BMD) in prostate cancer patients undergoing intermittent androgen suppression therapy (IAS) that allows for hormonal recovery between treatment cycles indicate decreased osteoporosis compared to continuous androgen suppression therapy (CAS). In the present study the effect of IAS on bone metabolism by determinations of CrossLaps, a biochemical marker of collagen degradation, were examined.

Method: In total 100 IAS treatment cycles of 75 patients with prostate cancer stages \geq pT2 were studied. Clinical data and monthly laboratory tests (testosterone, prostate-specific antigen; PSA) of these patients were monitored together with measurements of C-terminal telopeptide collagen fragments using CrossLaps® ELISA assays.

Results: During phases of androgen suppression (AS) lasting for 9 months serum testosterone (<1 ng/mL) and PSA (<2 ng/mL) levels were reversibly reduced, indicating partial growth arrest and apoptotic regression of the prostatic tumors. Serum CrossLaps concentrations peaked at the last 2 months of the AS phases (0.91 ± 0.25 μ g/L; mean \pm SEM) and were reduced below initial values (0.21 ± 0.43 versus baseline of 0.43 ± 0.06 μ g/L) during therapy cessation periods until tumor progression-related increases.

Conclusion: Measurements of the serum concentration of CrossLaps in prostate cancer patients receiving IAS indicated that treatment cessation phases rapidly reversed increased bone degradation associated with AS phases, in strong agreement with the clinical observations reporting reduced loss of BMD in IAS when compared to CAS. In terms of clinical outcomes, IAS seems to be as effective as CAS while showing reduced side effects, as demonstrated here by the reduction of androgen-induced bone matrix degradation.

Keywords: intermittent androgen suppression, prostate cancer, prostate-specific antigen, testosterone, bone turnover, CrossLaps

Prostate cancer is among the most common types of cancer and causes of cancer-related deaths in men worldwide.¹ Capsular transgression of prostatic tumors or relapse following radical prostatectomy results in a worse prognosis.² Treatment consists of hormonal manipulation to deprive the cancer cells of androgenic growth stimulation either by orchidectomy or use of luteinizing hormone-releasing hormone (LHRH) analogs and steroidal or nonsteroidal antiandrogens, respectively.³ Androgen suppression (AS) is conventionally performed as a continuous treatment and leads to apoptotic regression of the tumor cells in the majority of cases. However, surgical or medical castration results in median progression-free survival of only two to three years with treatment options of limited efficacy remaining.⁴ Responses to cytotoxic therapy are low, and only recently has a possible benefit of incorporating chemotherapeutic agents in treatment regimen for prostate cancer been highlighted.⁵

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Continuous androgen suppression therapy (CAS) may be counterproductive in the long term due to accelerated selection of androgen-independent tumor cell populations.⁶ In contrast, hormone dependence is maintained in intermittent androgen suppression therapy (IAS) owing to the availability of low levels of testosterone. Therefore, IAS was proposed as a new clinical concept, assuming that during limited regrowth in treatment cessation periods tumorigenic stem cells are residing in an androgen-responsive state.⁷ Since then, regrowing tumors in IAS patients were consistently shown to be sensitive to several cycles of androgen withdrawal and IAS to result in improved quality of life.^{7,8} A total of 140 patients were recruited since we initiated an IAS study at our institution in 1993, with the first patients reaching their seventh IAS cycle.⁹ Meanwhile, IAS has been established as a therapy seeming equivalent to CAS, leading to IAS being proposed as a standard therapy for progressing prostate cancer.^{10,11}

The amelioration of side effects of CAS achieved by regular treatment cessations in IAS, as reported in quality of life assessments so far, however, needs further clinical evaluation. CAS leads to increased incidence of osteoporosis and concomitant bone fractures.¹² Therefore, it was expected that the off-treatment periods during IAS would allow for recovery of testosterone levels and cessation of bone material degradation. Higano et al¹³ observed loss of bone mass density (BMD) after nine months of AS at a significantly greater rate than the expected 0.5%–1% annual loss, although interruption of AS attenuated the rate of bone loss without full recovery. In the present study levels of CrossLaps, a degradation product of collagen I, were analyzed retrospectively in serum samples to characterize bone metabolism during IAS.¹⁴

Method

Study population and treatment

All patients gave written informed consent according to approval of the local ethics committee at the Wilhelminenspital, Vienna, Austria. Between June 1993 and August 2003 all patients with disseminated adenocarcinoma of the prostate fulfilling the inclusion criteria of histologically confirmed tumors of stage $\geq T2$, having had no pretreatment by hormone ablation or chemotherapy, and experiencing rising PSA were recruited for a nonrandomized open IAS trial consisting of an initial nine month course of androgen suppression (LHRH agonist goserelin acetate/Zoladex® and cyproterone acetate/Androcur®), followed by treatment cessation and resuming of the therapy once PSA increases >4 and 20 ng/mL for local and metastatic disease, respectively.⁹ Leuprolerin/trenantone® was used for nine months of androgen suppression from 2003. Follow-up examinations

included digital rectal examination, transrectal sonography, yearly chest X-rays, and bone scans, respectively.

Laboratory measurements

Blood samples were taken from each patient prior to treatment and at monthly intervals thereafter and stored at -80°C . Serum testosterone concentrations were measured using an ELISA assay (Biomar Diagnostics, Marburg, Germany) according to the manufacturer's instructions. PSA levels were determined by the microparticulate enzyme immunoassay (MEIA, AxSYM PSA assay, Abbott, Wiesbaden, Germany), and CrossLaps® ELISA was obtained from Nordic Bioscience Diagnostics, Herlev, Denmark, and used according to the manufacturer's instructions. All determinations were done in duplicate.

Statistical analysis

Student's *t*-test was used for the statistical analyses, with $P < 0.05$ considered significant. All calculations were done using the Statistica software package (Statsoft, Tulsa, OK, USA).

Results

Characteristics of IAS cycles in the prostate cancer patients

All patients ($n = 75$; mean age \pm SD: 68 ± 7 years, range 53–84 years) had exhibited disease progression following radical prostatectomy and/or irradiation therapy. Lengths of treatment cessation periods (mean \pm SEM) for the respective off-treatment phases (PI–PVI) were (in months): $16.0 \pm 5.9^*$ ($n = 75$), 10.0 ± 3.0 ($n = 31$), 8.0 ± 2.5 ($n = 18$), 8.0 ± 1.5 ($n = 12$), 9.6 ± 2.0 ($n = 8$), and 6.5 ± 5.5 ($n = 2$), respectively. Hence, the first treatment cessation period (PI) was significantly longer compared to the subsequent pauses, that were not significantly distinct in length from each other.

Individual courses of testosterone, PSA, and CrossLaps levels under IAS

Individual time courses of concentrations of testosterone, PSA, and CrossLaps for a representative patient undergoing IAS are depicted in Figure 1. Mean values of the parameters that were measured in monthly intervals for cessation (PI: 12, PII: 9, and PIII: 8 measurements) and treatment (9 measurements averaged for each phase AI to AIV) periods, respectively, are shown. Testosterone and PSA were significantly elevated during treatment breaks compared to the AS periods and concentrations of CrossLaps increased periodically and reversibly during AS, indicating increased bone catabolism during AS and recovery during cessation phases.

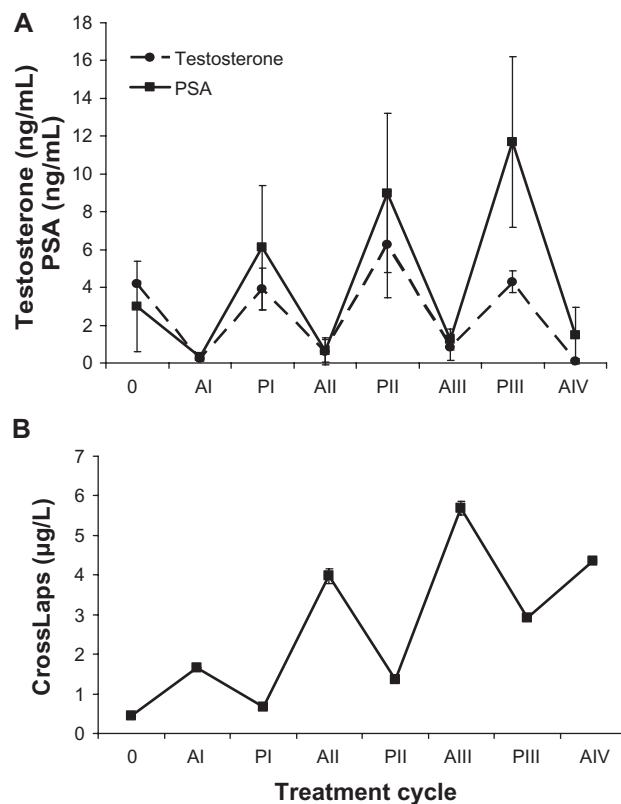


Figure 1 Individual time courses of testosterone, PSA (A), and CrossLaps serum levels (B) for a representative patient undergoing IAS (mean \pm SD calculated for each treatment period). Values cover the pretreatment time point, AS phases (AI–AIV), and treatment cessation periods (PI–PIII).

Mean courses of testosterone, PSA, and CrossLaps levels under IAS

Mean time courses of serum concentrations of testosterone (mean \pm SEM) for 100 IAS cycles observed in 75 patients are shown in Figure 2A. Measurements of the initial and successive treatment cycles were overlaid. AS triggered decreases of testosterone to values <1 ng/mL, followed by recovery to baseline levels in the third month of treatment cessation. With some variation testosterone concentrations continued to remain near pretreatment values for up to 62 months in patients with a prolonged first treatment cessation period. Similarly, the time course of mean serum PSA concentrations (mean \pm SEM) is presented in Figure 2B. During AS all patients showed reversible decline in PSA production to a mean level of <2 ng/mL. Treatment cessation resulted in recovery of PSA to approximately 5 ng/mL for up to 15 months, followed by further increases in the group of patients with prolonged responses and eventual tumor regrowth. The time course of CrossLaps concentrations as measured in 100 cycles of 75 patients representing a subpopulation of all IAS patients is shown in Figure 2C. Measurements at eight and nine months of AS and between 19 and 51 months

of treatment cessation were significantly different from the pretreatment value ($P < 0.05$). Therefore, bone catabolism peaked at the end of the AS period (0.91 ± 0.25 µg/L) and fell below pretreatment levels (0.43 ± 0.06 µg/L) during treatment cessation (<0.2 µg/L) before regrowth of the tumor/metastasis induced further degradation of bone matrix.

Discussion

Adenocarcinoma of the prostate in advanced stage is treated by surgical and/or antiandrogenic hormone ablation.^{3,15} CAS provides selective pressure on the androgen signaling pathway invariably resulting in outgrowth of cells adapted to very low androgen concentrations or androgen-independent tumor cells, respectively.⁴ A long-debated clinical therapy, namely IAS, is aimed at prolonging the hormone dependence of tumor cells by allowing for limited regrowth of hormone-sensitive cells between suppression periods.^{6,7} In clinical pilot studies it was demonstrated that IAS can be performed for several cycles, and results gained in a host of further studies provide firm evidence that IAS is not inferior to CAS in terms of survival.^{9,10} IAS is intended to prolong the androgen-dependent state and, most importantly, reduce side effects of CAS.

Adverse effects of CAS include skeletal, metabolic, and cardiovascular complications as well as sexual dysfunction, hot flashes, and cognition and mood disorders.^{8,16} In particular, it has been demonstrated that continuous androgen ablation reduces bone mineral density, which leads to increased risk of skeletal fractures.^{12,15} Several groups investigated the effects of IAS on BMD and reported reduction of bone loss upon prolonged treatment. Higano et al¹³ described increased bone loss during the AS phase of IAS and partial recovery upon cessation. Spry et al¹⁷ demonstrated significant improvement of hip BMD following two years of IAS, dependent on testosterone recovery. Malone et al¹⁸ reported no increase of osteoporosis in patients under IAS compared to age-matched individuals. Therefore, from clinical measurements of BMD in limited groups of IAS patients the reversal of AS-induced bone loss during the off-treatment periods is not clear.

The effect of IAS on BMD may be further studied using biochemical markers of bone metabolism. Collagen I accounts for more than 90% of the organic matrix of bone and is degraded by osteoclasts during remodeling. Thereby, crosslinked telopeptide fragments of collagen I are excreted into the bloodstream and can be measured by a CrossLaps® ELISA.¹⁴ This assay has been used for follow-up of antiresorptive treatment of patients with metabolic bone diseases.¹⁹ Our results show that AS resulted in rapid reduction of serum

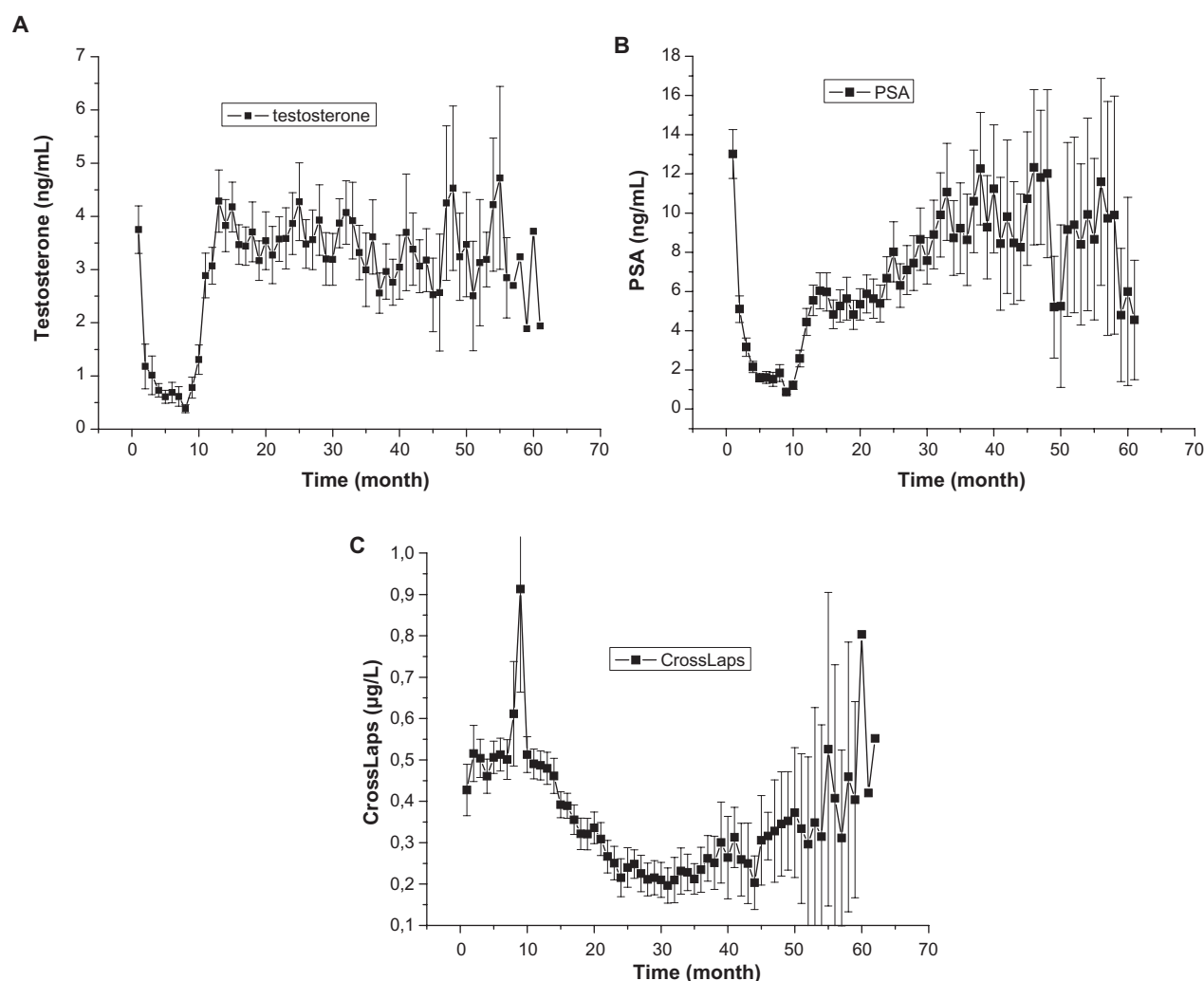


Figure 2 A–C Mean time course of mean serum testosterone concentrations (**A**; values between months 1–9 of AS significantly below initial), mean serum PSA (**B**) and mean serum CrossLaps (**C**) for 100 IAS cycles observed in 75 patients (mean \pm SEM; pretreatment value and months 1–9 of AS, followed by cessation period of IAS). Measurements of CrossLaps at eight and nine months of AS and between 19–51 months of treatment cessation are significantly different from the pretreatment value ($P < 0.05$).

testosterone and PSA levels, and significant induction of bone matrix catabolism along with release of CrossLaps. Shortly after cessation of AS the CrossLaps level was reduced to pretreatment concentrations of 0.395 ng/ml, typical for men at this age, and further declined gradually during the off-treatment period. After prolonged time without AS CrossLaps values exhibited a gradual increase, most likely due to regrowth of the tumor.²⁰

Conclusion

In conclusion, IAS resulted in rapid reduction of bone matrix degradation observed during AS in prostate cancer patients, as assessed by measurements of CrossLaps. This finding substantiates indirectly the decreased loss of BMD in bone scans in prostate cancer patients under IAS therapy, and supports that determinations of Crosslaps should be performed along

with bone scans in IAS patients to establish a quantitative relationship between the laboratory and clinical parameter. Since pretreatment concentrations of CrossLaps were restored within several months of treatment cessation and mean duration of the off-treatment periods PI–PV ranged from 8–16 months in our study, this antiosteoporotic effect of IAS is expected to be repeatedly effective for several treatment cycles.²¹ Thus, patients with an extended off-treatment interval and good long-term prognosis are expected to possess an improved quality of life, delayed hormone resistance, and reduced medication under IAS therapy.^{22,23}

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Disclosure

The authors report no conflicts of interest in this work.

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