Introduction to Cancer

Cancer

- Uncontrolled growth and spread of cells in the body
- A genetic disease, arising from genetic alterations that
    - Promote self- sufficiency
    - Allow escape from cell- cycle control
    - Confer resistance to apoptosis
    - Bestow immortality upon tumour cells
    - Enhance immunological surveillance evasion
    - Facilitate angiogenesis, invasion and metastasis
- Genetic aberrations involved are acquired somatic mutations/ chromosomal abnormalities
- Mutated "oncogenes" may lead to inappropriate, uncontrolled cell proliferation
- Mutated tumour suppressor genes may lead to the inability to stop cell proliferation
- Mutated cancer- susceptibility genes may predispose people to cancer

Epidemiology

- Second leading cause of death in Australia
- 1 in 2 people will get cancer in their lifetime
- The most common cancers are prostate, breast, colorectal, melanoma and lung

Tumours

- Benign
    - Grows slowly and do not invade local tissues or spread to other organs
    - Not "cancerous"
    - E.g. warts, moles and fibroids
- Malignant
    - Grows rapidly and does invade local tissues and/or spreads to other organs (metastasis)
    - Is "cancerous"

Degrees of Spread

- Local Spread
    - Into surrounding tissues
- Regional Spread
    - To nearby lymph nodes, tissues and organs
- Metastatic Spread
    - To other parts of the body via the blood stream and lymphatic system

- Anti- Androgen Drugs
    - Used as first line hormonal therapy combined with orchiectomy or GNRH agonist (preventing tumour flare), for castration resistant prostate cancer and metastatic or non-metastatic prostate cancer
    - First Generation
        - Blocks androgen receptor signalling but some activation remains
        - Lower potency
        - Used for early-stage prostate cancer in combination with GNRH agonist
        - Higher risk of resistance
        - E.g. bicalutamide, flutamide, nilutamide, cyproterone
    - Second Generation
        - Stronger androgen receptor inhibition
        - Higher potency
        - Used for metastatic and castration resistant prostate cancer
        - Lower risk of resistance
        - E.g. enzalutamide, apalutamide, darolutamide
    - Steroidal Anti- Androgens
        - Blocks androgen receptors on prostate cancer cells and suppresses testosterone production via progestogenic activity
        - E.g. cyproterone (first generation)
    - Nonsteroidal Anti- Androgens
        - Blocks androgen receptors on prostate cells
        - Side Effects
            - Erectile dysfunction, hot flushes, increased CVD risk
                - Less risk of osteoporosis than all other such drugs
        - E.g. bicalutamide (first generation), enzalutamide (second generation)
- Steroid Synthesis Inhibitors
    - Used for high risk or resistant advanced prostate cancer and metastatic disease, used with prednisone … key treatment for castration resistant prostate cancer by working at extra testicular sites
    - Mechanism of Action
        - Inhibits CYP17 enzyme, which converts pregnenolone to DHEA and androstenedione (testosterone precursors) … reducing androgen synthesis in the testicles, adrenal glands and the tumour itself
        - Lowers cortisol (hence the need for prednisone)
    - Side Effects
        - Hypertension, hypokalaemia, fluid retention, erectile dysfunction, hot flushes, increased CVD risk, increased osteoporosis risk
    - Considerations
        - Monitor blood pressure, electrolytes
        - Must be taken on an empty stomach
    - E.g. abiraterone (oral tablet)

Diagnosis

- Self-Examination
- Mammography
    - For lumps that are unable to felt during physical examination
    - Free mammograms every 2 years for women aged 50- 74
    - Lower breast density as they age allows for easy detection
- Ultrasound
    - High frequency sound waves that can distinguish benign cysts from tumours
- Biopsy
    - Ultrasound- guided biopsy
    - Then, using immunohistochemistry, we can determine the classification of cancer, by testing for expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor
        - Luminal A
            - Estrogen and progesterone receptor positive
            - HER2 receptor negative
            - PIK3CA, MAP kinase mutations
            - Most favourable prognosis, responsive to hormonal therapy
        - Luminal B
            - Estrogen and progesterone receptor positive
            - HER2 receptor positive
            - Tp53 mutations
            - Poorer prognosis than luminal A, luminal B tends to be higher grade, responsive to hormonal therapy
        - HER2 Enriched
            - Estrogen and progesterone receptor negative
            - HER2 receptor positive
            - Tp53 mutations
            - Poorer prognosis than luminal A and B, prognosis is improving with new therapies, responsive to HER2 targeted therapy
        - Basal Like/ Triple Negative
            - Estrogen, progesterone and HER2 receptor negative
            - Tp53 mutations
            - Poorest prognosis and very aggressive cancer, not responsive to hormonal therapy
- MRI
    - Can determine extent of spread
    - Stage 0 – non-invasive, ductal carcinoma in situ (DCIS) OR lobular carcinoma in situ (LCIS)
    - Stage I, II – early cancer with varying tumour sizes
    - Stage IIB, III – locally advanced breast cancer that has spread to lymph nodes close to breast, skin of breast and/or chest wall
    - Stage IV – metastatic breast cancer that has spread to distant organs like the brain, liver, lung and/or bone

- HER2
    - HER2+ activation drives aggressive growth
    - Monoclonal Antibodies
        - Trastuzumab
            - Binds to HER2 extracellular domain, inhibits the ligand- independent HER2 signalling
        - Pertuzumab
            - Binds to the dimerisation site on the HER2 domain, preventing ligand mediated pairing of HER2 with other HER receptors by steric hindrance
            - Complementary action with trastuzumab
    - Antibody Drug Conjugates
        - Trastuzumab/ Emtansine
            - Combines HER2 blockade of trastuzumab with cytotoxic microtubule inhibition of emtansine
            - Enhanced efficacy and reduced toxicity
            - Used as second line therapy in HER2+ breast cancer and first line for metastatic HER2+ breast cancer in those unable to have taxane therapy
        - Trastuzumab/ Deruxtecan
            - Combines HER2 blockade of trastuzumab with humanised topoisomerase inhibition of Deruxtecan
            - Used for unresectable or metastatic HER2 breast cancer after 2 or more failed anti- HER2+ regimens
    - Tyrosine Kinase Inhibitors
        - Lapatinib
            - Dual tyrosine kinase inhibitor of HER2, binds the intracellular binding domain of HER1 and HER2, causing cell signalling inhibition
            - Used for HER2+ metastatic breast cancer that has not responded to trastuzumab and chemotherapy
        - Neratinib
            - Reversible tyrosine kinase inhibitor of HER1, HER2 and HER4
- PARP
    - Inhibitors of DNA repair
    - Olaparib, talazoparib block PARP proteins, causing DNA damage and tumour cell death in BRCA mutated breast cancer i.e. triple negative and HER2(-)
- TROP2
    - Sacituzumab Govitecan (antibody drug conjugate) targets TROP2 and delivers chemotherapy payload
    - Used for metastatic triple negative breast cancer after failed previous treatment