TREATMENT OF BENIGN PROSTATIC HYPERPLASIA (BPH) & PROSTATE CANCER

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Aims and Objectives

- Enlist the drugs used for the treatment of BPH
- Classify alpha blockers
  Role of alpha blockers, 5-alpha reductase inhibitors and combination therapy in BPH
  Adverse effects of the drugs used to treat BPH.
- Enlist the drugs used for the treatment of prostate cancer
- Briefly describe the mechanism of action of drugs used in the treatment of prostate cancer

PROSTATE

Prostate and the seminal vesicles are part of reproductive system in males.

The prostate and the seminal vesicles make fluid for the semen.

During ejaculation sperms move out of urethra and at the same time fluid from the seminal vesicles and prostate also moves into the urethra. This mixture moves out of the urethra and penis leading to ejaculation.

BPH

Benign prostatic hyperplasia (BPH), also known as prostate enlargement, is a noncancerous enlargement of the prostate gland that affects almost all men as they age. Symptoms include:

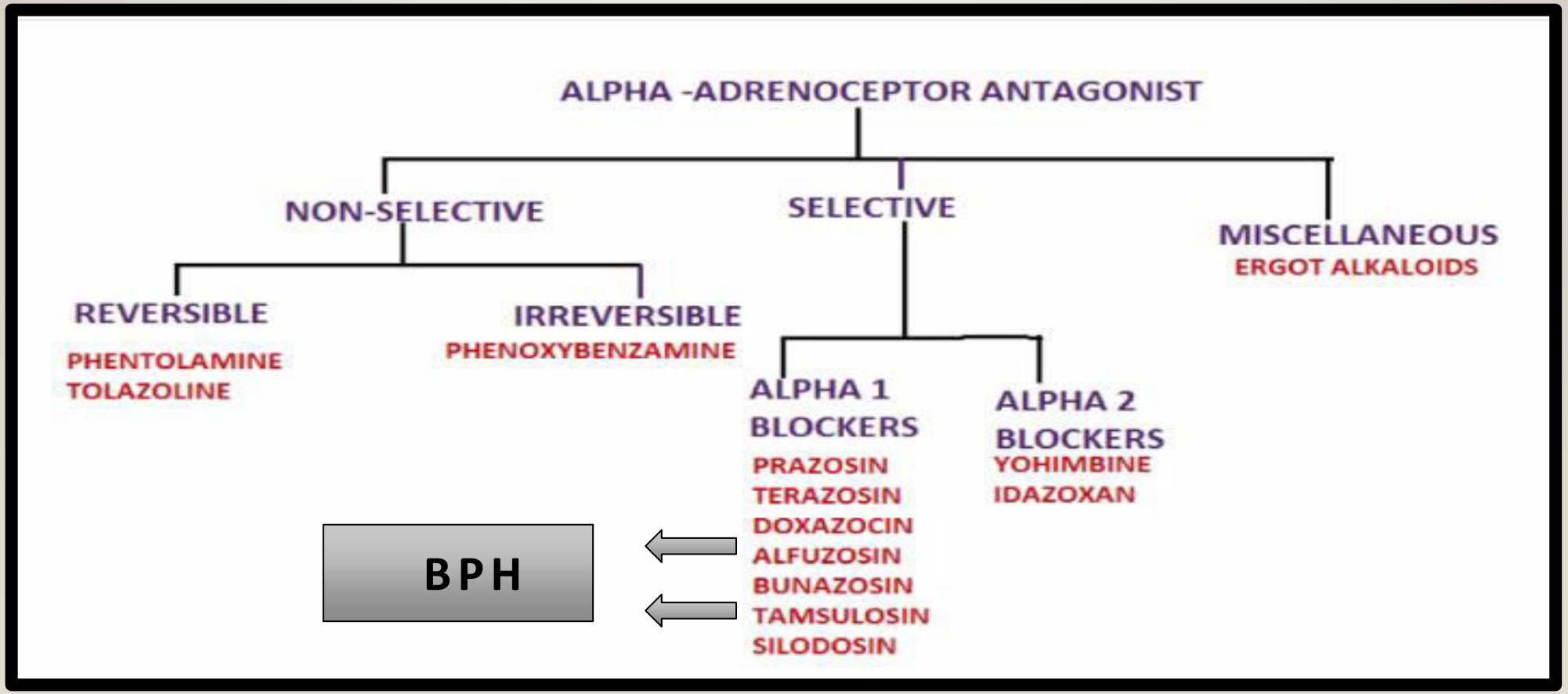
- Difficulty starting to urinate / Weak urine stream
- Dribbling at the end of urination
- Frequent urination (Urgency)
- Sensation of incomplete bladder emptying (hesitancy)
- Frequent awakening at night to urinate/ Incontinence

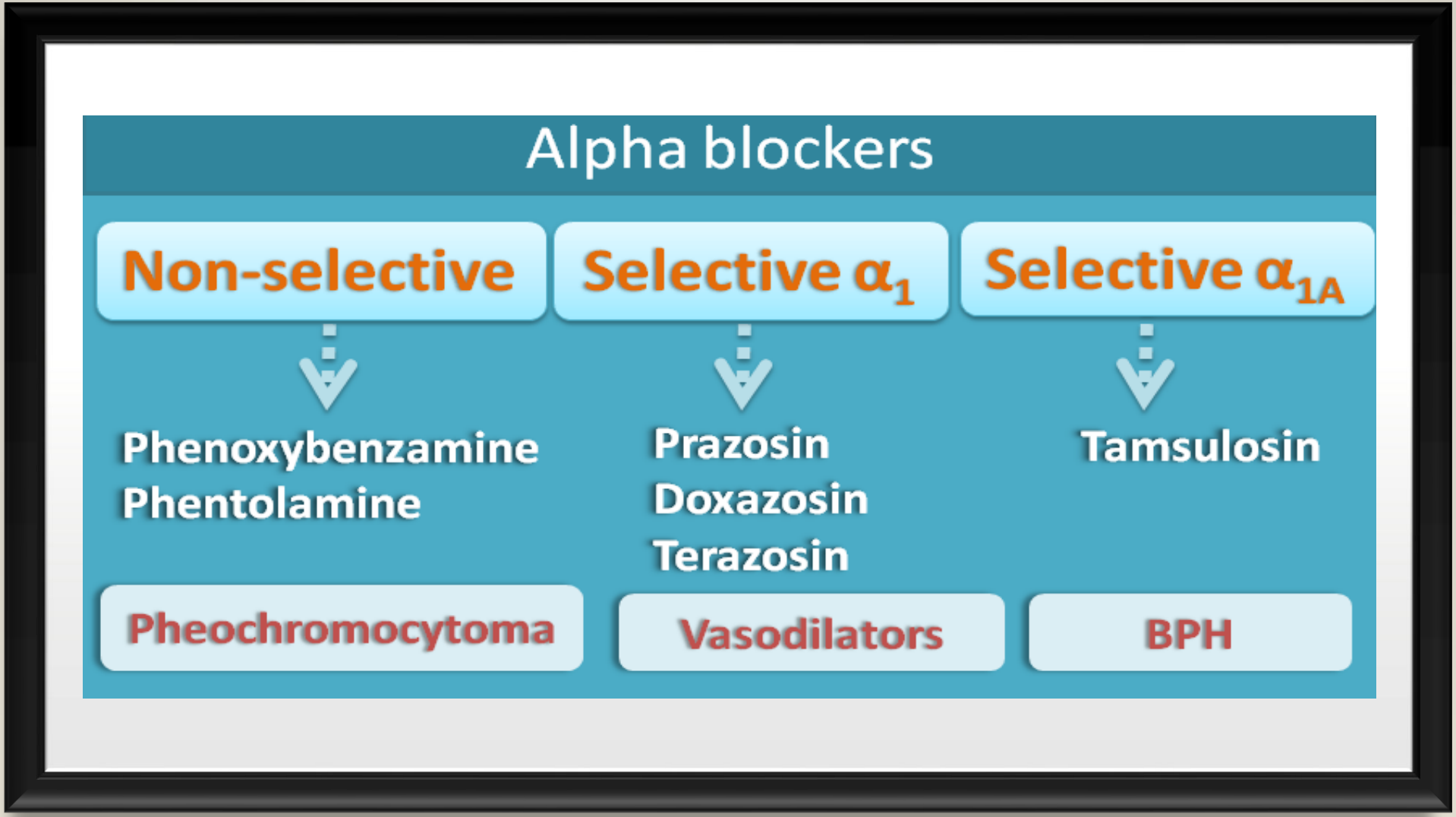
Pharmacotherapy of BPH

α_1 Blockers:

5-α- Reductase Inhibitors

α_1 Blockers:




Alpha blockers
Non-selective
Selective α_1
Selective α_{1A}
Phenoxybenzamine
Phentolamine
Prazosin
Doxazosin
Terazosin
Tamsulosin
Pheochromocytoma
Vasodilators
BPH

Mechanism of Action of Tamsulosin

Tamsulosin

Blockade of the α_1**a** receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow. It has the least effect on blood pressure because it is less selective for α1B receptors found in the blood vessels and more selective for α1A receptors in the prostate and bladder.

Side Effects of α_1 Blockers

α1-Blockers may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension

FIRST DOSE PHENOMENON:

First dose of these drugs may produce an exaggerated orthostatic hypotensive response, may lead to syncope This action, termed a “first-dose” effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime.

By blocking α receptors in the ejaculatory ducts and impairing smooth muscle contraction, α1 antagonists may cause inhibition of ejaculation and retrograde ejaculation.

Finasteride

Finasteride -------- 5 α-reductase inhibitor

It inhibits the conversion of testosterone to dihydrotestosterone (DHT). DHT causes the prostate to grow and enlarge. Inhibition of this conversion decreases the size of prostate and improves urinary outflow.

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5 -α– REDUCTASE INHIBITORS

FINASTERIDE AND DUTASTERIDE

For symptom improvement, 5-ARI monotherapy should be used as a treatment option in patients with **LUTS/BPH** with prostatic enlargement as judged by a prostate volume of > 30g on imaging, a prostate specific antigen (PSA) > 1.5ng/mL, or palpable prostate enlargement on digital rectal exam (DRE).

SIDE EFFECTS OF 5-ALPHA REDUCTASE IHIBITORS

- Sexual dysfunction, including erectile & Ejaculatory dysfunction, decreased libido.
- Gynecomastia, or enlargement of breast tissue in men
- Depression, Anxiety
- Infertility
- High-grade prostate cancer
- Cardiovascular morbidity/risk factors

COMBINATION THERAPY

5-alpha receptor inhibitors, alone or in combination with alpha blockers are recommended as a treatment option to prevent progression of LUTS/BPH and/or reduce the risks of urinary retention and need for future prostate-related surgery.

WHAT IS PROSTATE CANCER?

- When the cells in prostate start proliferating abnormally this leads to prostate cancer.
- Not all the tumors are cancerous.
- Some are benign called (BPH) Benign Prostatic Hyperplasia.
- Some are cancerous called prostatic cancers.

MAJOR GROUPS OF ANTI-CANCER DRUGS

1. Alkylating agents
2. Antimetabolites
3. Natural products
   - Vinca alkaloids
   - Epipodophyllotoxins
   - Taxanes
   - Antibiotics
   - Camptothecines
   - Enzymes
4. Miscellaneous Agents
   - Hydroxyurea
   - Imatinib
5. Hormones and antagonists

Treatment of prostate cancer

Prostate cancer is responsive to hormonal manipulation leading to elimination of testosterone production

- chemical castration/ medical castration.

Bilateral orchiectomy (surgical castration)

or estrogen therapy in the form of diethylstilbestrol was previously used as first-line therapy.

Hormones (first line)

estrogen are

- Physiological antagonists of androgens
- They antagonize the effect of androgens in androgen dependent prostatic carcinoma also impact the epigenetics and genetics androgen production.
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Fosfestrol (prodrug) is activated to **stilbesterol** in the prostatic tissue.
It achieves high concertation in the prostate therefore preferred in prostatic carcinoma.
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hormonal replacement with diethylstilbesterol is effective in symptoms control for 2 years.
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Hormones (second line)

- Second-line hormonal therapies include aminoglutethimide (Acromatose inhibitor) plus hydrocortisone,
- antifungal agent ketoconazole plus hydrocortisone,
- or hydrocortisone alone.

Aspect	Aromatase Inhibitors	Diethylstilbestrol (DES)
Mechanism	Inhibit enzymes in androgen biosynthesis	Synthetic estrogen with estrogenic effects
Target	Androgen biosynthetic pathway	Androgen production and signaling, impact on epigenetics and genetics
Action	Reduces androgen levels	Suppresses androgen production
Effect on Prostate Cancer	Inhibits prostate tissue growth	Impacts cancer growth
Pathway	Androgen synthesis inhibition	Estrogenic pathways
Strategy	Hormone level alteration	Hormone level alteration
Outcome	Affects cancer cell behavior	Affects cancer cell behavior

COMPARISON OF FIRST - AND SECOND-LINE HORMONAL THERAPY

Treatment of prostate cancer Hormone /anti-androgens

Presently, the use of

- luteinizing hormone-releasing hormone (LHRH) agonists— including
- leuprolide and goserelin agonists

(alone or in combination with)

- an antiandrogen (e.g, flutamide, bicalutamide, or nilutamide)—

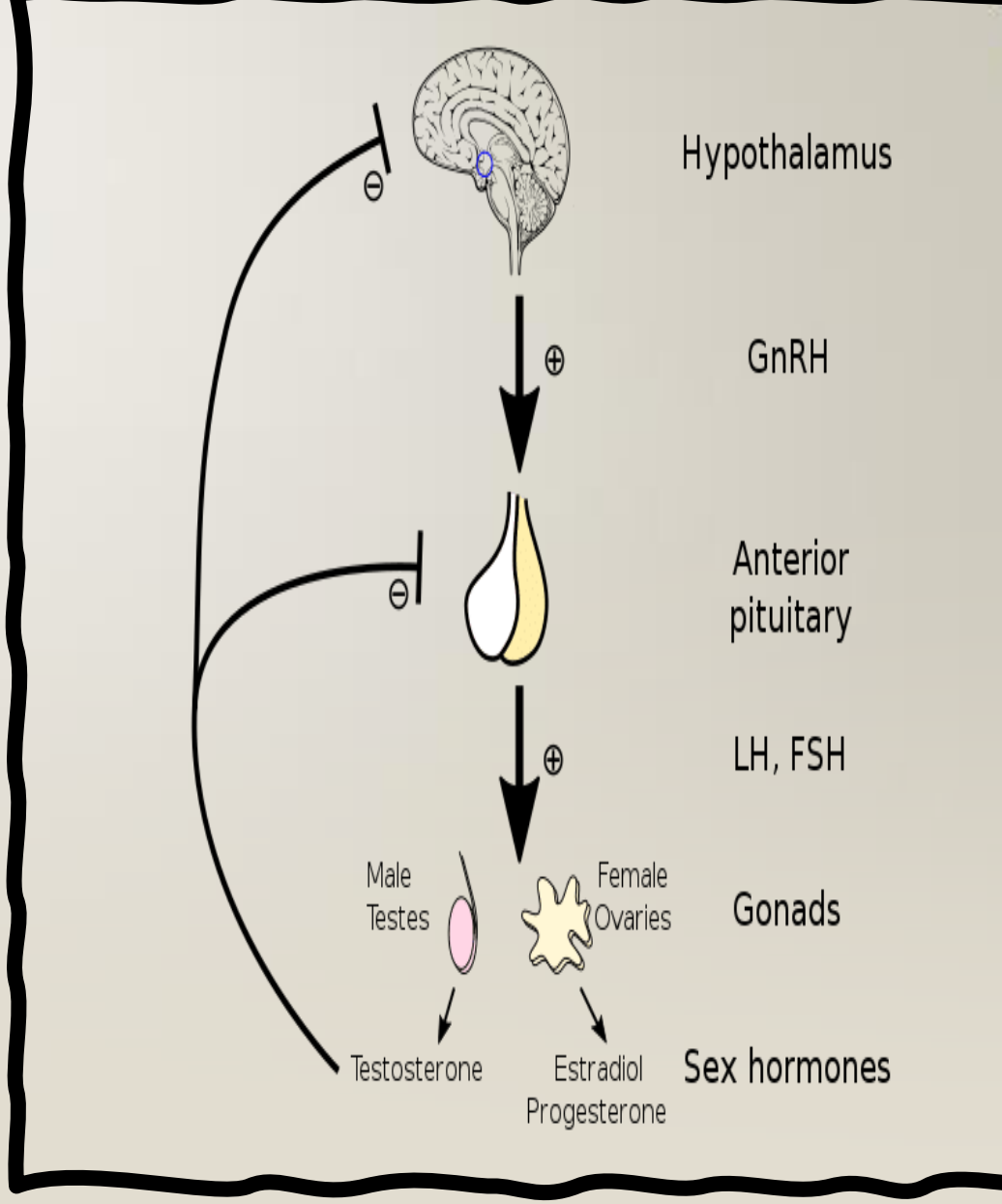
is the preferred approach.

- Finasteride -------- 5 α-reductase inhibitor.

luteinizing hormone-releasing hormone (LHRH) agonists

Leuprolide & Goserelin (LHRH)
Administration of these agents increase FSH and LH.
Continuous administration causes down regulation of receptors of LHRH in the pituitary. This leads to medical/chemical castration, making it a well-established therapy for advanced prostatic carcinoma.

Leuprolide & Goserelin (LHRH)
Hormonal therapy relieves bone pain in 70-80% of patients.
Goserelin is associated with the reduction in PSA levels.



Anti-Androgen
Flutamide

Flutamide:
it is an NSAID
Blocks the androgen at receptor level.

Androgens, such as testosterone and dihydrotestosterone (DHT), are male hormones that are necessary for the growth of prostate cancer cells. Androgens bind to and activate the androgen receptor (AR), a protein in prostate cells, which then stimulates the expression of genes that cause prostate cells to grow.

Flutamide

Bicalutamide

nilutamide

Finasteride

Finasteride -------- 5 α-reductase inhibitor

It inhibits the conversion of testosterone to dihydrotestosterone (DHT). DHT causes the prostate to grow and enlarge. Inhibition of this conversion decreases the size of prostate and improves urinary outflow.

It is usually used along with Flutamide (anti-androgen) for palliative treatment of advanced prostatic cancer.

Glucocorticoids

Glucocorticoids are used as adjuvant therapy because they have

- **Anti-inflammatory effect and decrease edema associated with tumors**
- **Foster a feeling of well being**
- **Suppress Hypersensitivity reaction associated with anti-cancer drugs**
- **Control hypercalcemia (caused by secretion of PTHr peptide, accounting for hypercalcemia in prostate cancer)**
- **Potentiate the antiemetic effect of Ondansetron/Granisetron/Metachlopromide**

Treatment Of Advanced Prostate Cancer Refractory To Hormonal Therapy

Mitoxantrone (antibiotic)+ Prednisone(glucocorticoid)

Effective as palliative treatment in those experiencing severe bone pain.

Mitoxantrone:(anthracycline derivative) (dihydroxyanthracenidione)

- release free radicals causing membrane lipid peroxidation
- Breakage of DNA strands
- Direct oxidation of purines/pyrimidines/thiols/amines .

Adverse effects:

Acute and chronic cardiotoxicity

Dark blue discoloration of fingernails/urine and sclera.

Myelosuppression/neutropenia/mucositis.

ECG abnormalities /pericarditis/myocarditis.

Treatment Of Advanced Prostate Cancer Refractory To Hormonal Therapy

Estramustine + Taxanes (Docetaxel/Paclitaxel).

Response rate is > doubled to 40-50%

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MOA of Estramustine.

Estramustine is a conjugate of estradiol and alkylating agent, which binds to microtubule-associated proteins and tubulin of cells, thereby inhibiting activity of microtubules and leading to anaphase arrest (Anaphase is the stage of mitosis after the process of metaphase, when replicated chromosomes are split and the newly-copied chromosomes are moved to opposite poles of the cell). It also has additional anticancer benefit given antiandrogen effects due to the estradiol component.

MOA of Taxanes:

They bind to β –tubulin, stabilizing the microtubules in abnormal form and inhibits further mitosis.

Treatment Of Advanced Prostate Cancer Refractory To Hormonal Therapy

Docetaxel (Taxanes)+ Prednisone(glucocorticoid)

This is combination has more increased the survival rate as compared to that achieved with Mitoxantrone Prednisone.

It is currently considered to be standard care for hormone refractory – prostate cancers.


Thank You