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Review Article

Pharmacotherapy of Carcinoma Prostate - Current Scenario

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ABSTRACT

Prostate is the primary site of cancer in men. This risk of prostate cancer increased with age. Nowadays, treatments combined multi-modal approach. It is very likely that, in the future, pharmacological treatment for prostate cancer will include combination therapies rather than monotherapies with many new therapies. With definite aim to remove the disease of prostate cancer from all around the world, there are so many studies are going on, exploring ways to help optimize prostate cancer treatment.

Key-Words: Prostate Cancer, Pharmacotherapy, LHRH, Agonist

INTRODUCTON

Prostate is the primary site of cancer in men. Prostate cancer, the most prevalent cancer in men worldwide, is the second leading cause of cancer related mortality in men in the western world, accounting for 15.3% of cancers. [1, 2] This risk of prostate cancer increased with age.[3, 4] In period between late 1980s to the mid-1990s, rapid increase in the incidence of prostate cancer noticed, [4, 5] while in the last decade, prostate cancer incidence has stabilized and death rates have declined. [4] This miracle made possible by the result of prostate-specific antigen (PSA) screening and early-stage prostate cancer diagnosis and treatment. [4, 5]

Nowadays, treatments combined with other types of treatment in a multi-modal approach. Prostate cancer, previously thought to be chemotherapy insensitive, is now treated at the metastatic stage by taxane-based chemotherapies. The combination of hormonal therapy and chemotherapy is currently studied at various stages of the disease, as early as localized or locally advanced prostate cancer. It is very likely that, in the future, pharmacological treatment for prostate cancer will include combination therapies rather than monotherapies.[6,7] To fight with the problem of prostate cancer, there are several new therapeutic strategies applied for the better understanding of the recent advances in pathogenesis of prostate cancer. [8] With all drugs used for the treatment, question arises how to combine these approved agents in advancement of the better results, with high-risk localized disease can increase cure rates. As Drs. Burgess and Raghavan noticed that expansion of the treatment armamentarium with drugs that work by

different mechanisms of action has generated optimism regarding the care of patients with advanced disease. This rapidly evolving treatment landscape has unearthed new opportunities, while at the same time introducing new questions in the field. [8] For better treatment prior to chemotherapy, is it necessary to integrate these agents with current therapies combines all. This includes the timing and use of the androgen-signaling-pathway blocking agents and therapeutic vaccines. [9]

The present treatment paradigm raises question for the future utility of the integration of novel androgen biosynthesis inhibitors and second-generation anti-androgens comparative with the current second-line hormone therapies, including ketoconazole and first-generation anti-androgens. [10, 11] As these effective therapies enter clinical practice. In these practices dosing and scheduling of therapies is another dilemma. Trials leading to the approval of new therapies for the prevention of adverse events were conducted in an era when patients had limited treatment options for disease control. Since many of the effective new therapies have a beneficial impact on the rate of adverse events, patients may require different schedules or, optimally, biomarkers to guide clinical decision-making.

Pathology

Pathology remains the gold standard for the diagnosis and local staging and grading of prostate cancer. [12] There is an urgent need for new biomarkers to predict outcome in prostatic carcinoma. However the search for such markers must be backed up with full and thorough assessment of all pathological criteria which might compete with a novel assessment.

Pathophysiology

There is need of stimulation from androgens for normal growth and function of the prostate cancer. [12] All the glands and organs associated are responsible for the proper functioning of the prostate as responsibility of gonadotropin-releasing hormone (luteinizing hormone (LH)-releasing hormone (LHRH)) production by hypothalamus. Result of the regular release of LHRH leads in the release of follicle-stimulating hormone (FSH) and LH from the pituitary gland, whereas continuous release of LHRH results in the suppression of FSH and LH release. [13] LH causes the Leydig cells in the testes to produce the androgen *testosterone*, which is converted to dihydrotestosterone (DHT) by 5-alpha reductase, or 5-AR. DHT has a greater affinity than testosterone for prostate androgen receptors. Growth factors and cellular signaling resulting from DHT stimulation are thought to cause progression to prostate cancer. [3, 14]

Screening

The Reduced morbidity, mortality and metastasis at the expense of overdiagnosis and overtreatment of prostate cancer is the main goal of the screening. [15] This is a debatable topic yet for prostate cancer. Lot of controversies lies regarding prostate cancer could be over diagnosed and over treated for marginal mortality benefits. [16, 17] After all controversies, The American Urological Association (AUA) recommended that screening for prostate cancer, using PSA and digital rectal examination (DRE), be started at age 40. [15]

Prevention

With reference to all research results antioxidants plays important role in prostate cancer prevention, while few recent studies showing vitamins C and E. [3, 18, 19]

Treatment

Surgery, radiation and hormone therapy are the main treatment modalities available. With increasing understanding of the molecular basis of the disease, the role of hormone treatment in prostate cancer management is being reexamined. [20]

By Drugs: To inhibit the pituitary gonadotropin secretion, the LHRH agonists as leuprolide, goserelin, and histrelin used as potent inhibitor with good pharmacologic effect [21, 22] Some nonsteroidal antiandrogens (bicalutamide, flutamide, and nilutamide) work by binding to androgen receptors in the tissues and preventing androgens from binding to their target. This is effective in androgen-dependent prostate carcinomas and has no impact on decreasing serum testosterone levels. [3, 23]

By Active Surveillance: There is need of active surveillance in the patients of localized prostate cancer. In this strategy DRE and PSA evaluation every 6 to 12 months, periodic needle biopsy, and withholding of pharmacologic, radiotherapeutic, and surgical intervention involved. Avoidance of adverse drug events of therapy and maintenance of quality of life; progression to incurable cancer and anxiety associated with untreated cancer are two of the disadvantages. [5]

By Hormonal Therapy: This therapy mainly used as standard for treatment advanced prostate cancer. It is known as androgen deprivation therapy (ADT). [24, 25] It can be either surgical castration or medical castration. [20, 24, 26] This raises pragmatic issues of compound toxicity and the emergence of adaptive pathways resistant to combination therapy. Given the multiple new effective agents recently approved for advanced prostate cancer and the additional agents currently in development, a high priority in the field for both clinical practice and research is the identification of robust surrogate efficacy biomarkers and endpoints. [27]

By Androgen Blockade: With reference to above treatments with LHRH agonists, nonsteroidal antiandrogens can prevent the surge phenomenon during the first 2 to 3 weeks of hormonal therapy. [5, 24, 25, 28]

By *Intermittent Androgen Deprivation:* This treatment used as potential treatment option to reduce both the short-term and long-term side effects associated with continuous LHRH-agonist use. [29]

***By Salvage Therapy*:** It is a multifactorial process for which few rigorous data or guidelines exist. A questionnaire survey of urologists was undertaken to obtain current perspectives on when to begin salvage therapy for biochemical failure after definitive therapy. Variables of age, grade, T-stage, nodal status, performance status, latency since prior therapy, PSA velocity, and ploidy were prioritized in four clinical situations; subsequent questions assessed consensus PSA cut-offs for beginning adjuvant therapy in 84 clinical scenarios. [30]

New Treatments

Researchers are trying to identify novel pharmacotherapies for prostate cancer. These focus on molecular targets of hormone refractory prostate cancer. [1, 31, 32] Newer avenues in androgen blockade have been investigated. Which, in contrast to agonists, bind immediately and competitively to receptors and block the receptor gene expression, leading to direct pituitary suppression. [33] Competitive blocking of the receptor results in a rapid, but reversible, decrease in LH, FSH, and testosterone without any flare.

Whether/When, To Discontinue Treatment

Another question open to investigation is whether, or when, to discontinue treatment, for which there are several definitions including prostate-specific antigen (PSA) level, clinical/symptomatic progression, or radiographic progression, for example: in the COU-301 trial, a rise in PSA level, or lack of PSA decline, on therapy was not a criterion for discontinuation of abiraterone, and thus patients may continue to gain

clinical benefit from remaining on therapy. [34]

Future Prospects

There are several therapeutic vaccines are being investigated to determine their utility for the treatment. The main benefit of the vaccines is targeted to specific tumor-associated antigens linked specifically to prostate cancer. [35, 36] These vaccines should be promoted as the future novel therapies for not even prostate cancer but for all type of cancers. [37] Clinical Endpoints in Prostate Cancer (ICECaP), has been assembled to explore endpoints that would be recognized by regulatory agencies in early trials. [8] Recent progress in our understanding of the pathogenesis of advanced prostate cancer has heralded a new era in treatment. Numerous agents now populate the treatment landscape, and an impressive number of novel agents are in development. However, many questions remain unanswered, paving the path for discovery in the future.

Current Indications and Limitations

New investigation by research and development against the prostate cancer is positive signals for the patients suffering from metastatic disease. Androgen deprivation therapy has a good place in the treatment of biological failure or PSA increase after treatment of localized disease, even without radiographic or other evidence of metastatic disease. [20] Beside the treatment, side effects including short and long-term complications such as hot flashes, fatigue, lipid perturbation, and osteoporosis, which are well known and common to all common therapies with increased risk of cardiovascular mortality in patients treated by radical prostatectomy followed by androgen deprivation. [20, 38]

Current Controversies

Controversy certainly exists about all the therapies should be initiated. Advocates of each therapy support that delaying progression translates into prolonged survival. On the other hand, advocates of delayed therapy note that there might sometimes be more side effects from therapy than from the disease itself. [39, 40] The debate about prostate cancer remains open and highly controversial.

Combination with Chemotherapy

A new avenue in pharmacological therapy for prostate cancer is the association between hormone therapy and chemotherapy. The role of systemic chemotherapy, once thought to be ineffective in prostate cancer, has more recently been shown to provide a small, but consistent survival advantage in the setting of hormone refractory metastatic prostate cancer. [1, 41, 42]

Additional results from ongoing trials, assessing the benefit of early use of chemotherapy in the course of treatment, are eagerly awaited. [1]

CONCLUSION

With definite aim to remove the disease of prostate cancer from all around the world, there are so many studies are going on, exploring ways to help optimize prostate cancer treatment. Controversy surrounds when to screen for prostate cancer and whether preventive medicine is beneficial. The use of hormonal therapy is emerging in patients with localized disease despite scarce data. With all above review of literature, it's a need to critically reexamine the treatments for the prostate cancer management with all type of therapies present. This study may be helpful in making of further strategies against the advanced prostate cancer.

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