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Novel Approaches for the Unfavorable Risk Patient

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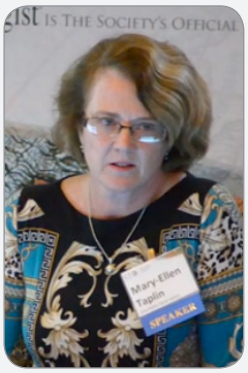

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Treatment of the High-Risk Patient: Historical Perspective

While research for prostate cancer (PRCA) has advanced significantly in recent years, clinicians still do not have a treatment approach that will lead to cure as seen with breast cancer and other malignancies. Managing the "high-risk" patient with PRCA remains a substantial challenge. High-risk localized PRCA is characterized by three main hallmarks: 1) bulky cancers (stage T3 or T4) or cancer within the capsule or seminal vesicles; 2) prostate-specific antigen (PSA) ≥20 ng/mL; and 3) a Gleason score of 8 to 10, representing a high degree of differentiation of the cancer from normal tissue. These features define a patient with high-risk localized disease as opposed to one having a low- or intermediate-risk PRCA. Untreated high-risk PRCA remains mostly a fatal disease, especially in young men not as threatened by comorbid disease and older men in good health [1,2]. Standard care for these patients comprises many choices, some of which are controversial. Prostatectomy may be considered in patients with favorable high-risk disease (e.g., high Gleason score but no palpable disease). Often the standard treatment is short- or long-term androgen deprivation therapy (ADT) combined with external beam radiation (EBR) [3]. Previous approaches combined ADT with prostatectomy and neoadjuvant chemotherapy, with adjuvant therapy not routinely used in PRCA. Hormone therapy in PRCA is castration therapy and may be accomplished with a variety of standard and newer options, including orchiectomy, anti-androgens (flutamide, bicalutamide, nilutamide, enzalutamide), leutenizing-hormone-releasing hormone (LHRH) agonists and antagonists (leuprorelin, goserelin, degarelix). A newer focus is on CYP17 inhibition. CYP17 is an enzyme involved in the formation of testosterone from its precursors, and drugs such as ketoconazole and abiraterone block this process, lowering androgen levels.

Androgen ligands are present both in the serum and the tumor tissue. Therapies either block the androgen receptor (e.g., bicalutamide, enzalutamide) or inhibit the ligand (e.g., ketoconazole, abiraterone) [4]. Earlier data from multiple studies in patients receiving ADT prior to prostatectomy demonstrated the proportion of patients who relapsed with increasing PSA post-prostatectomy was the same in the ADT and control arms, and in some cases, higher in the patients who received ADT. However, these studies were limited in the respect that they were performed before patient-risk labeling was in routine practice and contained a mix of patients, many of whom were actually low-risk, including those who would not even undergo surgery, receiving active surveillance instead [5-10]. One report that assessed duration of ADT before prostatectomy (3 months vs. 8 months) suggested that a longer duration of 8 months of therapy was better in terms of disease response; however, again, >70% of the patients in this trial were considered to have low-risk disease [11].

New Approaches to Neoadjuvant ADT

New clinical trials are focusing on the potential to cure a proportion of patients with high-risk PRCA by delineating the biology of the tumor, identifying which patients benefit from which treatments, and determining optimal treatment duration. PRCA adapts to ADT over time by increasing intracellular androgen uptake and synthesis either in local tissue or in metastases, resulting in increased serum testosterone levels. Castration-resistant prostate cancer (CRPC) cells are essentially "little pharmacies," making testosterone on their own. Within these cells, the androgen receptor is "on," PSA is being made, and a biologically active process is ongoing in the tissue [12- 14]. This set the stage supporting the concept of blocking the production of testosterone and dihydrotestosterone (DHT) by CYP17 inhibition with abiraterone/ketoconzaole. Suppression at this level also causes downstream hormone production to decrease to very low levels, making this a more intense form of ADT.

TAPS - Lupron-Bicalutamide-Dutasteride-Ketoconazole Trial

The Targeted Androgen Pathway Suppression (TAPS) trial was designed to drill up the intensity of ADT [15]. A total of 36 patients who were considered intermediate or high risk with clinically localized PRCA were randomized to leuprolide acetate (Z) along with either dutasteride (D), dutasteride plus bicalutamide (D + B), or dutasteride plus bicalutamide plus ketoconazole (D + B + K). The primary endpoint was suppression of tissue DHT >0.7 ng compared to serum castration (~1.0 ng/g), with secondary endpoints assessing serum androgen levels, tumor volume, and AR and androgen-related gene expression. Results demonstrated substantially lower DHT levels when combination therapy beyond just Z and B were used (0.02 ng/g with both Z + D and Z + B + D + K, and 0.04 ng/g with Z + B + D vs 0.92 ng/g with only Z + B). Enhanced suppression of DHT in patients receiving protocol treatment was seen with a concomitant rise in androstenedione (AED). This study demonstrated that more effective tissue androgen deprivation was achievable. The addition of high-dose SRD5A inhibition plus CYP17 inhibition resulted in prostate DHT levels 30-fold below that of standard castration therapy. This combination therapy more effectively suppressed serum testosterone and the adrenal androgen DHEA-S. However, the cancer AR-axis remained active despite the near complete ablation of tissue DHT levels, which correspond to tissue PSA expression, suggesting more effective treatments are still needed.

Abiraterone-Prednisone-Leuprolide Trial

Previous data have shown that ketoconazole is a less effective CYP17 than abiraterone, the newer agent within this class. One study assessed 58 patients with newly diagnosed intermediate- or high-risk PRCA undergoing radical prostatectomy randomized to either 12 weeks of the LHRA agonist leuprolide acetate or to leuprolide plus both abiraterone acetate and prednisone (ClinicalTrials.gov Identifier NCT00924469) [16]. A research biopsy was performed at 12 weeks to assess pathological response to therapy, prostate androgen levels, and AR signaling. Following this, all patients received leuprolide/abiraterone/prednisone combination therapy for an additional 12 weeks, and tissue was again assessed for the same parameters following radical prostatectomy. All patients that proceeded to prostatectomy had an undetectable PSA by that point. However, PSA did not correlate in any manner with the prostatectomy specimen findings. Pathology results demonstrated higher levels of treatment response in those who received 6 months of combination therapy versus those who received only 3 months. However, a significant proportion of patients in both groups had residual tumor remaining, demonstrated by positive margins and nodes, and overall results showed that patients either did very well or not well at all, with significant high-risk disease left at time of surgery. This data provided a potential dataset to look at molecular mechanisms for inherited resistance toward hormonal therapy. Combination therapy was found to significantly reduce serum DHT and DHEA levels compared with leuprolide acetate alone, and the addition of the combination regimen to leuprolide at 12 weeks led to significantly reduced DHT and DHEA levels at 24 weeks compared with leuprolide alone at 12 weeks. The study concluded that 6 months of neoadjuvant therapy prior to radical prostatectomy is feasible. Combination therapy with leuprolide/abiraterone/prednisone significantly lowered tissue androgens when compared with treatment with an LHRH agonist alone. Thirty-four percent of patients on 6 months of combination therapy had either pathological complete response (pCR; 10% of patients) or near pCR (24%), higher than historic controls. Long-term significance of pCR/near-pCR remains to be validated. Ongoing analyses will assess serum androgen metabolites by mass spectroscopy, tumor androgen receptor characteristics (amplification, mutation, splice variants, expression profiling), and whole exome sequencing of tumor tissue and normal prostate tissue. Future clinical plans include a proposed phase III trial of neoadjuvant or adjuvant abirateron-intensive ADT in high-risk patients, a phase II trial of neoadjuvant abiraterone/leuprolide/prednisone/ARN509, and a randomized phase II trial of MDV3100 (enzalutamide) alone versus enzalutamide/LHRA agonist/dutasteride.

Enzalutamide versus Enzalutamide-Dutasteride-Leuprolide

This new trial is designed as a randomized phase II trial of MDV3100 (enzalutamide) alone versus enzalutamide/LHRA agonist/dutasteride in combination in high-risk patients who will receive prostatectomy after drug therapy (ClinicalTrials.gov Identifier NCT01547299) . The primary endpoint is the pCR rate, and data are currently pending in this study.

Enzalutamide or ARN509 plus Abiraterone-Prednisone-Leuprolide

This new trial is a phase I trial of neoadjuvant abiraterone and leuprolide/prednisone in combination with a powerful AR antagonist, ARN-509. The phase I trial is currently in progress (ClinicalTrials.gov Identifier NCT01792687).

Overall, high-risk prostate cancer has a significant unmet clinical need for improved curative approaches. Development of new drugs presents new opportunities for improved response to treatment and potential cure. There remains a need to define optimal treatment regimens and duration of therapy, and phase III validation of drug trials will be imperative. To move the field forward, clinicians and researchers need to agree on an intermediate endpoint other than overall survival, such as pCR/near pCR, combined with freedom from biochemical relapse.

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