PROSTATE CANCER: A STATE OF THE HEART

Summary of Presentations from the Ferring Pharmaceuticals Sponsored Symposium, held at the 29th Annual EAU Congress, Stockholm, Sweden, on 13th April 2014

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MEETING SUMMARY

This symposium was focused on reviewing androgen deprivation therapy (ADT) in prostate cancer, highlighting the implications of this therapy in clinical practice and including a focus on the cardiovascular (CV) risk associated with ADT therapy.

Introduction: Current Challenges with ADT for Prostate Cancer

Professor Laurence Klotz

Prof Laurence Klotz began this session by giving a brief history of ADT, starting in 1780 when John Hunter discovered that castration resulted in the regression of the prostate. In 1940, Charles Huggins was awarded the first Nobel Prize in this area for the discovery that orchiectomy and oestrogen caused the regression of prostate cancer. Discovery of synthetic oestrogens and the development of first and second-generation, non-steroidal anti-androgens followed. A second Nobel Prize was awarded to Andrew Schally for the discovery of luteinising hormone-releasing hormone (LHRH) and the development of the first agonist, with the subsequent development of several first and second anti-androgen therapies. The recent arrival of gonadotropin-releasing hormone (GnRH) antagonists marks the evolution of drugs in prostate cancer management.

Prof Klotz then discussed developments in understanding the mechanism of castration resistance over the past decade, with reference to the cellular synthesis of androgens in an androgen-depleted environment. He emphasised the importance of testosterone as well as the timing of therapy in predicting patient outcomes; findings indicate that delayed therapy produces the same outcome as early therapy.

Prof Klotz stated that a focus of the session was the systemic, metabolic, and CV effects of ADT, as well as the role hormones play in atherosclerosis plaque formation and rupture. The ability of prostate cancer cells to synthesise their own androgen

hormones, also known as the back door pathway, allows them to proliferate by binding to the androgen response element in the genome to trigger various signal transduction pathways; findings that have changed the understanding of castration resistance. Non-genomic signalling, via MAP kinases/ERK and PI3K pathways, results in the direct stimulation of prostate cancer cells; the complexity of this signalling cross talk, in addition to the thousands of genes that are regulated by the androgen receptor, allows for potential therapeutic intervention at various stages.

Prof Klotz then discussed management challenges, and emphasis was placed on the decisions for initiation and duration of therapy and the choice of either intermittent or continuous therapy.

A Patient-Centred Approach to Making Treatment Decisions

Professor Alberto Briganti

Prof Alberto Briganti's presentation began with the case of a 57-year-old male diagnosed with a 4 + 3 bilateral extended prostate cancer. The patient displayed some CV risk factors, including diabetes and obesity. Following staging, the patient appeared to have no systemic disease in the bone or in the abdomen and pelvis; however, a prostate magnetic resonance imaging (MRI) scan showed a suspicious area of minimal extracapsular extension at the right apex. Prostate-specific antigen (PSA) levels were 21.6 ng/mL, indicating that he was a high-risk patient. He consequently underwent bilateral extended pelvic lymph node dissection (PLND). The final pathological report revealed that the patient had a Gleason score of 8, 2/21 positive lymph nodes, and a positive surgical margin, with complete recovery of urinary continence at 4 weeks after surgery. Post-surgery evaluation showed that the patient had a PSA of 0.07 ng/mL, had no spontaneous erections, and did not require a protective pad at 40 days.

Postoperative patient management was discussed and Prof Briganti concluded he would opt for a combination of radiotherapy and hormonal therapy for 3 years. However, he indicated that there were no guidelines on the duration of therapy and that a case for a shorter or longer duration of therapy could be made. The experts agreed, in particular given the patient's young age.

Follow-up after 2 years revealed that this patient had a PSA of 1.98 ng/mL 15 months post-therapy with a PSA doubling time of 2.08 months. Prof Briganti stated that the patient underwent imaging and discussed the use of this technique in guiding future therapy use.[1] He continued by explaining that specifically the patient underwent PLND and 14 nodes were removed, 3 of which were positive. PSA levels 6 weeks post-surgery were 0.11 ng/mL; 6 months post-salvage LND these rose to 0.91 ng/mL. At this point the patient also suffered a myocardial infarction and was treated with a percutaneous coronary intervention and drug-eluting stent. The patient was kept under observation and 16 months post-salvage had a PSA level of 6.58 ng/mL. A bone scan revealed malignancy in the left ischiopubic ramus, despite the patient being asymptomatic and selected for ADT.[2]

Using this case by way of example, Prof Briganti ended by asking the experts what should be considered when selecting and optimising ADT.

Hormonal Therapy: Selecting the Optimal Agent

Professor Laurence Klotz

Surgical castration, oestrogens, LHRH agonists and GnRH antagonists, anti-androgens, combined androgen blockade (CAB), and 17,20-lyase inhibitors are some of the treatment options available to a patient with CV risk factors and known metastatic disease. Due to the high rate of thromboembolic events with oral oestrogen, it has somewhat been abandoned as a therapy. The oestrogen patch, however, is not thought to induce thromboembolic events. Prof Klotz described a study comparing a LHRH agonist and a transdermal oestrogen patch in which the use of the patch did not increase the number of CV events versus the LHRH agonist, suggesting that this may be regarded as a potential therapeutic option.[3] LHRH agonists have a number of disadvantages including testosterone surge, the flare in patients with advanced disease that may accelerate disease, adverse systemic, and CV effects.[4–9]

Hormone-naïve patients are unlikely to display disease flare, particularly in countries with PSA screening; however, incidence of clinical disease flare in LHRH agonist trials has been shown to be up to 63%, despite CAB.[10] In a preclinical study,

men treated with CAB (LHRH agonist + anti-androgen) displayed massive bone metastasis perfusion associated with a flare, which does not occur with the GnRH antagonist (degarelix), indicating that CAB may not reduce tumour size.

A comparison of five studies in patients after orchiectomy was presented, which showed that LHRH agonists are associated with a breakthrough of testosterone levels, with 20% of patients unable to consistently drop their levels below 0.7 nmol/L (20 ng/dL).[11-13] Prof Klotz then went on to describe the importance of lower testosterone levels and shared evidence supporting a higher chance of PSA progression in patients with testosterone levels ≥50 ng/dL.[14,15]

Furthermore, analysis of patients on the continuous arm of the NCIC/SWOG/UK CCR PR-7 study,[16] with measurement of testosterone levels every 3 months, revealed that patients who failed to drop their testosterone below 1.7 nmol/L (50 ng/dL) had a greater chance of progression to castrate-resistance, supporting the idea that testosterone is important in prostate cancer progression.[16]

Prof Klotz continued his presentation by sharing data from the Phase III CS21 trial, evaluating the efficacy and safety of degarelix in 610 patients with prostate cancer requiring androgen therapy in comparison with leuprolide.[17] Treatment with the GnRH antagonist degarelix resulted in an immediate drop in testosterone levels and maintained the median levels below castration levels (≤0.5 ng/mL) from day 28 to day 364. Longer-term follow-up of up to 5 years showed that degarelix was able to control testosterone and PSA levels for a longer period of time.[18]

Prof Klotz also presented data from a pooled analysis (1,925 patients) showing that overall PSA progression-free survival was better in patients treated with degarelix versus LHRH agonists, accompanied by a lower probability of musculoskeletal events. There was also a lower probability of urinary tract events with degarelix.[19] This may be explained by previous data that have shown increased regression in men receiving degarelix.

Conventional wisdom dictates that morbidity associated with LHRH agonists is related tommetabolic syndrome (MetS); however, other factors such as the presence of GnRH receptors in inflammatory cells, follicle-stimulating hormone (FSH) receptor activity in the endothelium, adipocytes, and effects on bone mineral density, as well as oestrogen deficiency, may all contribute. Degarelix treatment is associated with a decrease in FSH levels of 88.5% versus 54.8% with leuprolide at year 1 of treatment;[17,20] this is of particular significance as FSH receptors are expressed in normal prostate, but expression is enhanced in prostate cancer and cardiomyocytes.[21] Prostate tumour blood vessels have also been shown to express FSH receptors, so lowering FSH levels may decrease vascularisation of prostate tumours.[22] FSH activation of osteoclast NF-kB causes hypogonadal bone loss and directly increases osteoclastogenesis and resorption; as such, antagonising this hormone may result in positive disease outcomes.[23] Comparison of necrotic plaque size in response to orchiectomy, leuprolide, and degarelix in a murine model has shown that the necrotic plaque area is significantly reduced in animals in the degarelix group.[24] This is of particular significance as plaque size is often a predictor of downstream CV events, supporting the hypothesis that these drugs have different effects on CV physiology.

Prof Klotz concluded his presentation by stating that degarelix is a superior treatment over LHRH agonist therapy as a result of possessing a longer time to PSA failure and improved overall survival and control of bone metastasis.

Getting to the Heart of the Matter: CV Risk and ADT

Professor Alexandre de la Taille and Professor Jan Nilsson

Prof Jan Nilsson began this session by explaining the epidemiology of CV disease (CVD) worldwide. There were nearly 17 million deaths due to CVD in 2011,[25] with most acute events caused by vulnerable atherosclerotic plaque rupture. Degradation of the fibrous plaque results in an occluding thrombus and consequently a myocardial infarction. Age is an important factor in the incidence of CVD events with older men having the highest incidence of CV events.[26] Identification and reduction of CVD risk factors are likely to have a significant impact in reducing CV-related mortality.[27,28]

Prof de la Taille then led a discussion on the incidence of CV disease in patients with prostate

cancer. A cohort study of 30,721 patients with incident prostate cancer revealed that overall mortality was 20% higher in prostate cancer patients with pre-existing CVD compared to those without ischaemic heart disease (IHD) or stroke.[29]

Management of prostate cancer has a long history of treatment with androgen therapy as well as being associated with an increased risk of CV-related side-effects. A pivotal study from 1967 in which 2,052 patients were treated using radical prostatectomy or orchiectomy, with or without oestrogen, reported several interesting findings.[30] Survival was significantly shorter in patients with Stage 1–3 prostate cancer receiving oestrogens, with a significant increase in deaths due to CVD.[30] Similar findings have been observed with LHRH agonists, CAB, and orchiectomy, where the incidence of CVD is higher in patients treated with these therapies.[31] CV risk has been observed to increase with age and comorbidities; men aged ≥65 years and receiving 6 months of ADT had shorter times to fatal myocardial infarction compared to those receiving radiotherapy alone.[32] This increase in CVD in men treated with ADT (orchiectomy, oestrogen, or LHRH agonists) appears to be 20–25%, making it an important health issue compounded by the fact that CVD is the second most common cause of death in men with prostate cancer. Different types of ADT result in different CV effects depending on the treatment administered to the patient.[31]

Prof de la Taille then presented pooled data from six randomised Phase III/IIIb trials of degarelix versus LHRH agonists in 2,328 patients, where patients were treated with degarelix, leuprolide, or goserelin. Outcome measures included death from any cause and CV events. Baseline data between groups were similar, with no differences in age or body mass index; however, at least one-third of patients had CVD history at inclusion.[33] Findings confirmed previous results presented by Prof Klotz; there was better overall survival in patients treated with degarelix than those treated with LHRH.[19] The overall incidence of CV events was lower in the degarelix-treated group (2.8% degarelix versus 4.4% of LHRH agonist patients) as was the risk of serious CV events. Patients with pre-existing CVD had significantly fewer CV events during the first year of treatment compared with the LHRH agonist-treated patients; they had relative risk reduction of 56% and absolute risk reduction of 8.2%. Pooling all CV risk factors in a multivariate analysis revealed that degarelix had a lower risk of a CV event.[33]

Prof Nilsson suggested that these differences in CV risk could be due to differences in the effect of different ADT. Conventional ADT has been associated with metabolic change, insulin resistance, accumulation of subcutaneous fat, and decreased lean body mass, leading to MetS that increases the risk of developing CVD. However, it must be noted that MetS and the metabolic changes induced by ADT are different. Low testosterone is implicated in MetS as it increases fat deposition with increasing insulin resistance.[34,35]

Plaque instability is a predictor of CV event risk; stable plaques will have a thick fibrous plaque, with less infiltration by inflammatory cells. Conversely, a vulnerable plaque will have a thin fibrous cap, increased amounts of lipids and inflammatory cells but will also be able to maintain lumen size. Events further destabilising this plaque will ultimately lead to a CV event. Inflammatory events during plaque rupture include the production of various cytokines. These activate macrophages degrade the fibrous cap. Ultimately, this leads to plaque instability and increases the risk of thromboembolic complications and CV events.[36] The presence of GnRH receptors in T cells allows GnRH or LHRH agonist binding, which leads to the increased proliferation and activity of these cells, causing fibrous cap disruption and plaque instability. In contrast, GnRH antagonists do not activate T cell proliferation and activity, and thus are not likely to contribute to plaque destabilisation through this mechanism.[37–40]

A comparison of leuprolide, degarelix, and orchiectomy in a preclinical study has shown that FSH and LH levels are significantly lower with degarelix than leuprolide, with significantly lower triglyceride levels and better glucose tolerance. Atherosclerotic plaque surface area is also smaller with degarelix than leuprolide or orchiectomy, which may clarify potential differences between types of ADT and CV risk.[24,41]

Prof de la Taille explained that, as a urologist, the first and foremost concern with treatment is the effectiveness of the therapy to treat prostate cancer and control disease symptoms while minimising side-effects. However, in the presence of CV risk, including obesity, diabetes, and prior myocardial infarction, degarelix may be the preferred treatment of choice.

As a cardiologist, Prof Nilsson concluded this session with the following advice; the correct management of prostate cancer patients with accompanying changes in lifestyle including exercise, smoking cessation, and controlling alcohol intake, as well as medical intervention such as statin therapy and therapy to manage diabetes, hypertension, and risk of thrombosis, are all important.[42] The presentation concluded that ADT is associated with an increased risk of CV events; however, the GnRH antagonist degarelix may be a promising drug, offering increased survival in the total patient analysis and significant risk reduction of CV events in patients with pre-existing CVD, due to its different mechanism of action. Risk assessment of CVD needs to be assessed prior to using ADT.

This session provided the attending physicians with an informative discussion on the management of CVD risk in patients with prostate cancer.

Prof Klotz then concluded the symposium. The choices regarding therapy should take CVD and risk factors into account and consider each patient individually, offering a tailored approach. Promising new therapies, including degarelix, offer clinicians increasing effective options with improved side-effect profiles.

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