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RESEARCH HIGHLIGHT

Androgen deprivation therapy for prostate cancer: not so simple

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Prostate cancer (PC) is the second most diagnosed visceral malignancy in men worldwide, with over 900 000 new diagnoses each year.[1] Approximately 50% of patients treated in industrialized nations will receive androgen deprivation therapy (ADT) at some point in their lifetimes.[2] The use of ADT as a treatment approach is likely to increase as new drug developments have focused on intensifying the effect of reducing androgen receptor activation. While the benefits of ADT are well-recognized in select treatment groups, relatively little attention has been paid to its side effect profile until recently. Given the widespread use of ADT, detailed analyses of its potential harmful effects are critically important. Past research has shown that ADT can cause fatigue, loss of bone density, decreased sexual function and libido, as well as possible increases in diabetes and cardiovascular disease.[3] Two new studies, by investigators from the University of Toronto add to our knowledge of the effects of ADT on physical and cognitive function in PC patients. They found that ADT had significant detrimental effects on both physical function and quality of life with a modest decrease in some areas of cognitive function.[4,5]

This study is the first prospective longitudinal study with a relatively large study population. They enrolled 87 patients with non-metastatic PC who were starting on ADT, and two matched control groups of 86 men each: one group with PC but not on ADT, and one group of healthy controls without a diagnosis of PC. They followed the groups for 1 year and measured multiple objective and subjective data points. Validated measures of future disability, morbidity, and mortality were used including grip strength to assess upper extremity strength and the 6-min walk test to assess endurance. Quality of life was measured with the Medical Outcomes Study SF-36 questionnaire. Measurements were taken at baseline and every 3 months up to 1 year.

Over the course of the study, grip strength in the ADT group declined significantly by the 3-month mark and remained low for the remainder of the study. In contrast, healthy and PC controls did not exhibit any decrease in grip strength. Similarly, in both PC and healthy controls, scores significantly improved for the 6-min walk test; whereas scores for ADT users remained flat. Subjectively, self-reported physical function on SF-36 surveys declined in the ADT group but remained stable in the PC and healthy control cohorts. Of the seven domains of quality of life evaluated, significant declines were seen in the ADT group in five areas including physical function, role function, bodily pain, vitality, and emotional function. These differences were observed within the first 3 months and scores remained depressed for the course of the study. To offset these untoward effects, the authors recommend initiating a physical exercise program in all patients starting ADT.

In a companion study using the same cohorts, the authors attempted to answer whether or not ADT affected cognitive function in users versus controls. Several prior studies had shown declines due to ADT in executive functions and visuospatial abilities; however, previous studies have been inconsistent in their findings often suffering from low sample size and inadequate controls.[6] The effect of therapy on cognitive function has been a pertinent topic recently, with terms like 'chemo fog' and 'chemo brain' now routinely used to describe the cognitive effects of systemic chemotherapy. In their report, the authors presented a prospective matched cohort study to more conclusively answer this question. The patients were evaluated using 14 cognitive tests covering eight unique cognitive domains (immediate span of attention, processing speed, verbal fluency, visuospatial ability, verbal learning and memory, visual learning and memory, executive functions of working memory, and executive functions of cognitive flexibility). Tests were administered in a standardized fashion at baseline, 6 and 12 months and adjusted for practice effect.

At the 6-month time point, none of the three groups showed changes by average group score. However, by 12 months, ADT users had small but significantly lower scores in immediate span of attention, working memory and visuospatial function than both control groups.

Over the last several decades, the use and indications for ADT have increased significantly with the most pronounced increases seen in earlier staged disease. The expanded use of ADT has lead to markedly prolonged exposure to drug therapy. The protracted use of ADT in patient groups with earlier disease has resulted in a heavier burden of side effects from ADT. These effects include weight gain, bone loss, erectile dysfunction, in addition to increased incidence of diabetes and cardiac disease. These two studies reviewed here add to our knowledge of ADT effects in patients with prostate cancer. Their results should serve as an aid in counseling patients about the effect of ADT on function and quality of life. These studies and others come at a critically important time in the field as several new agents are being developed to increase the effectiveness of ADT. These include drugs that further lower testosterone by inhibiting testosterone synthesis and agents that block androgen receptor activation.[7] As our knowledge in this area advances, it is hopeful that means of mitigating these treatment sequelae

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will be developed. Lastly, it is essential that the treating physician weigh the negative effects of ADT when considering committing patients to a long-term therapy.

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