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CASE REPORT

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The role of testosterone and prolactin in the development of advanced prostate cancer; and its successful treatment with cabergoline (dopamine agonist)

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Abstract

Advanced prostate cancer is a terminal "androgen-independent" malignancy, which results in death general within about five years. The development of prostate malignancy and progression to advanced prostate cancer, and the role of testosterone and prolactin have not been established. This presentation provides a review and concept of the development and progression of advanced prostate cancer and the implications of both hormones. Most importantly, evidence is presented to support the concept that advanced prostate cancer is "prolactin-dependent" malignancy. It is successfully terminated by cabergoline (dopamine agonist) treatment, which decreased plasma prolactin concentration by 88%. This is likely the first reported efficacious treatment for advanced prostate cancer.

Introduction

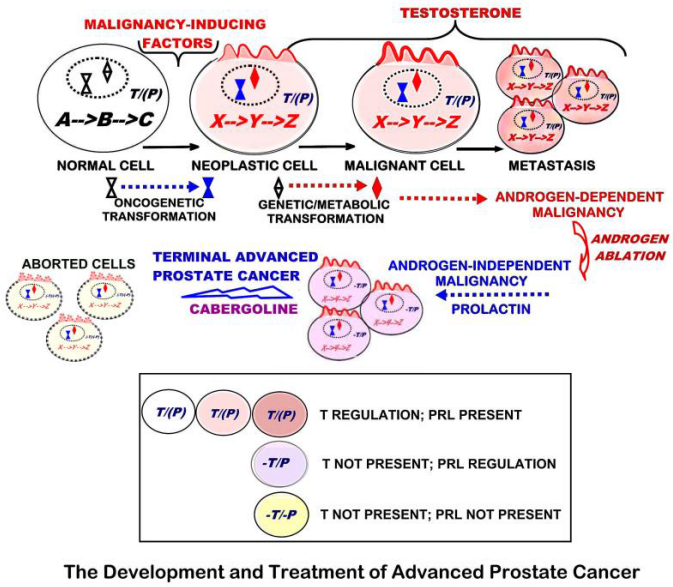
About 25,000 prostate cancer deaths/year occur in the U.S.; and 120,000/year world-wide. Most of these deaths result from terminal advanced prostate cancer; generally in less than five years. The cause of advanced prostate malignancy has not been established. This has deterred the identification of appropriate targets for efficacious treatment, and perhaps prevention, of this malignancy. The following presentation will address these issues.

Testosterone and prolactin in the development of advanced prostate cancer

The normal prostate acinar epithelial cells contain the receptors and pathways for regulation by testosterone and prolactin [1]. Testosterone is the "primary" regulator; i.e., "androgen-dependent" regulation. When testosterone is not available, prolactin regulation is manifested; i.e.,"androgen-independent/prolactin-dependent" regulation.

The oncogenic process leading to the development of prostate malignancy and its progression to advanced prostate cancer is subject to varying concepts and views; as we described in earlier reviews [2,3]. Our concept is based on the recognition that the hormonal regulation of the normal pros tateacinar epithelial cells and the malignant cells includes both testosterone and prolactin.

The malignant process (Figure 1) is initiated when the normal acinar epithelial cell is subjected to "malignancy-inducing factors"; which then induces "oncogenic factors" that transform the normal cell to a neoplastic cell. The neoplastic cell possesses malignant potential, which is manifested by its "genetic/metabolic" transformation, into provide the bioenergetic requirements for the malignant activities of the developing malignant cells. The primary site malignant cell then progresses to metastasis. This phase of prostate malignancy is promoted by testosterone as androgen-dependent malignancy. However, it is important to recognize that testosterone does not initiate the oncogenic transformation; and is not a cause of malignancy.



The Development and Treatment of Advanced Prostate Cancer

Figure 1. *Development and treatment of advanced prostate cancer.*

The preceding events provide the basis for androgen ablation treatment to eliminate the availability of testosterone and its enhancement of metastasis. When testosterone is no longer available, as with androgen ablation, androgen-independent malignancy (castrate resistant prostate cancer; CRPC) develops. Our concept proposes that this is manifested by prolactin; i.e. prolactin-dependent advanced prostate cancer.

Cabergoline (dopamine agonist) has been employed to suppress the pituitary lactotropic production of prolactin in women with hyperprolactinemia and men with pituitary adenoma [4-7]. Consequently, an efficacious treatment could be best achieved by deceased availability of plasma prolactin. We provided cabergoline treatment for a patient with terminal advanced prostate cancer [8]. Prior to treatment his CTC count (circulating tumor cell count) was 5.4; which predicts death in about 21 months. Seven weeks after treatment, the CTC count was 0. The plasma prolactin concentration decreased from 11.3 to 1.3 ug/ml (-88%).

This possibly represents the first reported case of a successful treatment that terminated advanced prostate cancer; and establishes the important role of prolactin in the development and treatment of this malignancy. It is now important to determine if cabergoline treatment will be effective in other individuals with terminal advanced prostate cancer.

The impact of unfounded prevailing views of prolactin regulation

The important role of prolactin in the development of advanced prostate cancer has been largely unrecognized and/or ignored within the medical community; including urologists and oncologists. This is apparent from a PubMed search of "prolactin and androgen-independent prostate cancer", or a search with "prolactin and castration resistant prostate cancer; which results in only about 12 citations; with only about 5 citations in the recent 10 years. A 2016 extensive review of prostate cancer, which includes over 300 references [9], makes no mention of prolactin.

In contrast, a PubMed search in the past 5 years for "advanced prostate cancer and androgen receptor" revealed 450 citations; for "androgen-independent malignancy and androgen receptor", 120 citations; for "treatment of advanced prostate cancer and androgen receptor" 420 citations. This dominant focus, along with the continued absence of an effective treatment, is testimony of the misguided prevailing views of the implication of androgen receptor in the development and treatment of advanced prostate cancer.

Another misguided view relates to the role and pathway of prolactin regulation of the prostate gland activities [10]; in regard to its implications in the development and progression of prostate malignancy. That view does not give appropriate recognition of the major role of prolactin regulation of cellular metabolic pathways by its rapid metabolic gene regulation, which is achieved via the direct PRL receptor/PKC pathway [1-3]. That metabolic activity would be associated with the development of androgen-independent malignancy of advanced prostate cancer. This is in contrast to the PrlR-Jak2-Stat5a/b signaling pathway that is manifested for the prostate gland "trophic" effects (e.g., growth, differentiation).

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Conclusions

1. Advanced prostate cancer has been an untreatable terminal malignancy; which causes patient death generally within 5 years.
2. Advanced prostate cancer is an "androgen-independent" malignancy.
3. Androgen receptor status is not a major factor in the development of androgen-independent advanced prostate cancer. Its dominant focus as a target for treatment has been misguided.
4. Terminal advanced prostate cancer is a "prolactin-dependent" malignancy. The termination of advanced prostate cancer is best achieved by elimination of plasma prolactin.
5. Treatment with cabergoline (dopamine agonist), which suppresses the lactotropic production of prolactin, successfully aborts advanced prostate cancer.

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