Hormone Therapy : First Line Treatment

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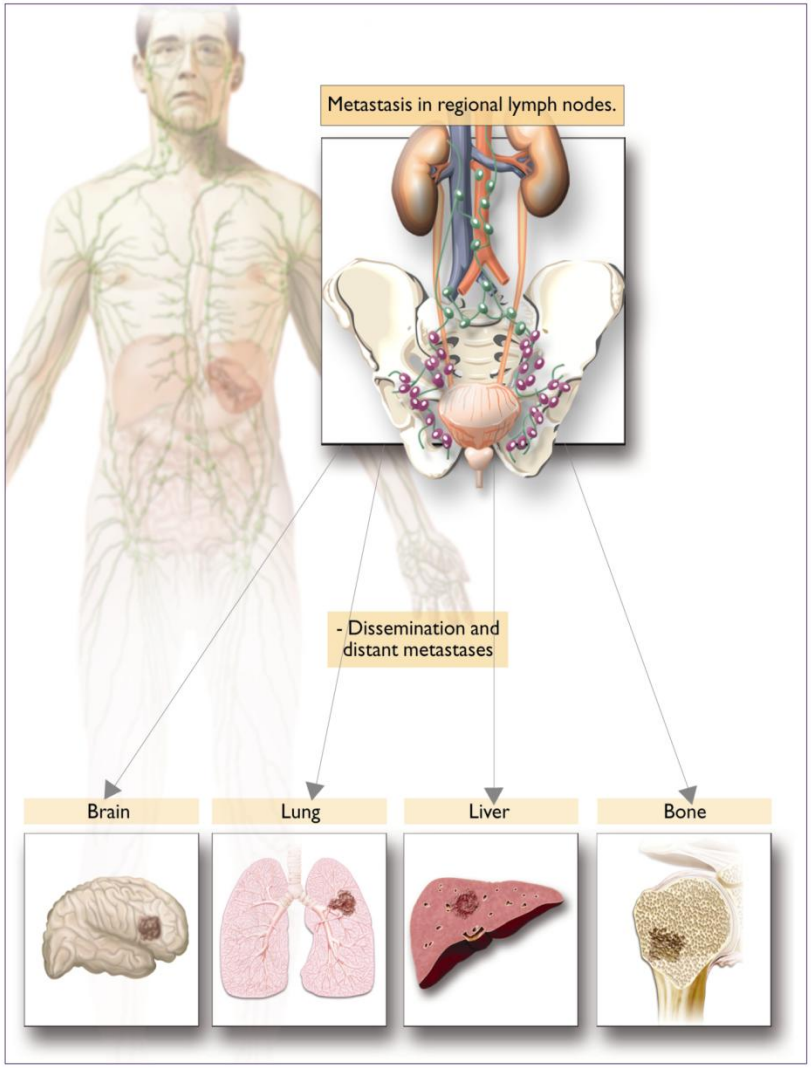
Hormone Therapy : First line Treatment

- Types of hormone treatment – LHRH analogues, LHRH antagonists, anti-androgens
- How and why therapies work
- The effectiveness of hormone manipulation on advanced prostate cancer
- The side effects, impact on quality of life how and side effects are managed

TNM staging – advanced

any T, any N, M+



- **Cancer spread to other parts of the body**

Prostate cancer that has spread beyond the gland and local tissues, affecting numerous lymph nodes and other sites, such as bone.

TNM classication:
any T stage, any N, M1.

Hormone Treatment

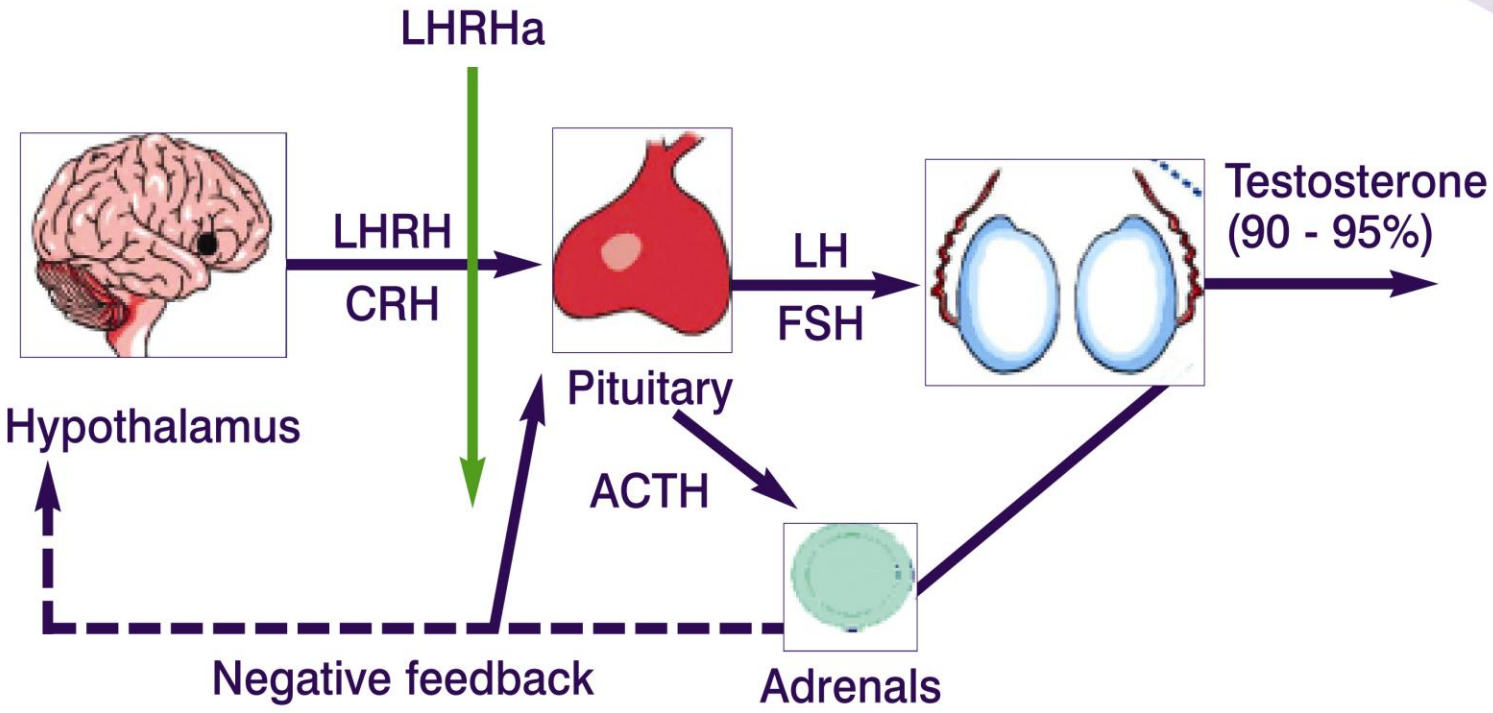
- In 1941 Huggins and Hodges described the effects of castration and oestrogen administration on the progression of metastatic prostate cancer.
- Since then androgen deprivation has been the mainstay of advanced prostate cancer management
- Hormonal treatment can effectively palliate symptoms but there is no evidence that it extends life

Castration

- Testosterone is essential for growth and perpetuation of tumour cells
- Testes are the source of most 90-95% testosterone
- Adrenal glands produce 5-10%

Androgen deprivation can be achieved by suppressing the secretion of androgens by surgical or medical castration
Castration level = testosterone of <20 ng/ml

Hypothalamic-pituitary-testicular axis



ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; LHRH, luteinising hormone-releasing hormone

Adapted from Newling DWW, Denis L, Mahler C, Debruyne FMJ, Lunglmayr, Robinson MRG, Richards B. Clinical and endocrinological results with a biodegradeable depot LHRH analogue (Zoladex) in the management of advanced prostatic cancer. In: Chisolm GD, editor. Zoladex - a new treatment for prostatic cancer. Symposium series no 125. London: Royal Society of Medicine Services Limited; 1987. p17-24

LHRH analogues

Long-acting LHRH analogues (gosereline, leuprolide, triptoreline)

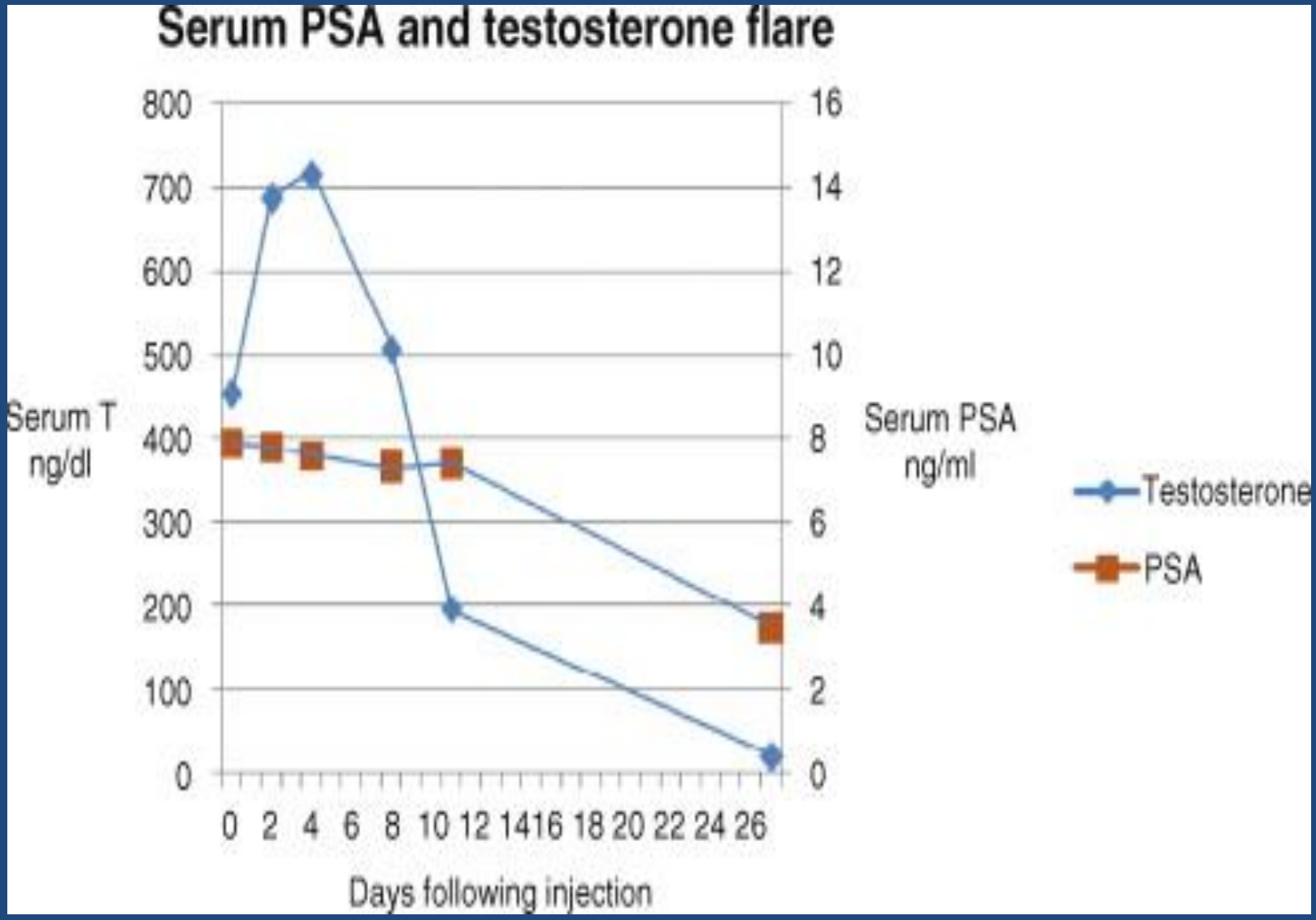
Administration monthly, 3 monthly, 6 monthly and yearly preparations (Vantas)

Results in low levels of circulating testosterone (castrate levels) with regression of androgen dependent tumours

As effective as surgical castration

Tumour flare

- Initially LHRHa stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release
- This then elevates testosterone production known as flare which begins 2-3 days after the first injection and lasts for about 1 week
- Patients with advanced, high volume disease are at risk of clinical flare (bone pain, acute BOO, obstructive uropathy, spinal cord compression)


Serum PSA and testosterone flare
800
700
600
500
400
300
200
100
0
16
14
12
10
8
6
4
2
0
Serum T ng/dl
Serum PSA ng/ml
0 2 4 6 8 10 12 1416 18 20 22 24 26
Days following injection
Testosterone
PSA

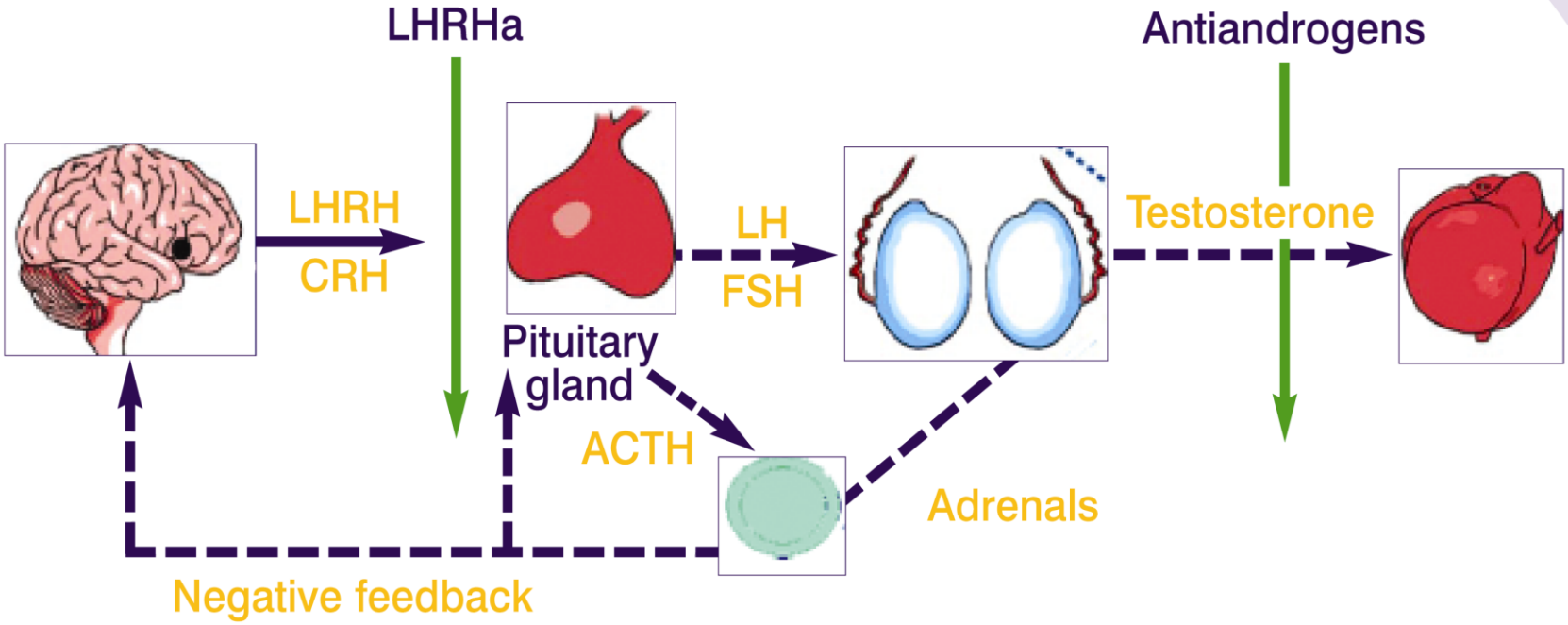
Anti-androgens

- Concomitant therapy with an anti-androgen decreases incidence of clinical flare
- Used also when PSA rising despite LHRHa (maximal androgen blockade)

Anti-androgens

- Bind to androgen receptors
- Competitively inhibit the action of testosterone and its major metabolite DHT
- 2 types of antiandrogen-
- Non steroidal (bicalutamide, flutamide)
- Steroidal (cyproterone acetate, megestrol acetate)
- Only recommended as monotherapy in locally advanced disease or in the adjuvant setting

Antiandrogens



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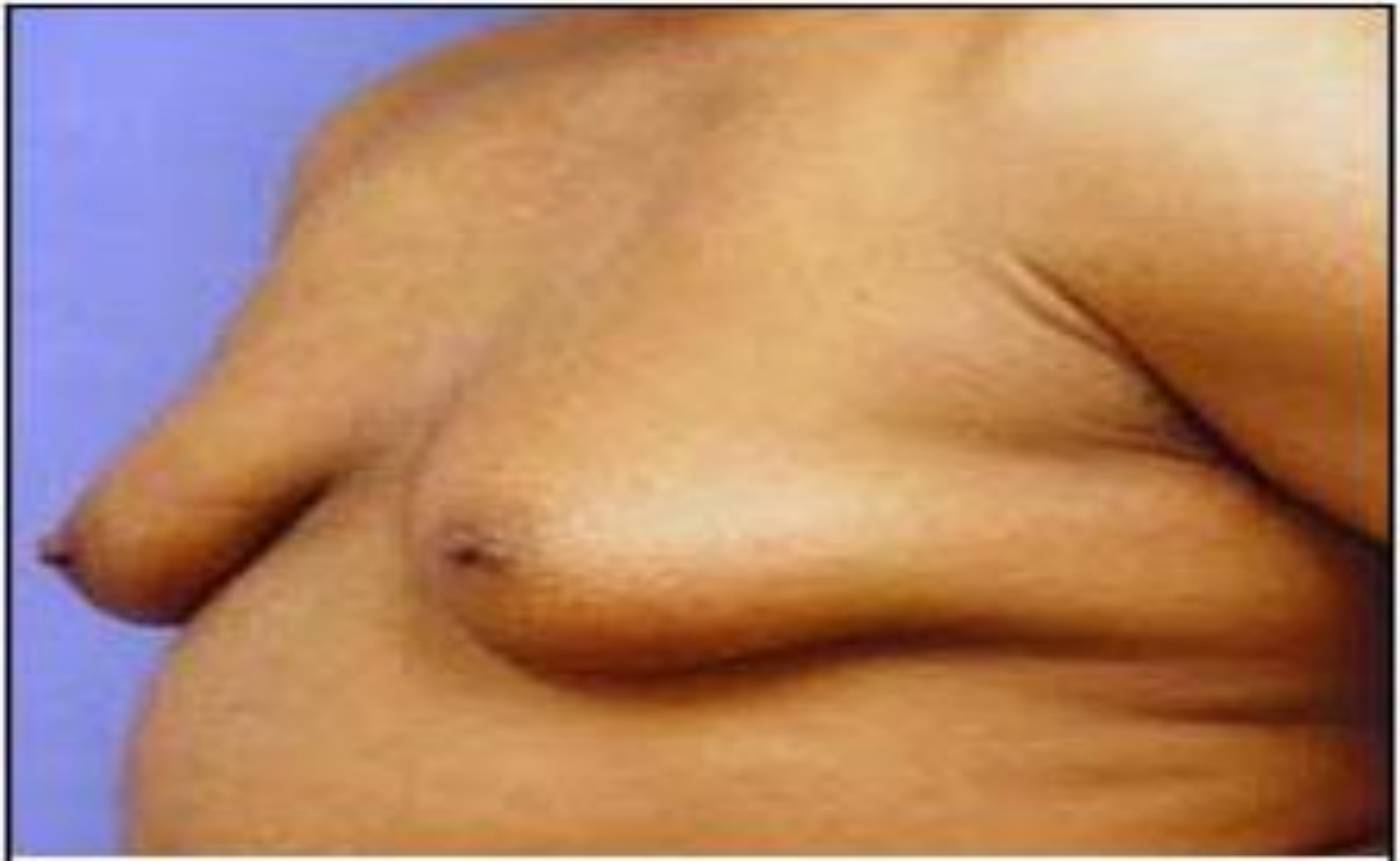
Effects of Antiandrogens

- Gynaecomastia/breast tenderness frequent
- Need to monitor liver function
  (CPA not recommended long term)
- Sexual interest maintained
- Physical capacity maintained
- BMD maintained

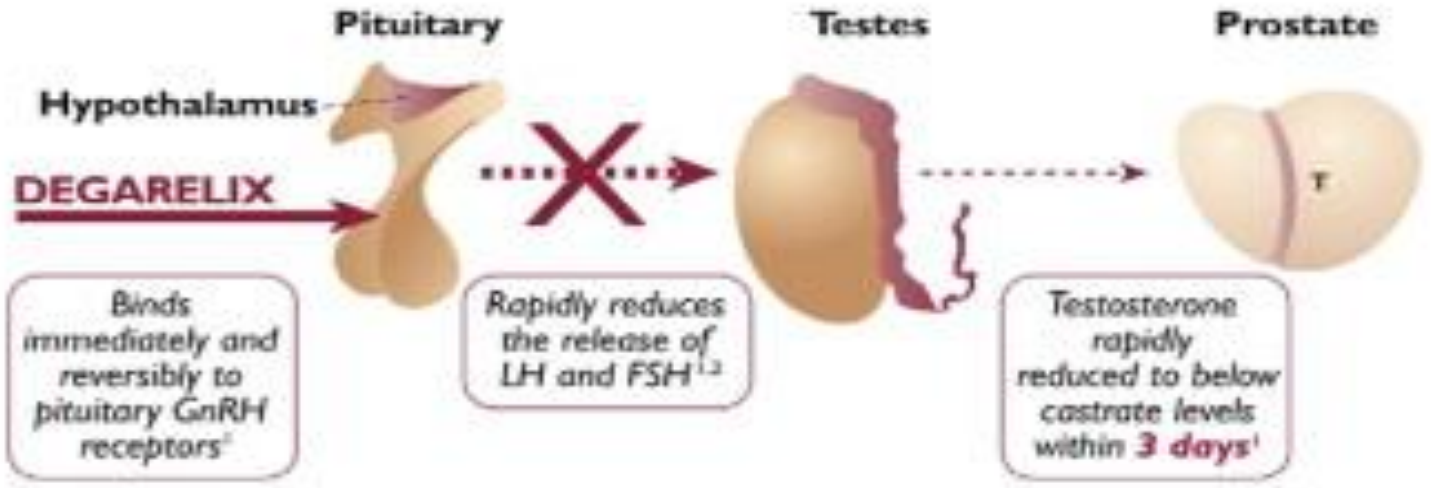


GYNECOMASTIA CAUSED BY
TREATMENT OF PROSTATE CANCER
WITH ANTI-ANDROGENS

LHRH antagonists

- Antagonist = receptor blocker
- Binds immediately and competitively to LHRH receptors in pituitary gland
- Fast and profound reduction in LH, FSH and in turn testosterone
- Reduces size and growth of tumour
- No need for anti-androgen, no flare (Klotz et al, 2008)

DEGARELIX



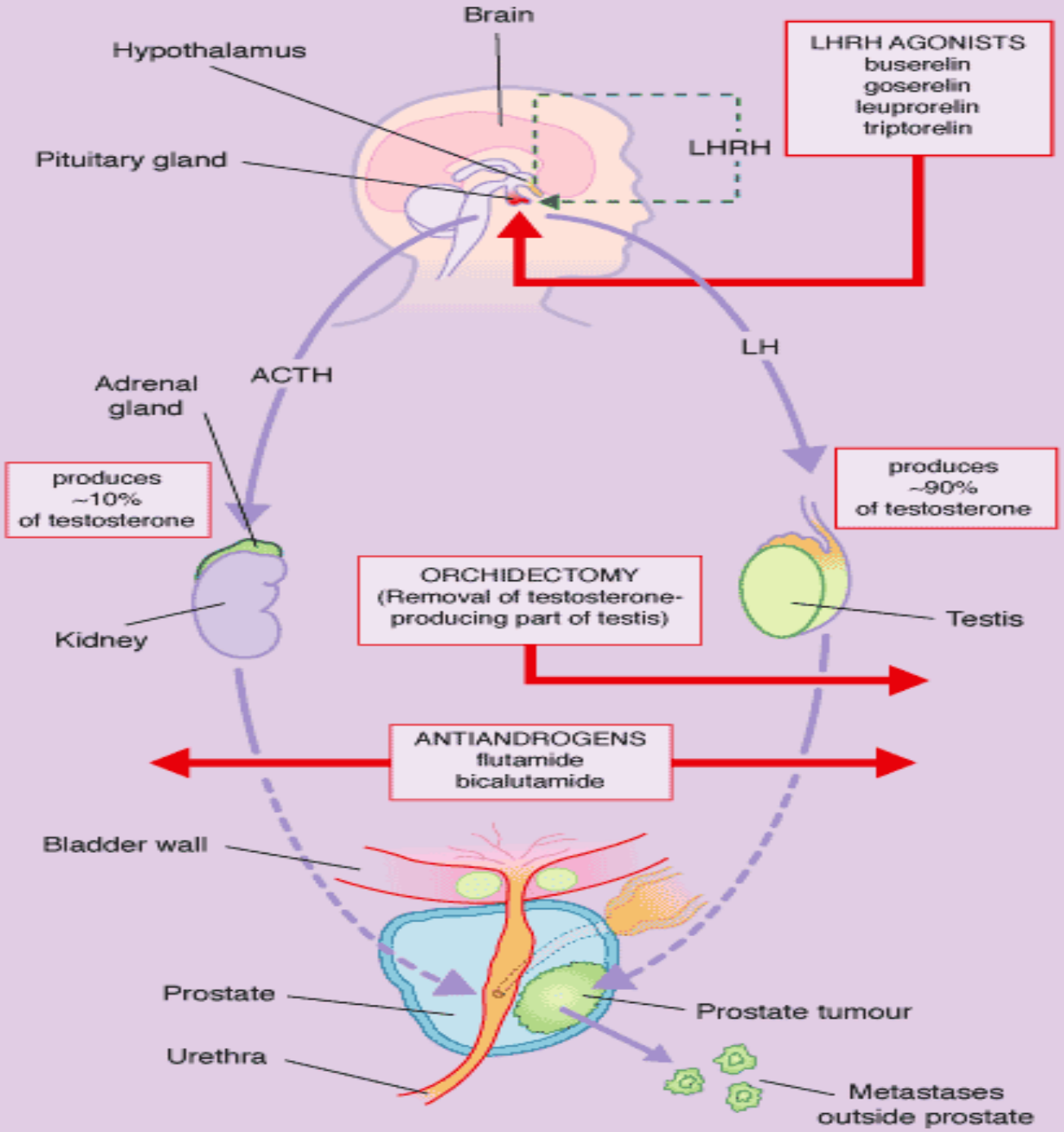
[1]Klotz L, Boccon-Gibod L, Shore ND, et al. *BJU Int.* 2008;102 (11):1531–1538.
[2]Van Poppel, H, et al. *Eur Urol.* 2008;54(4):805–813.

Why use LHRH Antagonist?

- Newly diagnosed patients with bone pain and neurological symptoms due to impending cord compression benefit most from immediate androgen deprivation (Heidenreich et al., 2012)

Disadvantages of LHRH antagonists

- Monthly formulation compared with LHRHa
- Local skin reaction especially after first dose administration
- More research required to confirm preliminary observed increased efficacy compared to leuprorelin

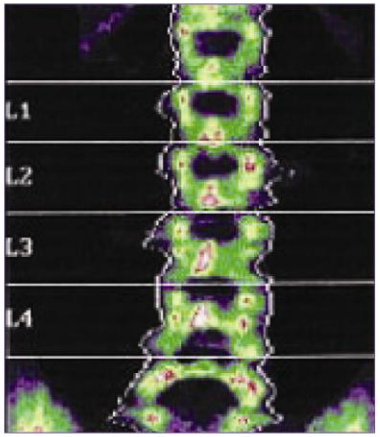

Brain
Hypothalamus
Pituitary gland
LHRH
LHRH AGONISTS
buserelin
goserelin
leuprorelin
triptorelin
ACTH
LH
Adrenal gland
produces ~10% of testosterone
produces ~90% of testosterone
Kidney
ORCHIDECTOMY
(Removal of testosterone-producing part of testis)
Testis
ANTIANDROGENS
flutamide
bicalutamide
Bladder wall
Prostate
Urethra
Prostate tumour
Metastases outside prostate

Side Effects of Hormone Therapy

- Similar side effects for both LHRH agonists and antagonists
- Can affect quality of life
- Education and information on side effects to empower patients
- Supportive environment in which men feel able to voice concerns (Yu Ko et al., 2010)

Luteinising Hormone-Releasing Hormone Analogue (LHRHa)

- **Common side effects**
  - Hot flushes, sweating, loss of libido
- **The use of LHRHa in men may cause a loss of bone mineral density**[1]



DEXA scan

1. Zoladex 3.6mg SmPC.

Side Effects of Hormone Therapy

- Erectile dysfunction
- Fatigue
- Weight gain
- Mood swings
- Loss of body hair
- Gynaecomastia
- Metabolic syndrome, diabetes and cardiovascular disease (Keating et al., 2010)

Advice for patients

- Chillow, steroidal anti-androgen for hot flushes
- Fatigue management advice
- Encourage lifestyle changes (loss of weight, increased exercise, improved nutrition)
- Weight bearing exercise
- Increase calcium and vitamin D intake
- Stop smoking, reduce alcohol
- Avoidance of heavy lifting

Benefits of Exercise

- Lipid alterations may occur 3 months into treatment
- Hormone therapy decreases insulin sensitivity and increases fasting plasma insulin levels
- Exercise is recommended as a protective tool
- Exercise also important for bone health

Multidisciplinary Team

- Crucial to involve other members of team as and when necessary (psychology, dietician, physio, benefits officer, palliative care team)
- Working closely with Oncologist and Urologist as patient's advocate
- Refer to Clinical Oncologist when castrate resistant

Impact on Quality of Life

- Little data available on Qof L during hormone treatment
- Recent study shows that both sexual and cognitive function significantly declined in men on hormone therapy (Cherrier et al., 2009)
- Bicalutamide shows significant advantage over castration in physical capacity and sexual interest

Intermittent Versus Continuous Hormone Therapy

- Benefits include preservation of Quality of Life in off treatment periods
- Proven benefit in QoL and no negative impact on overall survival, await data from phase 3 studies
- Initial cycle must be 6-9 months
- Treatment stopped if patient well informed and compliant, no clinical progression, PSA response <4ng/ml
- Strict follow up, resume treatment if PSA 10-15ng/ml

Immediate versus Delayed Hormones

- Lack of properly conducted randomised controlled trials
- Systematic reviews have suggested that there is no survival benefit but treatment seems to be most cost effective when started after onset of symptoms

Effectiveness of Hormone Therapy

Initial responses to therapy are often favourable with reduction in pain, regression of metastases, improvement in Qof L and rapid decline in PSA levels in 80-90% of patients (Harris et al., 2009)

- Metastatic disease invariably progresses after 18-24 months to castrate-resistant phase of disease

Effectiveness of Hormone Therapy

Hormone therapy is palliative, not curative

In M1 patients may have a life expectancy of 28-53 months

Only 7% of patients with metastatic cancer treated with hormone therapy are alive at 10 years

Survival depends on PSA level at diagnosis, Gleason score, volume of metastatic disease and presence of bony symptoms

Conclusion

- New approaches to treatment but no cure for advanced metastatic prostate cancer
- Nurses can help these men and their families navigate treatment options by giving support and information
- Main goal is to optimise their quality of life