Cognitive Impairment in Men with Prostate Cancer Treated with Androgen Deprivation Therapy: A Systematic Review and Meta-Analysis

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Purpose: Use of androgen deprivation therapy may increase the risk of cognitive impairment in men with prostate cancer. We performed a systematic review of the risk of overall cognitive impairment as an outcome in men receiving androgen deprivation therapy for prostate cancer.

Materials and Methods: Studies were identified through PubMed®, MEDLINE®, PsycINFO®, Cochrane Library and Web of Knowledge/Science™. Articles were included if they 1) were published in English, 2) had subjects treated for prostate cancer with androgen deprivation therapy, 3) incorporated longitudinal comparisons and 4) used control groups. In addition, prospective studies were required to assess an established cognitive related end point using International Cognition and Cancer Task Force criteria defining impaired cognitive performance as scoring 1.5 or more standard deviations below published norms on 2 or more tests, or scoring 2.0 or more standard deviations below published norms on at least 1 test. The effect of androgen deprivation therapy on cognitive impairment was pooled using a random effects model.

Results: Of 221 abstracts 26 were selected for full text review, and 2 prospective and 4 retrospective studies were analyzed. Androgen deprivation therapy was not associated with overall cognitive impairment when the prospective cohort studies were pooled (OR 1.57, 95% CI 0.50 to 4.92, $p = 0.44$) with significant heterogeneity between estimates ($I^2 = 83\%$). In retrospective data the relative risk of any cognitive impairment, including senile dementia and Alzheimer disease, was increased in men receiving androgen deprivation therapy, although the difference was not statistically significant (HR 1.28, 95% CI 0.93 to 1.76, $p = 0.13$) with moderate heterogeneity between estimates ($I^2 = 67\%$).

Conclusions: Analyses between overall cognitive impairment and use of androgen deprivation therapy defined according to International Cognition and Cancer Task Force criteria in a pooled analysis were inconclusive. In retrospective cohort studies the risk of overall cognitive impairment after androgen deprivation therapy was not significant. Better prospective studies need to be designed for the assessment of this end point.

Key Words: androgen antagonists, dementia, prostatic neoplasms, Alzheimer disease, cognition

Abbreviations and Acronyms

ADT = androgen deprivation therapy

ICCTF = International Cognition and Cancer Task Force

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For decades blockade of androgen receptor signaling has been known to delay progression of advanced prostate cancer and to improve the efficacy of some therapies such as external beam radiation therapy.[1,2] As a result, these medications are widely used, with more than 500,000 men currently being treated with androgen deprivation therapy in the United States.[3] Despite proved efficacy, these medications carry noteworthy side effects. Some, such as decreased libido, increased adiposity, reduced bone mineral density and declining muscle mass, are widely acknowledged.[4] Others, such as long-term risk of dementia, are more controversial.

There is evidence that androgens have a role in cognition. Results from the Baltimore Longitudinal Study of Aging suggest that men with lower free testosterone have faster decline in visual memory compared to men with normal free testosterone.[5] There also is laboratory evidence for this finding, with animal studies revealing that synaptic density of CA1 pyramidal cells and synaptic plasticity in the hippocampus are modulated by androgens.[6,7]

In contrast to familiar oncologic outcomes such as recurrence and survival, neurocognitive decline is difficult to measure. Studies of the impact of ADT on cognition document a heterogeneous group of neurocognitive outcomes, making generalizable inferences challenging. A prior meta-analysis of 14 longitudinal studies of ADT published between 2002 and 2010 pooled results by grouping measures into separate "domains" identified by the authors and thus was unable to assess the effect of ADT on overall cognitive impairment. The results suggested a heterogeneous effect of ADT on cognition, with just 1 cognitive domain (visuomotor ability) demonstrating consistently worse performance in men taking ADT for prostate cancer.[8]

Despite the potential adverse impact that cognitive impairment may have on prostate cancer survivors, there is no broadly accepted consensus about whether the association truly exists. Some experts remain skeptical and highlight the risk of unnecessarily delaying lifesaving ADT due to unproved risks.[9] Given uncertainty about the specific relationship between ADT and cognitive decline, we performed a systematic review and meta-analysis to assess the association of overall cognitive impairment with exposure to ADT for prostate cancer.

METHODS

Systematic Search Strategy

This study used PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[10] We performed electronic searches of English language publications referenced in PubMed, MEDLINE, PsycINFO, Cochrane Library and Web of Knowledge/Science from inception to December 21, 2016 with no restriction on the year of the study (fig. 1). We additionally examined citation lists from any relevant studies to identify other potential series. References that consisted of abstracts only were excluded. Details of the protocol for this systematic review were registered on PROSPERO (International Prospective Register of Systematic Reviews).[11]

Study Selection

Two reviewers (MS, NH) screened titles and abstracts independently. To be included, studies had to 1) be published in English, 2) have subjects treated for prostate cancer with ADT, 3) incorporate longitudinal comparisons and 4) use control groups. In addition, prospective studies were required to assess an established cognitive related end point using ICCTF criteria defining impaired cognitive performance as scoring 1.5 or more standard deviations below published norms on 2 or more tests, or scoring 2.0 or more standard deviations below published norms on at least 1 test.[12] Disagreements of eligibility were reconciled by a third reviewer (APC). Details of the study selection are illustrated in figure 1.

Data Abstraction and Study Quality

Two reviewers (MS, NH) abstracted data from each included study. The abstracted information from each series included study information (ie first author, journal and year of publication), study characteristics (ie sample size, cases and controls, and followup time), cognitive related end point and instrument used.

Study quality of all series was assessed using the quality assessment tool from the National Heart, Lung and Blood Institute (supplementary Appendix, http://jurology.com/).[13] Criteria were rated as either "yes," "no" or "other" (ie undetermined, not reported or not applicable), and an overall rating for the study was evaluated as either "good," "fair" or "poor."

Data Synthesis and Analysis

Prospective and retrospective cohort studies were presented separately. For prospective studies we relied on the criteria set forth by the ICCTF, which defines impaired cognitive performance as scoring 1.5 or more standard deviations below published norms on 2 or more tests, or scoring 2.0 or more standard deviations below published norms on at least 1 test.[14] Studies that failed to describe results according to ICCTF criteria were excluded. For retrospective series (eg population based studies, hospital based samples) the end points included were defined using ICD-9 diagnostic or procedure codes or other system based identification scheme. Effect estimates were captured via adjusted hazard ratios.

A random effects model was used due to the assumed heterogeneity between studies. We relied on Review Manager 5.0 (Cochrane Collaboration®) to produce the pooled estimates, forest plots and metaregression. Heterogeneity was quantified using the I^2 statistic and its significance was determined based on the accompanying Cochrane Q test p value. An I^2 value of 0% indicates no observed heterogeneity and increasing values represent greater amounts of heterogeneity. Values of 25%, 50% and 75%, respectively, indicate low, moderate and high levels of heterogeneity.[15] Comprehensive Meta-Analysis, version 3.0 (Biostat, Englewood, New Jersey) was used to carry out the data