Hormonal Treatment of Prostate adenocarcinoma

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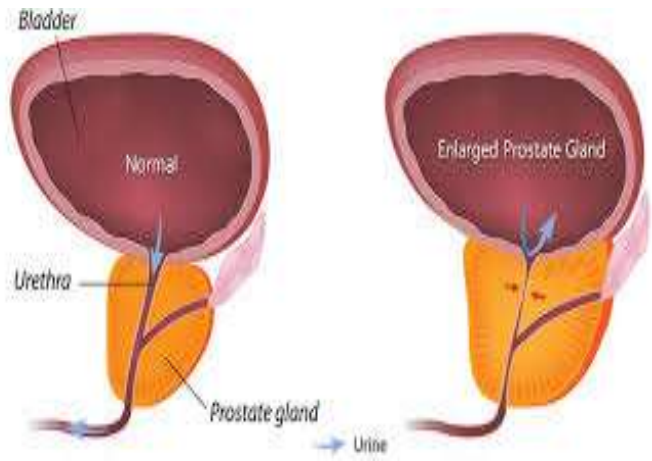
Prostate gland



Prostate Cancer

Types:

- Adenocarcinoma > 95%, Primary
- Transitional cell carcinoma
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Sarcoma

Prostate Cancer

- P ca is the most common non-skin cancer affecting men

- Men have 1 in 6 life time risk of developing P Ca.

- The second leading cause of cancer death in American men

- About 30% of men >50 years have P Ca at autopsy.

Prostate Cancer
Risk Factors

- Aging
- Smoking
- Hereditary

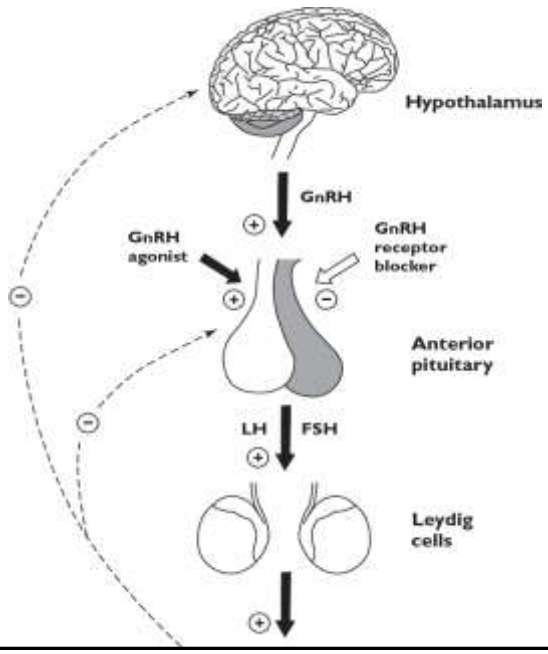
- *Environmental ???*
- *Dietary ???*

Prostate Cancer

- P Ca rarely causes symptoms early in the course of the disease.
- The majority of P ca arise in the periphery of the gland distant from the urethra.
- It is a Heterogenous, often, a slowly progressive disease.

Prostate Cancer

Vs



ANDROGEN DEPRIVATION THERAPY - ADT

I- Neoadjuvant ADT

a- Before RP vis strongly discouraged.

b- Before XRT prolongs survival

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II- Adjuvant ADT:

a- XRT (delay in recurrence).

b- +ve LN following RP resulted in improved OS

III- ADT for Advanced Disease

PSA recurrence (post RP, post XRT)

locally advanced

metastatic disease

FORMS OF ANDROGEN DEPRIVATION THERAPY

- Castration
  - A- Surgical
  - B- Medical
    - LHRH agonists
    - LHRH antagonists
- Antiandrogen
  - A- Steroidal
  - B- Nonsteroidal

Hormonal Treatment of Prostate Cancer

Current methods have shown that the mean value after surgical castration is 15 ng/dL. Therefore, a more appropriate level is defined as < 20 ng/dL.

This new definition is important as better results are repeatedly observed with lower levels compared to 50 ng/dL.

However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in P Ca is still < 50 ng/dL

Hormonal Treatment of Prostate Cancer: *LHRH agonists*

- Long-acting LHRH agonists are main forms of ADT. These synthetic analogues of LHRH, are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis.
- After the first injection, they induce a transient rise in LH and FSH leading to the 'testosterone surge' or 'flare-up' phenomenon, which starts 2-3 days after adminstration and lasts for about 1 week.

Hormonal Treatment of Prostate Cancer: *LHRH agonists*

- Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within 2-4 weeks.
- Although there is no direct comparison between the various compounds, they are considered to be equally effective and comparable to orchiectomy.

Hormonal Treatment of Prostate Cancer: *LHRH agonists*

Flare-up phenomenon

- Might lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression.

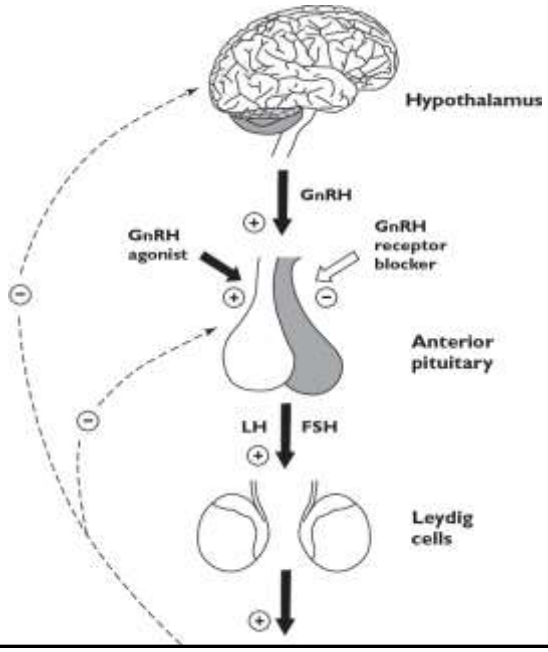
- Patients at risk are usually those with high-volume, symptomatic, bony disease.

- Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely remove the risk.

Hormonal Treatment of Prostate Cancer: LHRH antagonists, ***Degarelix***

- Luteinizing-hormone releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare.

- The practical shortcoming of these compounds is the lack of a long-acting depot formulation with only monthly formulations being available.



Hormonal Treatment of Prostate Cancer: LHRH antagonists, *Degarelix*

- Degarelix is an LHRH antagonist with a monthly subcutaneous formulation. The standard dosage is 240 mg in the first month, followed by monthly injections of 80 mg. Most patients achieve a castrate level at day 3.
- An extended follow-up has been published, suggesting a better PFS compared to monthly leuprorelin.

Hormonal Treatment of Prostate Cancer: *Anti-androgens*

These oral compounds are classified according to their chemical structure as:

- steroidal, e.g. cyproterone acetate (CPA)
- non-steroidal or pure, e.g. flutamide and bicalutamide.

Hormonal Treatment of Prostate Cancer: Anti-androgens

Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal anti-androgens and leads to an unchanged or slightly elevated testosterone level.

Conversely, steroidal anti-androgens have progestational properties leading to central inhibition by crossing the blood-brain barrier.

Hormonal Treatment of Prostate Cancer: *Anti-androgens*

- Cyproterone acetate:

  was the first licensed anti-androgen, the least studied.

- Flutamide:

  The non-androgen pharmacological side-effect of is diarrhea & Liver dysfunction

Hormonal Treatment of Prostate Cancer: *Anti-androgens*

Bicalutamide

- The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy.
- The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%).
- However, bicalutamide monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists.

Hormonal Treatment of Prostate Cancer: *Non-steroidal anti-androgens*

Do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density are frequently preserved.

Bicalutamide showing a more favourable safety and tolerability profile than flutamide and nilutamide.

All three agents share a common potential liver toxicity (occasionally fatal) therefore, patients' liver enzymes must be monitored regularly.

Hormonal Treatment of Prostate Cancer

- Median survival of M1 patients is at least 42 m
- M1 population is very heterogeneous. Several prognostic factors for survival have been suggested including the number and location of metastases, Gleason score, PS status and initial PSA.

Hormonal Treatment of Prostate Cancer

Based on a large SWOG 9346 cohort, PSA level after 7 months of ADT was used to create 3 prognostic groups:

G1: PSA < 0.2 ng/mL and a median survival of 75 M

G2: PSA < 4 ng/mL with a median survival of 44 m

G3: PSA > 4 ng/mL and only 13 m median survival

Hormonal Treatment of Prostate Cancer

First-line hormonal treatment

There is no level 1 evidence for, or against, a specific type of ADT, whether orchiectomy, an LHRH analogue or antagonist

Except in patients with impending spinal cord compression for whom either a bilateral orchiectomy, or an LHRH antagonist are the preferred options

Hormonal Treatment of Prostate Cancer: (Castrate Resistant PC)

CRPC is considered to be mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent.

In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells, and an over-expression of the AR has been observed.

This has led to the development of 2 new compounds targeting androgen axis: abiraterone acetate and enzalutamide. Both are currently approved for CRPC.

Hormonal Treatment of Prostate Cancer: CRPC

AA is a CYP17 inhibitor (Zytiga), significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside the cancer cells. Prednisone be used together with AA to prevent drug-induced hyperaldosteronism.

Enzalutamide (Xtandi) is a novel anti-androgen with a higher affinity than bicalutamide for the AR receptor. While non-steroidal anti-androgens still allow transfer of ARs to the nucleus, enzalutamide also blocks AR transfer

Hormonal Treatment of Prostate Cancer: *Intermittent versus continuous ADT (IAD)*

Eight RCTs of which only three were conducted in patients with M1 disease only. The five remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

The SWOG 9346

At best only 50% of M1b patients might be candidates for IAD, i.e. the best PSA responders.

The results did not show a significant inferiority for any treatment arm.

Hormonal Treatment of Prostate Cancer: *Intermittent versus continuous ADT*

- Other trials did not show any survival difference.
- These reviews and the meta-analysis came to the conclusion that there was no difference in OS or CSS
- There is a trend favouring IAD in terms of QoL.

Hormonal Treatment of Prostate Cancer: IAD

- Other possible long-term benefits of IAD include bone protection and a protective effect against metabolic syndrome.
- IAD is associated with a very significant decrease in treatment costs. IAD is feasible and accepted by the patients.
- The PSA threshold at which ADT must be stopped or resumed still needs to be defined in prospective studies .

Hormonal Treatment of Prostate Cancer: IAD

- ADT should be stopped only if patients have fulfilled all of the following criteria:
  - well-informed and compliant patient;
  - no clinical progression;
  - clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease.

Hormonal Treatment of Prostate Cancer: IAD

- Strict follow-up is mandatory, with clinical examination every 3-6 months.
- Treatment is resumed when the patient progresses clinically, or has a PSA rising 10-20 ng/mL in M1 patients.

- The same treatment is used for at least 3-6 months.
- Subsequent cycles of treatment are based on the same principles until the first sign of castration resistance become apparent.

- Patients who will benefit most from IAD are those with good PSA response

Hormonal Treatment of Prostate Cancer: Early vs. deferred ADT

The VACURG I and II trials, The MRC trial, The ECOG 7887 study

All of these studies were conducted in the pre-PSA era

- No improvement in OS was observed in the M1a/b population
- Early ADT significantly reduced disease progression and associated complications

- The ***ASCO*** guidelines conclude that it is not possible to make a recommendation on when to start initial HT in advanced asymptomatic PCa
- The ***ESMO*** guidelines do not comment on this topic

Treatment Strategy?

Balance