Asian Journal of Andrology (2012) 14, 175–176

www.nature.com/aja

EDITORIAL

Time to raise awareness regarding complications of androgen deprivation therapy

Asian Journal of Andrology (2012) **14,** 175–176; doi:10.1038/aja.2011.105; published online 27 February 2012

The worst thing about medicine is that one kind makes another necessary.

Elbert Hubbard (1856–1915)

No treatment is devoid of adverse effects, and androgen deprivation therapy (ADT) in men with prostate cancer (PCa) bears no exception. PCa is the most common non-cutaneous malignancy in men worldwide. In 2011, approximately 240 890 new cases of PCa were diagnosed in the United States and 33 720 men died because of the disease.[1] In intermediate- and high-risk patients with locally advanced disease, ADT, when added to external bean radiation therapy, has shown improved survival, while in men with metastatic PCa, ADT improves quality of life (QoL).[2–4] However, patients with localized cancer and those encountering biochemical recurrences after definitive therapy are also being started on ADT, even though survival advantage has not been conclusively demonstrated in these clinical settings. As a result, the use of ADT has significantly increased in the last 15 years.[5]

Testosterone has an effect on multiple organ systems. It is an important mediator of body composition as it increases lean body mass and muscle strength, and decreases fat mass. Testosterone is also important for male sexual function, bone mass, erythropoiesis, cognition and QoL. As the target serum testosterone level during ADT is <50 ng dl^{-1} (normal range in men between 280 and 1000 ng dl^{-1}), the resulting hypogonadism results in a variety of adverse effects pertaining to these organ systems (**Figure 1**). As the majority of men with PCa die of conditions other than their primary malignancy, recognition and management of these adverse effects is paramount. This special supplement of the *Asian Journal of Andrology* is intended to achieve this purpose. Bone loss and fractures are also an important consequence of ADT and articles focusing on skeletal health in patients undergoing hormone therapy will be published in another issue.

In the first manuscript of this issue, Connolly *et al.* provide an elegant and comprehensive overview of the indications and prevalence of ADT in PCa.[6] The section in the paper on controversial aspects of ADT is particularly insightful where they discuss the role of monotherapy *vs.* combined androgen blockade, intermediate *vs.* deferred hormone therapy and continuous *vs.* intermittent ADT. The authors also discuss alternate forms of ADT, e.g., gonadotrophin-releasing hormone antagonists, ketoconazole and abiraterone acetate, the latter being a potent inhibitor of androgen synthesis. This manuscript sets the stage for subsequent papers in this issue.

Grossmann and Zajac provide a thorough review on hematological changes in patients undergoing ADT.[7] They first present an overview of the relationship between androgens and erythropoiesis followed by the effect of ADT on hematopoiesis. The authors also discuss the influence of androgens on leucocytes and platelets. Finally, they provide an algorithm for the evaluation and monitoring of anemia during ADT and also comment on potential treatment strategies.

A frequent and potentially debilitating, though relatively overlooked, consequence of ADT are hot flashes. Vasomotor symptoms can occur in more than 75% of men undergoing ADT. Jones *et al.* give a comprehensive overview of the prevalence, potential mechanisms and treatment options of hot flashes in these patients.[8] In addition to discussing hormonal agents and antidepressants as treatment options, they also elaborate on non-medicinal therapeutic approaches such as behavior modifications and use of acupuncture.

Sexual dysfunction has a high prevalence in men undergoing ADT and is a major contributor to decreased QoL in these patients. Mazzola and Mulhall discuss the impact of ADT on sexual function.[9] In the first part of the paper, the authors elegantly summarize data from animal and human studies focusing on the physiological role of androgens on sexual behavior. They also discuss the central and peripheral mechanisms of action of androgens on sexuality. In the latter part of the manuscript, the authors focus on sexual dysfunction in men undergoing ADT. In their summary figure, they show the impact of ADT on various aspects of sexual health, including penile fibrosis, the finding that has given birth to the concept of penile rehabilitation.

Testosterone is an important mediator of body composition. Male hypogonadism, of any etiology, is associated with decreased muscle mass and strength and increased fat mass, and patients undergoing

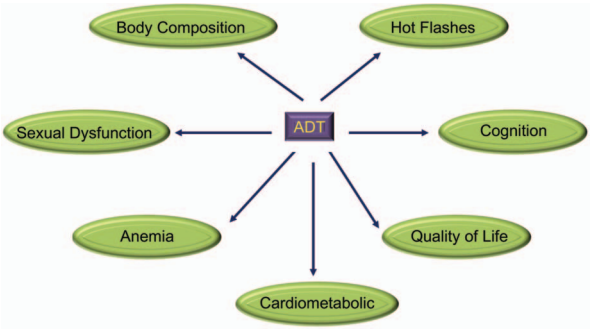

Figure 1 Organ systems predisposed to adverse effects during ADT.

ADT are no exception. The comprehensive review by Storer *et al.* summarizes the changes in body composition, muscle strength and physical function in men undergoing ADT.[10] The authors report data from both the cross-sectional and longitudinal studies, and divide the latter into short- and long-term studies based on the duration of hormone therapy, thereby highlighting the importance of the continued impact of long-term ADT on these outcomes.

Epidemiological data reveal an association between low serum testosterone levels and incident diabetes, metabolic syndrome, and cardiovascular disease and mortality. Similarly, men undergoing ADT have been shown to be at a higher risk of developing incident diabetes, coronary disease and sudden death. In their review, Collins and Basaria summarize data on cardiometabolic complications of ADT.[11]

ADT affects QoL of a patient in many ways. Casey *et al.* have categorized QoL issues into those related to body feminization, sexual changes, changes in relationship, changes in affect, fatigue and sleep disturbances, and physical effects.[12] This comprehensive review gives a broad insight into the QoL issues involving these patients which will serve as an excellent guide for the caregivers.

Finally, Jamadar *et al.* provide a superb overview of cognitive changes associated with ADT.[13] They suggest a potential harmful effect of ADT on spatial memory (and possibly verbal memory) in these men. The authors highlight the potential mechanisms by which testosterone influences cognition in men and also briefly touch upon the relative contribution of estradiol. The summary of studies in men undergoing ADT is comprehensive; however; the authors astutely note that many of these studies are handicapped by small sample size and lack of control groups, and they advocate larger studies.

This special issue should serve as a useful guide for clinicians in understanding the overall burden of adverse effects of ADT and the steps that should be taken to prevent/treat these complications. An informed clinician will also serve as a tremendous resource for his patients and their families. Future research in each of these areas should lead to development of concrete guidelines, focusing on both prevention and treatment of these adverse effects. This will bring us closer to our common goal: improvement in clinical care of these patients.

Shehzad Basaria
Department of Medicine, Division of Endocrinology and Metabolism, Boston University School of Medicine, Boston, MA 02118, USA
(shehzad.basaria@bmc.org)

1 Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics 2011. *CA Cancer J Clin* 2011; **61**: 212–36.
2 Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO *et al.* Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997; **337**: 295–300.
3 Messing EM, Manola J, Sarodsy M, Wilding G, Crawford ED *et al.* Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node positive prostate cancer. *N Engl J Med* 1999; **341**: 1781–8.
4 Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. *J Clin Endocrinol Metab* 2008; **93**: 2042–9.
5 Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer* 2005; **103**: 1615–24.
6 Connolly RM, Carducci MA, Antonarakis ES. Use of androgen deprivation therapy in prostate cancer: indications and prevalence. *Asian J Androl* 2012; **14**: 177–86.
7 Grossmann M, Zajac JD. Hematological changes during androgen deprivation therapy. *Asian J Androl* 2012; **14**: 187–92.
8 Jones JM, Kohli M, Loprinzi CL. Androgen deprivation therapy-associated vasomotor symptoms. *Asian J Androl* 2012; **14**: 193–7.
9 Mazzola CR, Mulhall JP. Impact of androgen deprivation therapy on sexual function. *Asian J Androl* 2012; **14**: 198–203.
10 Storer TW, Miciek R, Travison TG. Muscle function, physical performance, and body composition changes in men with prostate cancer undergoing androgen deprivation therapy. *Asian J Androl* 2012; **14**: 204–21.
11 Collins L, Basaria S. Adverse effects of androgen deprivation therapy in men with prostate cancer: a focus on metabolic and cardiovascular complications. *Asian J Androl* 2012; **14**: 222–5.
12 Casey RG, Corcoran NM, Goldenberg SL. Quality of life issues in men undergoing androgen deprivation therapy: a review. *Asian J Androl* 2012; **14**: 226–31.
13 Jamadar RJ, Winters MJ, Maki PM. Cognitive changes associated with ADT: a review of the literature. *Asian J Androl* 2012; **14**: 232–8.