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Seminar article

Approaches to minimize castration in the treatment of advanced prostate cancer

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Abstract

Background: Androgen deprivation therapy (ADT) remains the cornerstone of primary systemic treatment for men with metastatic disease and is a commonly applied therapy in the biochemically relapsed setting. Despite the high response rate with ADT, resistance is universal. Furthermore, over the past decade, there has been a growing appreciation for the significant short-term and long-term toxicities of continuous ADT (CADT). The rationale to develop alternative androgen receptor (AR) targeting strategies that seek to minimize or eliminate the need for upfront castration therapy is 2-fold—(1) delay the emergence of AR-independent disease, potentially improving long-term disease outcomes and (2) mitigate the short-term and long-term side effects of CADT, improving quality of life and potentially lessening comorbidities related to ADT including osteoporosis, diabetes, and potentially cardiovascular disease. The 2 most rigorously studied alternatives to CADT include intermittent ADT and peripheral androgen blockade with the use of first-generation or second-generation AR antagonists. Both intermittent ADT and peripheral androgen blockade have been evaluated in the biochemically relapsed and metastatic setting in multiple phase 2 and 3 studies.

Aim: In the current review, we aim to discuss the data from these studies, as well as the emerging noncastrating strategies.

Keywords: Biochemically recurrent prostate cancer; Androgen deprivation therapy; Peripheral androgen blockade

Introduction

Medical castration, or androgen deprivation therapy (ADT), remains the cornerstone of systemic therapy applied across clinical disease states in localized and advanced prostate cancer, including those with high-risk localized disease, in biochemical relapse, metastatic castration-sensitive, as well as castration-resistant settings (M0 and M1) (Fig.). Though ADT is initially effective in lowering serum prostate-specific antigen (PSA), inducing tumor regressions, and alleviating cancer-related symptoms in the vast majority of men, disease progression is universal with a median time to castration resistance of approximately 2 to 3 years depending upon disease state and risk category. There is considerable variability in the duration of response to ADT. The nadir PSA after induction period of treatment as well as depth of testosterone suppression may serve as potential predictors of duration of response to primary therapy [1,2]. In addition to having a limited duration of effectiveness in a substantial number of patients, there is a considerable risk of noncancer-related morbidity and mortality related to long-term ADT. In particular, ADT is associated with an increased risk of osteoporosis, diabetes, and potentially cardiovascular disease [3–8]. The risk of cardiovascular disease appears to be especially pronounced in those with preexisting disease and recent cardiac events [9]. Also, of significant concern are the multitude of adverse effects associated with ADT that can affect the quality of life (QOL), especially in patients who are on long-term treatment. Given the limited duration of effectiveness in a large subset of patients, and toxicities of castration therapy, there is a clear need to develop

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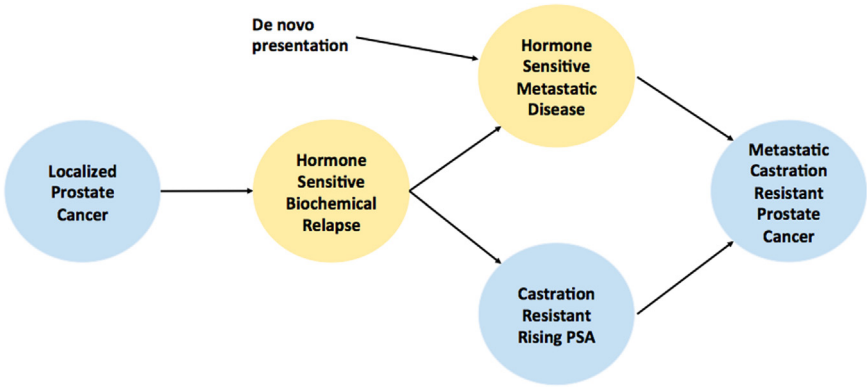

Fig. The clinical disease states in prostate cancer in which systemic androgen deprivation therapy is applied. Highlighted in yellow are the disease states that are the focus of the review. (Color version of figure is available online.)

noncastration approaches targeting the androgen receptor (AR) and the androgen signaling pathway with a more favorable risk/benefit profile.

Though, strategies to minimize the toxicity of ADT are relevant across a multitude of clinical disease states in the spectrum of prostate cancer, in the current review, we would predominantly focus on patients with advanced prostate cancer, including those with hormone-sensitive, biochemically relapsed, and metastatic disease (highlighted in Fig.). To date, the 2 most widely evaluated alternatives to continuous castration therapy in patients with advanced prostate cancer include intermittent ADT (IADT) and peripheral androgen blockade (PAB) with either first-generation or second-generation AR antagonists. Because with both of these approaches, the androgen levels are not completely inhibited compared with continuous ADT (CADT); these approaches may lead to less toxicities. In the subsequent sections, we summarize the current data and remaining unanswered questions with each of these approaches, as well as look forward to emerging and future directions with respect to noncastrating AR targeting approaches in biochemically relapsed and metastatic hormone-sensitive prostate cancer.

Risk stratification and early vs. delayed treatment in biochemically relapsed prostate cancer

Before choosing an alternative AR targeting strategy, it is worth considering whether patients need systemic therapy of any kind as opposed to continued surveillance [10]. This is especially true in biochemically relapsed prostate cancer (BRPC), a setting in which there are no adequately powered phase 3 clinical trial data that prove a long-term survival benefit with initiating ADT before the development of metastatic disease. In 2008, the Johns Hopkins group reported the results of a retrospective study of 422 men with biochemical recurrence who deferred ADT until the development of metastatic disease [11]. In this study, the median overall survival (OS) from the time of recurrence was approximately 11 years. Though cross-trial comparisons have limited value, and these data are from a single institution, it is worth noting that the median survival in the Hopkins study is comparable with that observed in the phase 3 studies of ADT administered in patients with nonmetastatic, rising-PSA only disease [12].

On the contrary, it is clear from numerous studies that patients with biochemical relapse and a rapid PSA doubling time (PSADT) are at significant risk for the development of metastatic disease and prostate cancer-related mortality [13,14]. In 1,451 men with PSA recurrence from a large cohort study of 8,669 men treated with localized prostate cancer therapy, a PSADT of less than 3 months was associated with an approximately 50% chance of prostate cancer–specific mortality at 5 years [14]. This is comparable with the median survival for patients with de novo metastatic disease, underscoring the high-risk nature of those with a very rapid PSADT. A key understanding in the setting of biochemical relapse is that systemic disease requires systemic treatment, and local disease requires local treatment. Although some individuals with a slow PSADT and certain factors (such as positive surgical margins) may have localized recurrence, patients at the higher end of the risk spectrum (e.g., PSADT <6 mo) frequently harbor microscopic, nonradiographically evident *systemic* disease.

In men with BRPC, the timing of initiation of ADT is controversial [15,16]. The recently reported phase 3 "Timing of Androgen Deprivation" trial was designed to study whether immediate vs. delayed ADT was associated with improved long-term survival in biochemically relapsed and locally advanced patients for whom definitive local therapy was not an option [17]. Though a statistically significant improvement in OS was observed among patients assigned to immediate ADT, the study was significantly underpowered with relatively few events to definitively address the issue of optimal timing of initiation of treatment. The OCOG sponsored "Early vs. Late Androgen Ablation Trial" is currently ongoing and may shed additional light on this important issue (NCT00439751).

In the absence of definitive phase 3 clinical trial data, deciding between early vs. deferred AR-directed therapy in