TIMING OF ANDROGEN DEPRIVATION TREATMENT FOR MEN WITH BIOCHEMICAL RECURRENT PROSTATE CANCER IN THE CONTEXT OF NOVEL THERAPIES

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Abstract:

Purpose: There were 3 recent U.S. Food and Drug Administration approvals for drugs to be used in nonmetastatic castration resistant prostate cancer, a state that arises from the unproven start of continuous androgen deprivation therapy (ADT) for biochemical recurrent prostate cancer (BCR), before metastatic disease is evident. This report examines the outcome of men with BCR who defer ADT until time of metastasis.

Materials and Methods: Retrospective review of men diagnosed with clinically localized prostate cancer who underwent radical prostatectomy at Johns Hopkins Hospital and Walter Reed National Military Medical Center and developed BCR with a prostate specific antigen doubling time of not more than 10 months (806 patients). The primary end points were metastasis-free survival and overall survival from time of local treatment among men who delayed ADT until time of metastasis. Results: The median metastasis-free survival of men with BCR and a prostate specific antigen doubling time

<6 months and 10 months who delay ADT until metastasis is 144 months (95% CI 48 - not reached) and 192 months (95% CI 72 - not reached), respectively, with a median overall survival of 168 months (95% CI 96 - 276 months) and 204 months (95% CI 120 - 276), respectively.

Conclusions: Metastasis-free survival and overall survival of men with BCR who delay hormone therapy is long. This underscores the need to reevaluate when to start primary ADT in this patient population.

Comment

In this new edition of the CAU Journal Club, we analyze the article by Dr. Marshall and collaborators published in the Journal of Urology in September. Motivated by recent trials on NARA (New Androgen Receptor Antagonists) for the treatment of non-metastatic castration resistant prostate cancer (nmCRPC) with favorable results on overall survival, the authors analyze life expectancy in patients with biochemical recurrent prostate cancer (BCR) after radical prostatectomy in whom the initiation of androgen deprivation therapy (ADT) was delayed until the development of metastases and, therefore, who did not develop nmCRPC.

Continuous ADT for RCB has not been shown to prolong survival and is associated with toxicities.

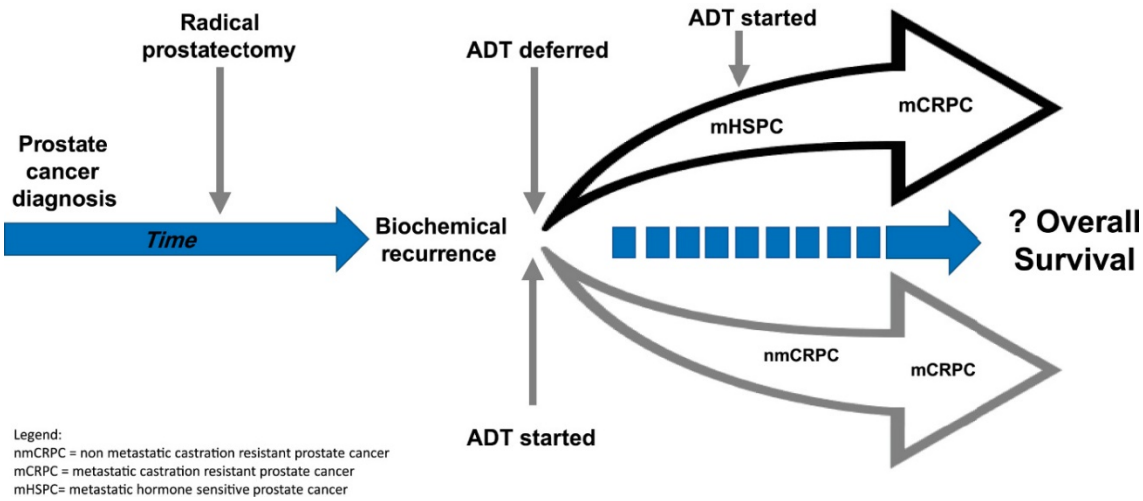
The primary aim was to know the overall survival and the secondary objective was to evaluate metastasis-free survival in patients with prostate cancer with biochemical recurrent after radical prostatectomy with curative intent in patients who had androgen deprivation therapy deferred until the development of metastasis.

This is a retrospective study within two prospective cohorts developed in two centers in the United States (Johns Hopkins University and Walter Reed National Military Medical Center), which included 806 patients diagnosed with clinically localized prostate cancer who underwent surgery. as curative treatment and who subsequently developed RCB with a PSAT doubling time (PSADT) of less than 10 months, according to the eligibility criteria of the pivotal nmCRPC assays.

The results obtained showed that the median age was 61 years, 79% being Caucasian. Positive margins were reported in 38% of the surgical specimens. The majority were

Gleason 7 (54%), followed by Gleason 8-10 (29%) and Gleason 6 (17%). The median PSADT was 5.6 months and the mean follow-up time was 9 years.

A PSA doubling time of less than 6 months was associated with a higher risk of metastasis development, while older age, a higher pathological T stage, a higher Gleason score, and a faster PSADT were associated with a higher probability of death for prostate cancer. The metastasis-free survival time in men with BCR and PSAT doubling time of less than 10 months that delay ADT until metastasis is 192 months with a median overall survival of 204 months. In contrast, in patients with PSADT less than 6 months, the median metastasis-free survival was 144 months and the overall survival was 168 months.



At the vanguard of NARA treatment for patients with non-metastatic castration-resistant prostate cancer, clinically significant favorable outcomes in overall survival and metastasis-free survival have been reported. However, it must be emphasized that non-metastatic castration-resistant prostate cancer is the result of a controversial practice of early start with ADT that remains unsubstantiated by level of evidence I. After progression with the first-line androgen receptor targeting agent, subsequent responses to alternative compounds only have a modest effect due to the development of androgen receptor resistance mechanisms, which is why it is proposed according to this study,

that in those patients with prostate cancer with RCB, hormonal therapy is postponed until the development of metastases since its immediate indication has not been shown to improve general survival and is associated with toxicities.

This study compares the overall survival of its series with the arms of the pivotal studies SPARTAN and ARAMIS, obtaining similar results.

Within the limitations of this publication, they acknowledge that the population included was only patients who had RCB after surgery with curative intention, excluding other types of treatment such as radiotherapy or primary ADT alone.

Furthermore, the start of follow-up was from the initial diagnosis and not from the moment of BCR.

The authors conclude that patients who were treated with curative intent with radical prostatectomy, who subsequently had biochemical recurrence and in whom the start of treatment with ADT was delayed, had prolonged global and metastasis-free survival times.

Marshal et al. contribute and enrich the discussion of when the initiation of androgen deprivation therapy is indicated in patients with BCR and PSADT for less than 10 months. They allow us to reflect on the consequences of continuous treatment with ADT and its toxicity, on resistance to castration and the need to incorporate new drugs.

In addition, they performed a comparison between their series of natural history of the disease with that of the large pivotal studies of NARA and obtained comparable results (although in different populations), with respect to the overall survival between the administration of these new antagonists of the androgen receptors and delayed onset of ADT.

In this publication, PSA doubling time is the main predictor of metastasis-free time and overall survival, without giving it the relevance of time to biochemical recurrence and the Gleason score in other similar series of natural evolution at this stage.

New prospective and randomized studies will be necessary to further understand this advanced stage of prostate cancer and the best time to start treatment.

Finally, the incorporation of new imaging technologies such as PSMA - PET, will be a fundamental contribution to find an answer to several of these questions.

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Trivia

1. Which of the following statements is correct, regarding biochemical recurrence in prostate cancer

a) Post radiotherapy, PSAT = PSA nadir plus 2 ng / ml
b) Post radiotherapy, PSAT = PSA nadir plus 0.2 ng / ml
c) Post radical prostatectomy, PSAT ≥ 0.2 ng / ml
d) Post radical prostatectomy, PSAT ≥ 2 ng / ml
e) a + c
f) b + d
g) none

2. In relation to serology, what is considered castration-resistant prostate cancer?

a) Elevated PSA plus testosterone <50 ng / dl
b) Elevated PSA plus testosterone> 50 ng / dl
c) Elevated PSA plus testosterone = 50 ng / dl
d) None

3. In patients with localized prostate cancer without metastasis, who are at high risk of progression?
a) If they present a TNM stage greater than or equal to T2c
b) A Gleason score of 8 to 10
c) PSAT> 20 ng / ml
d) All
e) None