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REVIEW

Current Clinical Aspects of Androgen Deprivation Therapy for Locally Advanced and Metastatic Prostate Cancer: A Scoping Review for Urologists and Medical Providers

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Abstract: Prostate cancer (PCa) currently stands as the most common malignancy and the second most common cause of death in men worldwide. Dr. C. Huggins revolutionized the field of PCa treatment through his work investigating the therapeutic effects of androgen deprivation. These early surgical castration methods were expanded upon by integrating reversible pharmacologic castration via biologic agonists. Following this, intermittent ADT (iADT) became a medical substitute for its continuous counterpart. This data synthesis aims to highlight and assess the pertinent adverse effects of ADT, to compare mortality for PCa treatment plans, and consequently provide direction for clinicians in choosing the suitable systemic ADT approach. We performed a thorough systematic search across the PubMed database to identify prospective randomized clinical trials (RCTs) comparing continuous and intermittent androgen deprivation therapy (cADT and iADT). Our qualitative analysis aimed to evaluate the potential of iADT as an alternative treatment approach, emphasizing recent clinical outcomes. The analysis of randomized control trials in the literature revealed no discernable statistical difference in PCa-specific mortality in comparison of iADT and cADT treatments. Further, in the analysis of mortality due to non-PCa causes, iADT patients fared more favorably compared to cADT. Due to iADT's characteristics of being more cost-efficient and less likely to cause undesirable side effects, urologic healthcare professionals should be made aware of these findings when counseling patients on the optimal form of ADT and consulting for future treatment guidelines.

Keywords: androgen deprivation therapy, prostate cancer, cancer mortality

Introduction

Prostate cancer (PCa) continues to be a very prominent malignancy, ranking as one of the most common cancers globally, affecting millions of men each year (Table 1).[1] One defining characteristic of prostate cancer is disease progression without specific symptoms, leading to advanced stages undetected.[2] Once diagnosed and depending on tumor stage, a multitude of treatment options exist, including radical prostatectomy without or with local pelvic lymphadenectomy, adjuvant and early salvage radiotherapy, focal therapies, and systemic therapies.[3] For more than 80 years, androgen deprivation therapy (ADT) has proven to be effective in advanced tumor stages by suppressing serum androgens which are essential in the biology of tumor growth and progression.[4] Currently, ADT is used as monotherapy or combined with other treatment modalities. For instance, ADT improves outcomes when combined with radiation therapy for localized disease in high-risk cases.[5] Another example is ADT administered in cases with histologically proven node-positive disease which has shown improved cancer control and survival outcomes.[5] The objective of this review article is the comparison of the different forms of ADT, highlighting adverse effects, quality of life, and on cancer-specific as well as all-cause mortality for PCa patients.

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Table 1 Abbreviations Used in Text

Abbreviation	Full Term
ADT	Androgen Deprivation Therapy
BMD	Bone Mineral Density
cADT	Continuous Androgen Deprivation Therapy
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin-Releasing Hormone
HPG	Hypothalamus-Pituitary-Gonadal
iADT	Intermittent Androgen Deprivation Therapy
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone-Releasing Hormone
PCa	Prostate Cancer
PSA	Prostate Specific Antigen
PSADT	Prostate Specific Antigen Doubling Time
RCT	Randomized Control Trial

History and Biology of ADT

The fundamental concept of Androgen Deprivation Therapy (ADT) for prostate cancer (PCa) has remained largely consistent for the past eight decades, since Charles B. Huggins showcased the role of testosterone in the progression of PCa.[6] In 1941, he initially documented the remarkable clinical outcomes achieved by lowering serum testosterone levels (Figure 1a) in men with advanced prostate cancer, revolutionizing the treatment of this malignancy.[7]

The Hypothalamic-Pituitary-Gonadal (HPG) axis (Figure 2) in men represents a neuroendocrine system crucial for testosterone serum levels and the reproductive function. It involves the release of gonadotropin-releasing hormone (GnRH)

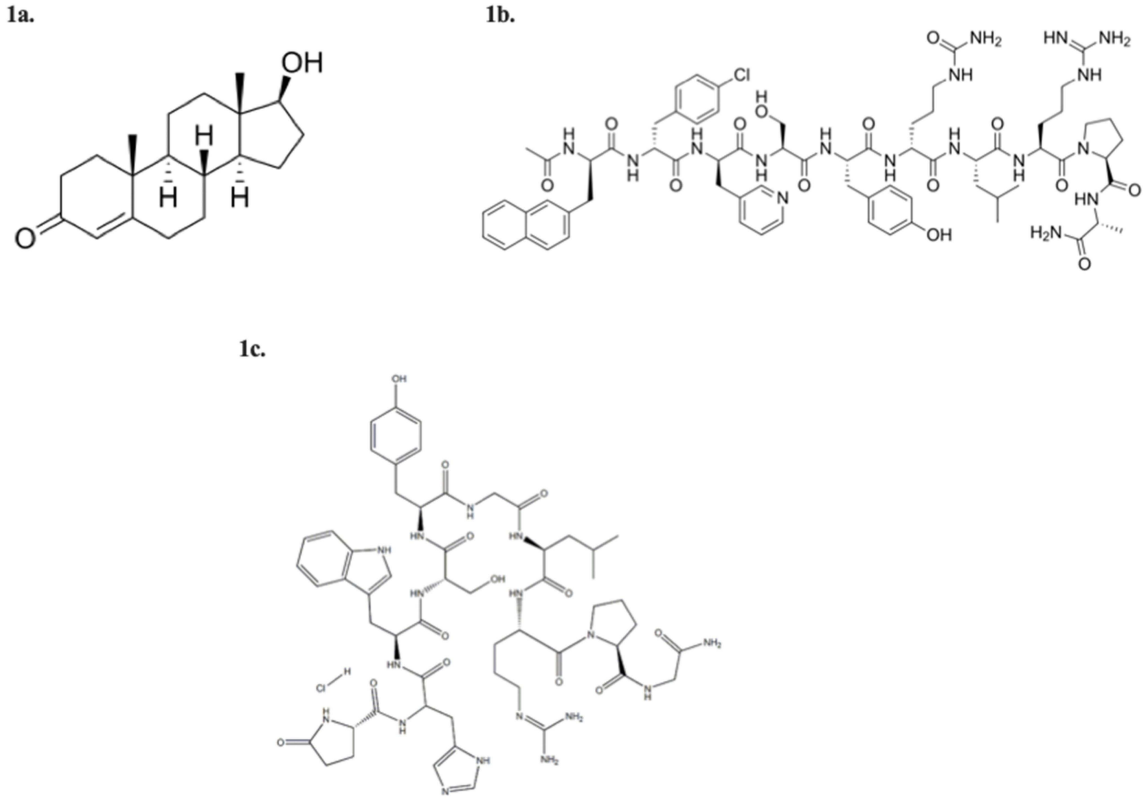

Figure 1 (a–c) Molecular Structure of Testosterone, Gonadotropin-Releasing Hormone, and Luteinizing Hormone.

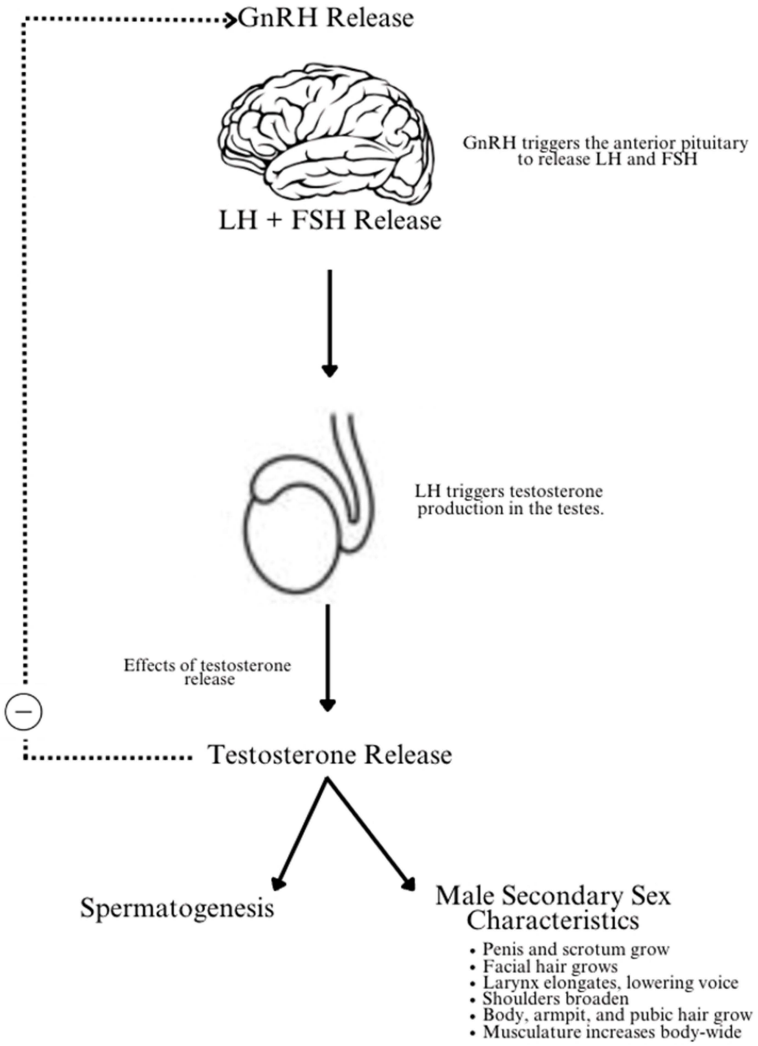

Figure 2 Hypothalamic-Pituitary-Gonadal Axis.

(Figure 1b) from the hypothalamus, stimulating the pituitary gland to release luteinizing hormone (LH) (Figure 1c) and follicle-stimulating hormone (FSH). The serum level of LH regulates the testosterone production in the testicles, whereas FSH affects the level of spermatogenesis.[8] ADT disrupts this axis, thus inhibiting the production of endogenous testosterone, generating a condition of medical castration with the aim to control or slowing down the disease progression of PCa. The most primitive form of ADT, a bilateral orchiectomy, continues to be utilized globally, especially in developing countries with less advanced healthcare systems.[9] Medical, as opposed to the original surgical, ADT options are the standard in developed countries and where they are available. Intermittent (iADT) involves cyclical treatment, where the ADT is temporarily halted, often referred to as 'treatment holidays' by clinicians, enabling the recovery of serum androgen levels to return to at or near physiological levels.[6]

ADT in advanced stages of PCa is considered to be palliative and may prolong the disease process only. Many of these patients under ADT will ultimately develop tumor recurrence and progression, a status also called "castration resistance". The clinical idea of iADT has been demonstrated in animal studies, showing that iADT delays treatment resistance (castration resistance) when compared to cADT.[10] As ADT also causes well-known and significant side effects, iADT has been clinically studied as an alternative for more than two decades.[6]

Continuous ADT

ADT is also used to great extent as an adjuvant or neoadjuvant to synergistically bolster treatment regimens alongside other prostate cancer treatment modalities. A good example is radiation therapy, which is a well-proven primary curative

treatment modality for organ-confined prostate cancer. The combination of ADT and radiation therapy has shown to be beneficial when used for high-risk cases. The first clinical trials showing this synergistic therapeutic effect were conducted more than 35 years ago by proving prolonged biochemical-free survival, a greater disease-free survival, as well as an overall survival rate when compared to patients receiving radiation treatment only.[11] Subsequent studies have confirmed these findings of decreased all-cause 10-year mortality and a 40% decrease in mortality that can be directly attributed to prostate cancer in ADT patients.[11] Investigators have suggested that the clinical efficacy of ADT adjuvant to radiation therapy is based on synergistic biochemical effects: ADT decreases the androgen-dependent cellular repair of radiation-induced DNA strand breaks.[11] Modified studies also advocated a co-dependence between radiation and the timing of ADT administration: ADT started prior to initiation of radiation therapy was more effective than adjuvant ADT started concurrent with or after radiation therapy.[11] In contrast to these synergistic effects of ADT and radiation therapy, ADT has not shown similar improved clinical outcomes when combined as neoadjuvant or adjuvant to radical prostatectomy.[12] Although tried in the past and based on these results, there is currently no indication for neoadjuvant ADT prior to radical prostatectomy. However, some investigators still think that further research into the role of adjuvant ADT post-radical prostatectomy is required.[13]

Limitations of ADT Due to Relevant Adverse Effects

Testosterone (Figure 1) is a critical sex hormone that contributes to a vast scope of biological processes and hormonal control in many different capacities. While the suppression of testosterone, characteristic of ADT, is a critical and efficacious aspect in prostate cancer treatment, such an important hormone cannot be reduced or manipulated without significant secondary systemic effects.[14]

Many adverse effects of ADT impact patients' quality of life with symptoms such as hot flashes, gynecomastia, changes in sexual and metabolic function, and cognitive changes.[15] Studies have indicated that up to 80% of patients receiving GnRH-Agonists, which is one of the most common forms of ADT used clinically, report hot flashes at some point during treatment which are often persistent for a long period.[15] Additionally, many ADT patients complain about gynecomastia, the extent of which may depend on the specific ADT treatment modalities.[16] Hot flashes and gynecomastia both severely affect the quality of life in ADT patients, which secondaryly disturbs mental health and well-being.[17]

It is well established in numerous research studies that ADT has been historically associated with metabolic syndrome, which increases patient's risk of serious diseases such as diabetes, cardiovascular events, and stroke.[18] As metabolic syndrome also impacts blood pressure, blood sugar levels, and serum triglyceride levels, ADT patients often experience weight gain, increase in body fat percentage, and decrease in lean body mass.[19] Based on these metabolic changes, ADT is highly associated with decreased insulin sensitivity, higher serum levels of hemoglobin A1c, and thus, an increased incidence of diabetes mellitus requiring specific treatment.[20] Due to low serum levels of androgens under ADT, patients also experience low libido and erectile dysfunction with no reported differences between patients under medical castration or after bilateral orchiectomy.[5]

Other significant adverse effects of ADT encompass heightened risk of developing osteopenia with secondary bone fractures, as well as alterations in cognition and mood.[5] Osteopenia is defined as decrease in bone mineral density (BMD) and is a known adverse effect of ADT. Studies have verified that an objective and unbiased decrease in BMD is seen within one year of ADT initiation, and the severity of BMD also correlates well with ADT duration.[20] Declining BMD is highly associated with fall-related bone fractures under prolonged ADT administration. Around 20% is the increased rate of bone fractures under ADT compared to 12% in prostate cancer patients not undergoing ADT.[20]

Reports on changes in mood and cognition associated with ADT are inconsistent as these clinical features are difficult to measure. While links between ADT and dementia or Alzheimer-related memory changes have been reported, other study results were inconsistent and inconclusive. One of the main limiting factors for verifying these clinical parameters is the advanced age of most prostate cancer patients undergoing ADT. As an example, one study of 1.2 million Medicare patients treated for prostate cancer without ADT indicated that 9% of those patients were ultimately diagnosed with Alzheimer's and 19% with other forms of dementia.[20] However, this study also found similar rates in patients undergoing ADT.[20] On the other hand, studies have linked the general state of hypogonadism to cognitive decline in terms of decreasing performance on memory and visuospatial testing.[21] Still, the increased prevalence of depression and anxiety is

the only change for mental health changes well documented amongst ADT patients. In one systematic review and meta-analysis of 18 different studies, there was a 41% increase in depression amongst 169,000 ADT patients.[20] Corresponding to these findings, another review also reported an increased prevalence of anxiety in a cohort of ADT patients compared to patients not receiving ADT. The incidence of anxiety also correlated well with the duration of treatment.[20]

Whereas some studies have been inconclusive on negative effects of ADT on cardiovascular health, other studies suggested a link between increased cardiovascular morbidity and mortality.[20,21] Though some researchers suggest that further studies are necessary, many clinicians are convinced that there is enough evidence of linking ADT to negative cardiovascular outcomes, and thus they warrant caution when initiating ADT treatment, especially in patients with pre-existing relevant cardiovascular comorbidities such coronary artery disease and myocardial infarction in the past.[20]

There are several other possible adverse effects associated with ADT such as anemia, fatigue, and renal injury.[20] As androgens are important for normal homeostasis in many body systems, continuous ADT has wide-reaching effects, and providers must balance the risks and benefits for this treatment option in PCa patients, in particular, in the individual context of pre-existing comorbidities. Experienced clinicians have brought up the evidence-based hypothesis that administering ADT in an intermittent fashion (iADT) may assuage these hypogonadal symptoms, thus easing the adverse effects under treatment while still accomplishing similar therapeutic control of PCa compared to continuous ADT.

Emphasis on Intermittent ADT

The conceptual basis of iADT was determined through animal studies that demonstrated suspended tumor progression compared to those subjects on cADT.[10] Further, the clinical rationales in favor of the iADT modality are based on mitigating adverse effects and pharmaceutical toxicity, all while optimizing its oncologic benefits. This is in contrast to the traditional cADT that is associated with detrimental side effects, leading many clinicians to consider iADT as a promising substitute that delivers reduced morbidity and a higher quality of life, without diminishing the assumed therapeutic benefits of suspending the disease progression of PCa. When comparing the two modalities based on mortality, a meta-analysis, consisting of twelve randomized clinical trials, revealed no statistically significant difference (Table 2).[22] Lastly, the analysis of non-PCa mortality favored iADT over cADT as a trend, though it did not quite reach statistical significance.[22]

Though iADT is typically not initiated at the start of PCa treatment, it is typically considered appropriate to be deployed 9–12 months into treatment of traditional ADT or until PSA nadir has been reached, ideally reaching PSA < 0.1 ng/mL. The "off-treatment" period in these iADT cycles depends on fluctuating PSA levels, as well as discussions built

Table 2 Comparison of iADT and cADT Outcomes

First Author	Journal	Year	Total (n)	iADT (n)	cADT (n)	Follow up Median, Max	PCa Mortality: iADT noninferiority	Non PCa Mortality: iADT noninferiority
Calais da Silva	*European Urology*	2009	626	314	312	51 mo, 12 y	N[a]	Y
Calais da Silva	*European Urology*	2014	918	462	456	66 mo, 12 y	N[b]	Y
Crook	*New England Journal of Medicine*	2012	1386	690	696	6.9 y, 11.2 y	N[b]	Y
de Leval	*Clinical Prostate Cancer*	2002	68	35	33	29 mo, 5.4 y	N[c]	X
Hussain	*New England Journal of Medicine*	2013	1535	770	765	9.8 y	N[c]	Y
Irani	*European Urology*	2008	129	67	62	42.8 mo	N[a]	N
Ito	*Cancer*	2020	280	144	136	8.2 y, 11.6 y	N[b]	N
Organ	*American Journal of Clinical Oncology*	2013	31	18	13	26.8 mo	X	X
Salonen	*Journal of Urology*	2012	554	274	280	65 mo, 11.6 y	N[b]	Y
Salonen	*European Urology*	2013	554	274	280	65 mo, 11.6 y	X	Y
Tunn	*Prostate Cancer and Prostatic Diseases*	2012	201	109	92	6.9 y	N[c]	Y
Verhagen	*World Journal of Urology*	2014	258	131	127	X	X	X

Notes: [a]Hazard ratio upper limit threshold not defined by this article; [b]Confidence interval expands beyond this article's hazard ratio upper limit threshold; [c]Authors only state iADT had more deaths, no data provided.

through the physician-patient relationship. Some urologists elect to restart iADT for their patients after these "treatment holidays" when the patient's PSA doubling time has reached less than 6 months or when serum PSA levels have reached 6–10 ng/mL, with an upper threshold of upwards above 10 ng/mL.

Based on the reported clinical trials, these two ADT methods should be considered as comparable cancer control in a long-term setting. Because these patients often live for many years under treatment, non-cancer-related mortality or all-cause mortality is relevant factors to be considered. Furthermore, iADT is much more cost-efficient for multiple vested interests: both patients and the health-care system. Despite these advantages compared to cADT, iADT remains highly underutilized in its eligible patient population.[22] This is also illustrated and reflected in the current clinical guidelines of the American Urology Association, still favoring cADT over iADT regardless of the growing body of evidence demonstrating advantageous findings. As the current guidelines are still favoring cADT, many clinicians may default to the more traditional modality. By long-term interrupting the HPG axis, cADT leaves patients vulnerable to generalized hypogonadal symptoms such as metabolic syndrome, osteoporosis, fatigue, and sexual dysfunction, all severely affecting their quality of life.[23] These adverse effects are even exacerbated in specifically older frail male patients.[21]

Gaps in Research and Future Prospects

The previous clinical trials comparing iADT and cADT have shown issues such as small cohort numbers, as well as heterogeneity of study design and protocols, all factors causing limited statistical power. Therefore, in the future, we propose that clinical trials focus on standardized study protocols and larger sample sizes to yield increased statistical power, thus minimizing treatment bias.[24] As medical knowledge and technology will evolve in the future, and patients' autonomy will continue to be prioritized, clinicians will consider more individualized assessments depending on their patient's preferences to optimize each individual treatment.[25] Physicians and guidelines are burdened to balance possible side effects, functional status, and other factors impacting quality of life throughout the disease progression. This is a complex and complicated task for the medical providers to best fit their patients' needs. Only an individual approach will enhance patient autonomy, address the very diverse biology of prostate cancer and improve the individual care. iADT has the ability to be highly versatile and adaptive in individually targeting PCa, situating it as a favorable factor in the future of PCa care.

Conclusions

Based on this scoping review of the literature, there are statistically no significant differences in PCa-specific or all-cause (non-cancer) mortalities in patients undergoing iADT versus cADT. Hence, both treatment methods can be deemed comparable in terms of long-term oncological results. Nevertheless, intermittent androgen deprivation therapy (iADT) presents a greater cost-effectiveness coupled with reduced treatment toxicity attributed to its treatment intervals, commonly known as "treatment holidays". Future clinical trials ought to prioritize comparable study protocols and substantial sample sizes to attain uniform data, enhance statistical robustness, and mitigate therapeutic biases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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