

Botulinum Toxin: The Promising Future of Prostate Cancer Treatment

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Abstract

Peripheral nerves have been shown to modulate the growth and spread of tumours in the prostate, feeding both cancer cells and the stroma in the tumour environment. Several *in vitro* and *in vivo* studies have reported the effect of botulinum toxin (BT) on tumour tissue in the prostate. BT in humans has been observed to cause increased apoptosis of cancer cells, with morphological changes characterized by extensive degenerative and atrophic areas of cancer, reduced cytoplasm, and pyknotic nuclei, compared to the characteristics of cancer tissues injected with saline solution. Based on this set of physiological and pathogenic knowledge, experimental, epidemiological, and clinical evidences have been generated that demonstrates the effect of BT on the control of prostate cancer, which represents a powerful therapeutic tool that would reduce mortality from prostate cancer.

Introduction

Botulinum toxin (BT) is a potent poisonous neurotoxin produced by the bacterium *Clostridium botulinum* and related species [1]. Its action consists of inhibiting neuromuscular junctions by blocking the release of acetylcholine and desensitizing sensory nerves. When applied to the prostate, its effects are not only limited to the neuromuscular junction but also extend to the neuroglandular junction [2].

The use of BT in the prostate was first described by Doggweiler et al. [3], who studied its effect in 30 rats, finding generalized atrophy of acinar cells, as well as diffuse glandular apoptosis. This effect was confirmed in 2 subsequent studies in rats and dogs, respectively [4,5]. In humans, Kuo et al. [6] confirmed the effect of generalized atrophy of glandular cells obtained before and after injection of BT; and Chuang et al. [4] described a negative regulation of α 1A-adrenergic receptors in the rat prostate without changes in androgen receptors.

BT can induce prostatic involution without causing local inflammation or significant systemic side effects. This should stimulate new research on its effect on both benign and malignant prostate lesions, for which with current evidence it is possible to propose correctly designed

clinical trials aimed at experiencing its action in prostate cancer [2].

Development

Nerves are critical regulators of the prostate and are involved in the embryological development of the pelvic floor [7]. As in the homeostasis of the non-diseased prostate [8], and the tumorous prostate for many decades, nerves were only recognized as pain carriers. [9] However, peripheral nerves have shown to modulate tumour growth and spread, feeding both cancer cells and stroma in the tumour environment [10,11]. This nervous dependence of tumours received initial attention due to invasion perineural, in which cancer cells migrate and invade nerves [12]. Although the perineural invasion was recognized long before as a complex physical interaction between cancer cells and nerves, a growth-stimulating interaction between each other has been experimentally demonstrated in the past two decades between cancer cells and neurons. Molecular signals derived from the tumour guide nerve infiltration into the tumour environment, while nerves that infiltrate the tumour provide molecular support to promote tumour growth and spread [9].

Ayala et al. [13] demonstrated that the growth and directionality of sensory neurons, and the proliferation and

migration of prostate cancer cells were mutually beneficial when grown together. Thaker et al. [14] demonstrated that stress-activated adrenergic signals promote tumour growth, which means the critical participation of sympathetic nerves in tumour progression. In 2013 Magnon et al. [15] demonstrated that adrenergic signals in stromal cells are essential for tumour genesis and that the lack of cholinergic signals in stromal cells prevents prostate cancer metastasis.

The innervation of prostate cancer appears to be initiated by neurotrophic growth factors, such as the precursor to nerve growth factor secreted by tumour cells; in addition, and the contribution of brain-derived neural progenitor cells has also been reported [16].

Prostate cancer induces axonogenesis and neurogenesis. This process begins at the level of preneoplastic high-grade prostatic intraepithelial neoplasia [17]. Also, nerve cancer interactions during perineural invasion result in a survival advantage for cancer cells [18].

Based on this set of physiological and pathogenic knowledge, experimental, epidemiological, and clinical evidence have been generated. These demonstrate the effect of BT on the control of prostate cancer, which represents a powerful therapeutic tool that would reduce mortality from prostate cancer.

Karsenty et al. [19] reported inhibition of the growth of LNCaP and PC3 cells *in vitro* and *in vivo* (prostate cancer xenografts in mice) after application of botulinum toxin. TB significantly reduced LNCaP cell proliferation, as well as increased apoptosis in a dose-dependent manner, but did not affect PC3. Proietti et al. [20] conducted similar experiments with a dose of 15 U/mL of TB and observed a reduction in the mitotic index in the LNCaP and PC 3 lines. Furthermore, botulinum toxin increased the expression of phosphorylated phospholipase A2 (PLA2). It was suggested that TXB-A inhibits the expression of activated PLA2, which may reduce the synthesis of arachidonic acid and eicosanoids.

Eicosanoid products of the cyclooxygenase (COX) and lipoxygenase (LOX) pathways are important mediators of the proliferation of prostate cancer cells in culture and regulate tumour vascularisation and metastasis in animal models. Pharmacological agents that block either COX or LOX products effectively reduce the size of prostate cancer xenografts. Recently, PLA2 enzymes, which regulate the provision of arachidonic acid to both COX- and LOX-derived eicosanoids, are found to also regulate the growth of prostate cancer cells and tumours [21]. Dong et al. [22] showed that secretory PLA2 is overexpressed in almost all human prostate cancer specimens and its elevated levels are correlated with high tumour grade. It is reasonable

that BT is expected to act not only by producing apoptosis of neoplastic cells but also on factors that promote tumour growth.

In the study by Coarfa et al. [23], BT treatment in humans resulted in increased apoptosis of cancer cells in the BT treated side ($p=0.0020$). A similar denervation gene array profile was identified in tumours arising in denervated rodent prostates, in patients with spinal cord injury, and in the BT treated side of patients. The induced denervation exhibited a characteristic genetic profile, indicating translation and bioenergetic arrest. Examination of the tissue removed at the time of prostatectomy revealed marked morphological changes on the BT-injected side, with extensive cancer atrophic and degenerative features, reduced cytoplasm, and pyknotic nuclei, as compared to features in the saline-injected cancer tissues. Apoptotic cancer cells were also identified in regions of perineural invasion. No significant changes in proliferation were observed, as assessed by Ki67 staining.

An interesting aspect with impressive therapeutic implications is the use of BT as an enhancer for chemotherapy or radiotherapy. Ansiaux et al. [24] shown that local administration of BT type A in mouse tumours (fibrosarcoma and hepatocarcinoma) substantially increases tumour oxygenation and perfusion, leading to a substantial improvement in tumour response to radiotherapy (20 Gy of 250 -kV) and chemotherapy (cyclophosphamide, 50 mg/kg). This observed therapeutic gain results from an opening of the tumour vascular bed by BT type A because BT type A could inhibit the neurogenic tone in the tumour vasculature.

Vezdrevanis et al. [25] described the case of a 68-year-old man with metastatic prostate cancer with a baseline serum PSA level of 521 ng/mL, Gleason score 4 + 4 = 8, and extensive bone disease. Transrectal ultrasound revealed a single localized hypoechoic area, which was administered an intraprostatic transperineal injection of BT type A, with a dose of 1 000 units (Dysport™/Ipsen) diluted in a solution of water for injection of adrenaline at 0.5%. Two months after treatment with BT, transrectal ultrasound of the prostate did not reveal any hypoechoic lesions, the total volume of the prostate fell from 48.8 to 34.3 cm³ (30% reduction), and the serum PSA level decreased to 101 ng/mL.

Concerning the possible adverse effects caused by the local application of BT, sufficient clinical evidence has been described to show that the therapeutic application of BT is safe and easy to carry out [26]. In the series by Arnouk et al. [27] it was reported that complications were rare and appear to be related to urethral manipulation (gross hematuria, transient urinary retention, and acute prostatitis) rather than a direct result of BT injection.

Rodrigues et al. [28] in a 2-year follow-up study described that the side effects of BT injection are limited to acute prostatitis.

Given the vascular nature of the prostate, systemic absorption of the toxin could occur. However, no systemic complications have been reported after intraprostatic injections, even with 300 U of BT [29]. It is known that the diffusion of BT from the injection site depends in part on an active binding component that targets receptors, to nerve endings or on gland surfaces; so, the diffusion halo can vary in size and shape, depending on the number of receptors [30].

Additionally, Silva et al. [31] observed that the intraprostatic injection of botulinum toxin does not cause a deterioration of sexual function, that is, it does not affect the erectile, orgasmic, or ejaculatory function and does not alter libido.

Although more research is required to clarify the mechanisms of action of BT on malignant tumour cells in the prostate, research to experiment with the action of BT in prostate cancer should be promoted.

Conclusion

Promoting research on the use of BT as a treatment for prostate cancer would allow findings that will lead to new therapeutic approaches since the chemical denervation produced by BT consistently affects the growth and expansion of prostate cancer.

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