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Chapter 7

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

 the best test for monitoring the patient while she is receiving Herceptin (trastuzumab)? Three monthly echocardiogram Herceptin appears to be directly toxic to the cardiac muscle itself with relative sparing of the electrical conductivity of the heart. As such regular echocardiograms are the best test to assess treatment safety, a reduction of greater than 10% in ejection fraction indicating the need to stop treatment. • Bisphosphonate therapy prevents skeletal complications resulting from osteolytic bone involvement in patients with breast cancer. An intravenous bisphosphonate (eg: zoledronic acid) is indicated for treatment of lytic bone metastases. The evidence demonstrating benefit of oral bisphosphonate therapy such as alendronate in the treatment of bone metastases is conflicting. oestrogen receptor (ER)-positive tumours + pre-menopausal women Tamoxifen oestrogen receptor (ER)-positive tumours + post-menopausal women Anastrozole ER-negative or are refractory to endocrine treatment chemotherapy Patients with HER2 overexpression chemotherapy + trastuzumab. patients with HER2-negative metastatic breast cancer Bevacizumab Prognosis • Poor prognostic factors include: high-grade tumour, positive lymph node status, oestrogen-receptor-negative tumour, progesterone-receptor-negative tumour, young age (< 40 years), premenopausal at diagnosis increased tumour size.

Paget's disease of the breast • Overview Paget's disease of the breast is a rare (1-4% of breast cancers) form of breast cancer that affects the nipple and areola. underlying invasive breast cancer, or ductal carcinoma in situ (DCIS) almost always present unlike Paget's disease of the vulva Malignant cells infiltrate into the epidermis via the mammary duct epithelium, leading to thickening of the affected skin. • Features Presents with dermatitis or macular rash over nipple or areola It presents insidiously and is similar in appearance to eczema; as such it often goes undiagnosed for several months.

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• Diagnosis Skin biopsy with immunohistochemistry is the first line investigation. Investigations should also be done for underlying malignancy: biopsy if a lump is palpable, imaging if no lump is palpable. • Management usually surgical with post-operative radiotherapy • Prognosis high chance of recurrence.

Radiotherapy • External beam radiotherapy or use of targeted intraoperative radiotherapy does not render the patient radioactive. No radiation precautions need to be taken • Use of brachytherapy methods can involve insertion of radioactive seeds or beads which may require some radiation protection precautions depending on the site. • Use of an unsealed source, for example radio-iodine treatment of thyroid cancer, has substantial need for precautions and patients need to be isolated in a lead-lined side room, often for several days.

Chemotherapy • Adjuvant chemotherapy is commonly given in many cancers to reduce the risk of local or distant recurrence or metastasis. • multi-drug chemotherapy resistance Upregulation of which protein is associated with multi-drug chemotherapy resistance? P-glycoprotein P-glycoprotein, which is also known as multidrug resistance protein 1, is a member of the adenosine triphosphate (ATP)-binding cassette transporters which actively remove harmful substances from the cytoplasm. If upregulated these proteins can pump chemotherapeutic agents out of tumour cells leading to drug resistance. Chemotherapy complications • Oral mucositis Severe mucositis is common with head and neck cancer treatment due to the combination of chemotherapy and external beam radiotherapy. Admit the patient for IV fluids and nutritional support Often patients require a PEG or RIG to provide adequate nutritional support during their potentially curative treatment. Oral hygiene is the mainstay of treatment in prevention of mucositis however it will not treat an existing mucositis. Chlorhexidine mouthwash can improve a grade 1-2 mucositis.

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Haematology&Oncology Salivary Gland Tumors • Most commonly occur in the parotid gland generally benign if the tumor involves a non-parotid gland it is more likely to be malignant • Types pleomorphic adenoma the most common benign salivary gland neoplasm. 70% to 80% of all benign salivary gland tumours. more common in females (middle-aged women > 40) It is found mostly in the parotid gland (84%). 90% of parotid gland pleomorphic adenomas arise lateral to the facial nerve. benign with high rate of recurrence but may become malignant Usually they do not enhance following intravenous contrast injection in CT. The optimal treatment is superficial or total parotidectomy with facial nerve preservation Warthin's tumor benign more common in males heterotopic salivary gland tissue located in a lymph node surrounded by lymphatic tissue mucoepidermoid carcinoma most common malignant tumor note: muco = malignant generally, involves parotid gland combination of neoplastic mucus and squamous cells • Physical exam painless, moveable mass found at the angle of the jaw pleomorphic adenoma disturbance in CN VII function more likely to be malignant pleomorphic adenoma

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Palliative care prescribing: pain The breakthrough dose of short acting morphine should be 1/6th of the total 24-hour dose. WHO recommendations • Standard practice would be to follow the World Health Organization recommendations for the management of cancer pain, which suggest analgesia should be given: By the mouth - that is, using the oral route for all drugs including morphine and other opioids unless patient is vomiting, semi-conscious, has dysphagia, etc. By the clock - persistent pain requires preventative treatment and as needed (prn) analgesia only is not acceptable. By the ladder - that is, the WHO analgesic ladder. • The WHO analgesic ladder is as follows: Step 1 - Non-opioid +/- adjuvants (e.g. paracetamol/NSAIDs)

 Step 2 - Weak opioid + non-opioid +/- adjuvants (e.g. co-codamol 30/500) Step 3 - Strong opioid + non-opioid +/- adjuvants (e.g. morphine, fentanyl, oxycodone). • Nerve pain often also has a nociceptive opioid responsive element and hence opioids (with a combination of nonsteroidal anti-inflammatory drugs [NSAIDs]) should be tried first (eg: ibuprofen and tramadol) and used as part of the WHO analgesic ladder. Morphine would be tried next, followed by the other agents. Starting morphine • Morphine is the opioid of choice for treating moderate to severe cancer pain. • Choices between morphine preparations when starting treatment, offer patients with advanced and progressive disease regular oral modified-release (MR) or oral immediate-release morphine(IR) (depending on patient preference), with oral immediate-release morphine for breakthrough pain oral modified-release morphine should be used in preference to transdermal patches Immediate release preparations are used for titration as they offer greatest flexibility. Most patients should be started on 5-10mg orally every 4-hours, with the same dose prescribed as a breakthrough (or 'rescue') dose wherever needed. Once drug requirements are constant, the patient can be converted to modifiedrelease morphine. Once a patient has been titrated on immediate release opioids these can be converted to the equivalent dose of a modified release preparation. If a patient has good pain control on one drug, the modified release version of this drug should be used. • Morphine doses if no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required When increasing the dose of opioids, the next dose should be increased by 30-50%. An appropriate starting dose of morphine sulphate immediate release (IR) should not be more than 10mg every 4 hours. Alternatively, morphine sulphate modified release (MR) 30mg 12 hourly could be used. • Opioids Side effects: Constipation: laxatives should be prescribed for all patients initiating strong opioids Morphine causes constipation by enhancing intestinal ring contractions. This results in hypersegmentation which in turn impairs peristalsis. 90% of patients taking morphine require a laxative and a stimulant is the best choice (such as senna). Senna is the most commonly used laxative for this indication Nausea: patients should be advised that nausea is often transient. If it persists then an antiemetic should be offered drowsiness is usually transient - if it does not settle then adjustment of the dose should be considered Preferred opioids for patients with chronic kidney disease • Opioids should be used with caution in patients with chronic kidney disease. Alfentanil, buprenorphine and fentanyl are preferred Fentanyl patches are difficult to titrate because they are used for 72 hours. therefore, only used once a patient has a stable opiate usage. Fentanyl is a selective μ receptor agonist.

Haematology&Oncology It has extensive first-pass metabolism so is not especially effective orally. However, buccal absorption is good so lozenges are an effective mode of administration and have a rapid onset of action (five minutes). This is therefore very useful for patients with "breakthrough pain". It is very useful in renal failure as it is metabolised mainly in the liver and it has inactive metabolites. What is the most appropriate opioid to prescribe for a syringe driver in renal failure? Alfentanil Combination therapies antagonism • Partial opioid agonists (for example, buprenorphine), when used in association with morphine, may produce a reduction in the analgesic effect due to partial antagonism. • This is an aspect of pain management that needs to be considered when using combination therapies. Oxycodone • Oxycodone is often used as a second line opioid for patients who experience either inadequate analgesia or excessive side effects with morphine. • It has similar analgesic properties to morphine but is twice as potent. • It is available in immediate-release and modified- release oral preparations and can also be used parentally. • Oxycodone can be used in moderate renal failure, but only as breakthrough pain relief. Modified release preparations should be avoided. • Parental oxycodone is twice as potent as oral oxycodone. • The total daily dose of immediate and modified release oral oxycodone is the same. • causes less sedation, vomiting and pruritis than morphine but more constipation. Opioid side-effects Usually transient Usually persistent Nausea Drowsiness Constipation Conversion between opioids • calculate the total daily dose of morphine salt, (include the doses of breakthrough pain) then convert it to the appropriate amount From To Conversion factor Oral codeine Oral morphine Divide by 10 Oral tramadol Oral morphine Divide by 10 From To Conversion factor Oral morphine Oral oxycodone Divide by 1.5-2** **historically a conversion factor of 2 has been used (i.e. oral oxycodone is twice as strong as oral morphine). The current BNF however uses a conversion rate of 1.5

From To Conversion factor Oral morphine Subcutaneous morphine Divide by 2 Oral morphine Subcutaneous diamorphine Divide by 3 Oral oxycodone Subcutaneous diamorphine Divide by 1.5 Transdermal perparations: The current BNF gives the following conversion factors for transdermal perparations • transdermal fentanyl a transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily fentanyl 75 patch is equivalent to 180mg daily intake of morphine salt fentanyl 100patch is equivalent to 240mg daily morphine salt. • transdermal buprenorphine transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily. Diamorphine • Diamorphine has a rapid onset so could be used for breakthrough pain if the renal function is normal. • Constipation is a characteristic sequel to treatment • Hallucinations also tend to occur. • An aperient (laxative) should always be added to the treatment regime. • Addiction is not a problem. • An intramuscular injection is three times more effective than the same oral dose. • the best option for controlling pain associated with vomiting in palliative care Subcutaneous diamorphine by continuous infusion (able to effectively titrate the dose to achieve adequate analgesia) Codeine • The analgesic effect of codeine depends on its conversion to morphine by the CYP2D6 hepatic enzyme. Up to 10% of Caucasians are CYP2D6 poor metabolisers and are unlikely to derive any analgesia from it. • If hepatic metabolise

is impaired for any other reason (drugs or hepatic impairment) patients are also unlikely to benefit from codeine. Methadone • acts as a neuropathic agent by NMDA antagonism. • Methadone can be used as a third line opioid for patients with complex pain that is poorly responsive to other opioids and adjuvants • Opioids which are safe in CKD 4 and 5 include fentanyl, buprenorphine and methadone. Incident pain • defined as pain which comes on as a result of an action or activity, for example during personal care (pain throughout the day is otherwise well controlled). • Treated with rapid onset and short-acting opioid such as: Sublingual fentanyl morphine sulphate immediate release liquid. A breakthrough dose (1/6th of the total daily dose) of morphine should be given 30 minutes prior to the activity as indicated in the BNF.

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Haematology&Oncology Other notes: • Nifedipine relieves painful oesophageal spasm and tenesmus associated with gastrointestinal tumours and could be used to relieve odynophagia. • Corticosteroids used to treat pain from central nervous system tumours • Oxybutynin painful bladder spasm may be relieved by oxybutynin. • Hyoscine to reduce air way secretions in palliative care Both hyoscine and atropine when given subcutaneously are thought to be equally appropriate for drying up secretions. hyoscine s/c can be given up to three times per day in boluses of 10-20 mg. • Cyclizine Cyclizine is a commonly used antihistamine antiemetic and its primary site of action is the vomiting centre (which is rich in histamine and muscarinic cholinergic receptors). Cyclizine has a strong affinity for muscarinic receptors and therefore anticholinergic side effects (dry mouth, drowsiness, blurred vision, constipation, etc) are common, especially in the first few days. • Gabapentin Gabapentin is a commonly used adjunctive agent for neuropathic pain. mechanism of action: (Activation of GABA inhibitory system). Four to six weeks of treatment are often needed before the patient experiences benefit. • Bisphosphonates inhibits osteoclastic bone resorption useful for bone pain and the associated hypercalcaemia, especially in breast cancer and myeloma. Whilst bisphosphonates have a role in bone metastases they are not suitable for acute pain. The risk of osteonecrosis of the jaw is much greater for patients receiving intravenous bisphosphonates in the treatment of cancer. All patients receiving bisphosphonates for cancer should have a dental checkup before bisphosphonate treatment. other patients who are prescribed bisphosphonates should have a dental examination only if they have poor dental health. The beneficial effect of bisphosphonates can be delayed for up to two weeks and can last for one month, and treatments are therefore usually given monthly (typically for 6 months). increase analgesia while waiting for the bisphosphonates to work and review over the next few days to see whether you could reduce them again. Acupuncture is playing an increasing role in pain management. Which structures are involved in mediating the effects of acupuncture? Cerebral cortex and A beta nerve fibres. • The A beta nerve fibres are the path for fast transmission of sensation. • Acupuncture also has a central effect.

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Opioid toxicity in palliative care most opiates are renally excreted, leading to opiate toxicity. Fentanyl, buprenorphine and methadone are metabolised by the liver and are therefore safer in

renal failure Transdermal fentanyl absorption is increased by heat (e.g. hot water bottle) or pyrexia, potentially leading to opioid toxicity • May be precipitated by: Renal impairment with renally excreted opiates increase transdermal fentanyl absorption by heat eg: fever reduction in opioid requirement. This is a common occurrence in patients who have radiotherapy for bone metastases if their medication dose is not adjusted. • Features: Reduced conscious level, hallucinations, vomiting, myoclonic jerks and pinpoint pupils. • Management stop the long acting opioid temporarily to allow the excess drug to be excreted and then rely on short acting opioid for any breakthrough pain that might occur. once the patient recovered, the long acting opioid can be reintroduced at a much-reduced dose. Although the patient is opioid toxic, giving naloxone would not usually be the right thing to do. Naloxone antagonises opioid receptors in the nervous system and this can cause patients significant pain and distress as their analgesia is reversed. Unless the patient is in a peri-arrest situation where use of naloxone could be justified, it is better simply to withdraw the regular opioid until the patient recovers.

Palliative care prescribing: nausea and vomiting Opiate induced nausea • Haloperidol 90% of patients taking morphine require antiemetics (morphine stimulates D2 receptors in the CTZ). Haloperidol is the first-choice antiemetic for opiate induced nausea in the palliative care setting. Haloperidol acts as a central dopamine (D2-receptor) antagonist. The chemoreceptor trigger zone (CTZ) is rich in dopaminergic receptors. Opioid related nausea is thought to be predominantly due to dopamine pathways in the CTZ. haloperidol dopamine receptor antagonist (D2) activity drug-induced parkinsonism (DIP). Post-chemotherapy or radiotherapy induced nausea • Ondansetron (5HT3 antagonist) is mainly used in post-chemotherapy or radiotherapy induced nausea. • In UK 5HT3 antagonists are licensed only for post-chemotherapy and post-operative nausea. • Which antiemetics is most useful following treatment with a platinum-based chemotherapy? Ondansetron Examples of platinum-based chemotherapies are cisplatin, carboplatin and oxaliplatin

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Nausea associated with cerebral disease (brain metastases) • If he patient's history raises the possibility of brain metastases, cyclizine would be the most appropriate first line agent. It targets the dopamine and cholinergic receptors and is widely accepted as the best antiemetic for nausea associated with cerebral disease. Treatment of vomiting associated with breast cancer chemotherapy • modern palliative chemotherapy for breast cancer would be unlikely to cause severe nausea and vomiting. • The patient may have anticipatory vomiting (before attending for treatment) almost certainly associated with anxiety about chemotherapy. Therefore, treatment with a benzodiazepine as an anxiolytic as well as an antiemetic would be the most logical.

Palliative care prescribing: hiccups Management of hiccups • Metoclopramide is the first choice to treat hiccup as well as nausea. • chlorpromazine is licensed for the treatment of intractable hiccups • Other options include: baclofen, nifedipine, haloperidol, gabapentin • dexamethasone is also used, particularly if there are hepatic lesions In the presence of hepatic or cerebral cancer a trial

of dexamethasone may induce some remission

Palliative care prescribing: Constipation Causes • Constipation is common in patients with advanced cancer, particularly in those taking opioid medication, with reduced oral intake and reduced mobility. • Hypercalcaemia can cause constipation (a constipation in cancer do blood tests, including bone profile) Hypercalcaemia is a common problem in palliative care. prostate cancer with bone metastasis is a frequent cause. Treatment • Polyethylene glycol (Movicol) would seem the best choice in this scenario. It has an osmotic action and helps to retain water in the gut to aid faecal passage. It is generally better tolerated than some other oral laxatives and has been shown to be more effective than lactulose in the management of chronic constipation. • Lactulose (an osmotic laxative) is usually avoided in palliative care as it can cause abdominal cramps and excessive flatulence. Its sweet taste can be unpalatable for some patients it needs to be consumed with large volumes of liquid which is sometimes not practical for palliative care patients. • Co-danthramer is a combination of danthron (a stimulant laxative) and poloxamer (a stool softener) and is a popular choice for constipation in palliative care. It is licensed only for use in patients with a terminal illness and should not be given to those who are incontinent (of urine or faeces) due to the risk of developing a 'danthron burn' through prolonged contact with the skin.

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Palliative care prescribing: agitation and confusion Causes • hypercalcaemia, • infection, • urinary retention can even develop in patients who have not received any hydration for several days. Assessment for catheterisation should be one of the first management steps in a newly agitated patient. • medication. Management • Treatment of underlying cause • If specific treatments fail, then the following may be tried: first choice: haloperidol other options: chlorpromazine, levomepromazine Terminal agitation In the terminal phase of the illness then agitation or restlessness is best treated with midazolam Midazolam is the drug suggested by the Liverpool Care Pathway (LCP) (starting dose of 2.5 - 5 mg sc PRN). benzodiazepines are traditionally the first line for terminal agitation.

Palliative care: Breathlessness Opioids are the first line treatment to reduce the sensation of breathlessness in Palliative care • Breathlessness is a significant problem in the palliative care setting and not just in patients with lung cancer. • Palliation of breathlessness involves: First-line: Opioids Opioids are very effective agents to reduce the sensation of breathlessness - they reduce inappropriate respiratory drive. They rarely cause respiratory depression when used correctly. Second line: Benzodiazepines (effective agents after opioids). Other therapies Psychological support and physiotherapy are very useful adjuncts to medications. However, these take time and if the patient is distressed, they are not helpful in the immediate cases (unless breathing techniques have been taught). Oxygen has a small role in the management of breathlessness in palliative medicine, unless the patient is hypoxic. It can be necessary when patients become psychologically dependent on supplementary oxygen.

Palliative care: end of life care • Glucocorticoids are prominent in end of life care Benefits of steroids Improve general feelings of wellbeing Relive fatigue and improve energy Relive nausea Control of pain 15% improvement in pain If the patient is unable to obtain satisfactory pain relief despite an escalating opiate regimen Commence trial with dexamethasone One of the sources of pain associated with liver metastases is due to stretching and irritation of the liver capsule for which a trial of dexamethasone may provide an analgesic effect. Liver capsule pain tends not to be opioid responsive, therefore increasing the modified or immediate release morphine would not be the correct option. Dexamethasone is the usual agent of choice • The most important aspect of management is to try to keep the patient calm and relieve distress with a large dose of midazolam (10mg). In a massive terminal haemorrhage, a large dose of midazolam (10mg) can be given as part of 'crisis management' to relieve distress. Red or green towels or blankets should be available to soak up and mask the colour of blood

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Epstein-Barr virus: associated conditions • Epstein-Barr virus infects B lymphocytes and squamous epithelial cells of the oropharynx. The virus can transform B cells and epithelial cells to produce tumors • Malignancies associated with EBV infection Burkitt's lymphoma (both African and sporadic Burkitt's) Hodgkin's lymphoma nasopharyngeal carcinoma Epstein-Barr virus is detectable in over 90% of nasopharyngeal cancers the most common type is the undifferentiated form. HIV-associated central nervous system lymphomas • The non-malignant condition hairy leukoplakia is also associated with EBV infection. September 2019 exam: What type of virus family is associated with nasopharyngeal carcinoma? Herpesvirus (Epstein-Barr virus is one of the herpes viruses)

T cell lymphoma (Adult T-cell lymphoma (ATLL) • makes up about 10-20% of non-Hodgkin's lymphomas • has a worse prognosis than B cell lymphoma. • Adult T-cell leukaemia/lymphoma (ATLL) is a potentially aggressive type of mature T-cell non-Hodgkin lymphoma. • It is linked to the viral infection, HTLV-1 (human T-cell lymphotropic virus 1). • It is more prevalent in countries where infection with HTLV-1 is common, such as Japan, China, the Caribbean, South and Central America and West Africa. • ATLL occurs in 2%-5% of people who are infected with the HTLV-1 virus. • The HTLV-1 virus is a retrovirus, and is in the same class of virus as the HIV/AIDS virus. It is believed that the HTLV-1 virus is a key factor in the development of this rare lymphoma which is transmitted through sexual contact, exposure to contaminated blood or breastfeeding. • slightly more common in men than in women, • In acute ATLL, symptoms develop rapidly and include: fatigue, skin rash enlarged lymph nodes hypercalcaemia may also be present which can cause confusion, bone pain and severe constipation. • lymphomatous form of ATLL presents with: enlarged lymph nodes. • Chronic ATLL is slow growing and frequently characterised by: enlarged lymph nodes Skin rash and fatigue. • Smouldering ATLL develops slowly and presents

with very mild symptoms such as a few lesions on the skin. • Patients with the chronic or smouldering types of ATLL can progress to the acute form in about 25% of cases. • for the acute and lymphomatous types: Therapies include antiviral drugs, such as acyclovir and interferon, together with chemotherapy regimens

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Testicular cancer Epidemiology • Most common solid malignant tumor in young men in the US Classification: • germ cell tumors (comprise more than 90% of all tumours and more commonly malignant) Germ cell tumours are classified as either: pure seminomas The triad of a testicular lump, a mass on chest X-ray and a raised (3-HCG (human chorionic gonadotrophin) are suggestive of testicular seminoma Testicular mass • ↑LDH pure seminomas germ cell tumor • ↑AFP mixed non-seminomatous germ cell tumour

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 seminoma is the most common type of testicular germ cell tumor. ~40% Good radiosensitivity; slow growth, late metastases, and better overall prognosis compared to nonseminomas Lactate dehydrogenase (LDH) is most likely to be elevated (in 40– 60%) A raised (3-HCG is found in around 15% of seminomas Orchidectomy with chemotherapy is curative in 90% of cases (3-HCG) levels may be a useful correlate with response to treatment mixed non-seminomatous germ cell tumours (NSGCTs) Elevated AFP levels are most consistent with NSGCT Choriocarcinoma is the most aggressive of the NSGCTs. Highly malignant and most aggressive Early hematogenous metastasis to the lungs or brain is common. Most testicular GCTs cause scrotal swelling, with a palpable mass, choriocarcinoma is different in that the local tumour may be small or nonpalpable. Beta-human chorionic gonadotropin (Beta-HCG) is usually markedly elevated in pure choriocarcinoma but is only elevated in 10-15% of seminomas. Gynecomastia occurs due to elevation of beta-hCG levels and is therefore common in choriocarcinoma, but only rarely seen in patients with a seminoma. On ultrasound scanning, choriocarcinoma is associated with haemorrhage and necrosis and may appear more cystic, inhomogeneous, and calcified than a seminoma. Calcifications and cystic areas are less common in seminomas than in nonseminomatous tumours. can cause precocious puberty in boys. Young men are more at risk for germ cell tumors. teratoma is a testicular germ cell tumor that is benign in children and malignant in adults. • Non-germ cell tumors (make up less than 10% of all testicular tumours) Leydig cell tumours golden brown color on morphology Eosinophilic cytoplasmic inclusion bodies called Reinke crystals are found in Leydig cell type of testicular tumors. Sertoli cell tumours, gonadoblastomas. • Testicular lymphoma is the most common testicular tumor in older men. Most common testicular tumor in men > 60 years of age Testicular lymphoma is a cancer that arises from metastasis from metastatic lymphoma to the testes. Usually extranodal non-Hodgkin lymphoma Risk factors • Cryptorchidism Patients with history of cryptorchidism have a 10- to 40-times increased risk of testicular cancer this risk is greater for the abdominal versus inguinal location of undescended testis. Orchidopexy does not reduce the risk of subsequently developing a malignancy. An abdominal testis is more likely to be seminoma, while a testis surgically brought to the scrotum by orchiopexy is more likely to be non-

seminomatous germ cell tumours (NSGCTs)N.

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• family history • infertility • Klinefelter syndrome, Down syndrome (increased risk for germ cell tumors) Features • testicular mass Most commonly presents as a hard, painless nodule on one testis noticed by the patient or at a regular clinic examination. • fatigue, weight loss, • gynaecomastia Rarely gynaecomastia can be the trigger by which a young man will seek medical attention; testicular examination should therefore be done in every case. What is the mechanism by which patients with testicular cancer develop gynaecomastia? Raised oestrogen levels testicular cancers ↑β-HCG ↑oestrogen stimulates hypertrophy of breast tissue. • Testicular tumors metastasize early via the lymphatic system (drain to the para-aortic lymph nodes first) into the retroperitoneum, with the exception of early hematogenously metastasizing choriocarcinomas. Until proven otherwise, a firm nodule on the testis should be considered cancer Investigation β-hCG may be elevated in patients with seminomatous or nonseminomatous tumours, AFP is increased only in patients with nonseminomatous tumours. • Ultrasound of the testis is 90% to 95% accurate in diagnosis. • tumour markers used for diagnosis and in monitoring the treatment response. β subunit of human chorionic gonadotropin (β-hCG): may be elevated in patients with seminomatous or nonseminomatous tumours α-fetoprotein (AFP): increased only in patients with nonseminomatous tumours Raised AFP in a boy with testicular swelling are highly suggestive of a yolk sac tumor. placental ALP increased in seminomas, Lactate dehydrogenase (LDH) LDH is elevated in 40–60% of men with testicular germ cell tumours may be the only tumour marker which is elevated in some men with seminomas. It is neither sensitive nor specific as a marker for tumour recurrence, although the level at baseline does have prognostic value in men with advanced disease. • Raised oestrogen levels • transillumination test is negative in testicular germ cell tumors. HCG is always elevated in cases of choriocarcinoma and sometimes in seminoma. AFP is always elevated in yolk sac tumors. In mixed germ cell tumors, both AFP and HCG may be elevated.

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Haematology&Oncology If testicular tumor is suspected, the testis is removed and sent to pathology without prior trans-scrotal biopsy Treatment • Radical orchiectomy to confirm histological diagnosis is initial treatment in most cases. • followed by additional staging studies such as a CT scan of the abdomen and pelvis and radiograph of the chest. • In testicular cancer the BEP combination is used: Bleomycin, Etoposide and Cisplatin (Platinum). Etoposide works by inhibiting topoisomerase II and causing DNA degradation. Etoposide is also used in the treatment of small cell lung cancer, leukemias, and lymphomas. adverse effects: myelosuppression and alopecia. Prognosis • ~95% cure is expected with treatment The rapid deterioration, seen over the course of a few hours, is most suggestive of haemorrhage into a metastasis. Teratomas are well known to metastasise via haematogenous spread, including to liver, lung, bone and brain.

Laryngeal cancer Treatment • Initial therapy for stages I and II is radiation therapy or surgery. early-stage disease could receive curative therapy with surgery or radiation alone. External beam radiation is the curative and function sparing treatment for patient who prefer not to lose his ability to speak and he is willing to stop smoking immediately. • Chemotherapy is not necessary in patient who has local and potentially curable disease. • In the setting of lymph node-positive or locally advanced disease, the benefit of concurrent chemoradiotherapy is recommended. • Cetuximab is a monoclonal antibody and is effective when combined with radiation, it has been found to improve local control and overall survival rates.

Von Hippel-Lindau syndrome Definition • VHL syndrome is an autosomal dominant condition predisposing to neoplasia. Aetiology • due to an abnormality in the VHL gene located on short arm of chromosome 3 von-Hippel-Lindau= 3 words for chromosome 3. • VHL gene normally act as a tumor suppressor gene VHL gene normally is responsible for regulating the hypoxia-inducible factor (HIF), a transcription factor. In patients with VHL, there is constitutive expression of HIF resulting in angiogenesis and cancer development. Epidemiology • it has over 90% penetrance by the age of 65. • prevalence is 1 in 39,000. • Mean age at presentation of 27 years.

Types • Type 1 VHL is associated with tumours in eye, brain, spinal cord, kidney and pancreas. • Type 2 is associated with phaeochromocytoma: Features • haemangioblastomas of the CNS (The most common presentation) retinal haemangiomas: vitreous haemorrhage Retinal haemangioblastomas is the initial presentation in 40% of patients. Annual ophthalmological exam for haemangioblastoma is the most appropriate screening investigation cerebellar haemangiomas is another common initial presentation. CNS haemangioblastomas tend to be infratentorial. cerebellar haemangiomas secretes erythropoietin-like substance, leading to a secondary polycythaemia. haemangioblastomas are typically not cancerous, but they can compress the brain and spinal cord resulting in headaches, vomiting, paralysis, and ataxia. • cysts in various organs (e.g., kidney, pancreas, liver) renal cysts (premalignant) ↑risk of developing clear cell renal cell carcinoma. Renal cell carcinoma (Clear cell) is the commonest cause of death (70% of patients having renal cysts and carcinomas by age of 60 years). extra-renal cysts: epididymal, pancreatic, hepatic • phaeochromocytoma occurs in 20% of patients, although the incidence is much higher in those with von Hippel Lindau type 2 • endolymphatic sac tumours Diagnosis • genetic testing mutations in the VHL gene. Ideally, genetic testing in affected families should take place around the age of 5 years. Treatment • Asymptomatic small haemangioblastomas observation. • Renal cell carcinoma surgery. Monitoring • Affected individuals require: yearly urinalysis, catecholamine screening, fluorescein angiography 3-yearly brain magnetic resonance imaging.

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CT scan showing a cerebellar haemangioma in a patient with Von Hippel-Lindau syndrome. MRI showing renal cysts in patient with known Von Hippel-Lindau syndrome.

Haemangiomas • Hemangiomas are benign vascular tumors that lead to a messy clump of dilated blood vessels. • Hepatic hemangioma a benign liver tumor composed of masses of blood vessels the most common benign tumor affecting the liver. The most common site of hemangiomas in internal organs is the liver. mesenchymal in origin and usually, are solitary oral contraceptives and steroids may accelerate the growth of a hemangioma. Investigations biopsies are contraindicated because of the risk of bleeding. A good way to determine if a structure is hypervascular is to look for IV contrast enhancement. • Capillary hemangioma cherry hemangioma: also known as (Campbell de Morgan spots) benign capillary hemangioma of the elderly that does not regress benign skin lesions which contain an abnormal proliferation of capillaries. frequency increases with age. The most common benign capillary skin tumor found in elderly affect men and women equally. Features erythematous, papular lesions typically 1-3 mm in size non-blanching not found on the mucous membranes As they are benign no treatment is usually required.

• Infants with large hemangiomas should have ultrasonography of the abdomen to rule out the presence of other hemangiomas in the viscera. • Propranolol is the first line of treatment of hemangiomas causing disfigurement.

Cytotoxic agents The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents. Alkylating agents Cytotoxic Mechanism of action Adverse effects Cyclophosphamide Alkylating agent - causes cross-linking in DNA Cytotoxic antibiotics Cytotoxic Mechanism of action Adverse effects Bleomycin Degrades preformed DNA Lung fibrosis Doxorubicin Stabilizes DNA-topoisomerase II complex inhibits DNA & RNA synthesis Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Haemorrhagic cystitis, myelosuppression, transitional cell carcinoma Cardiomyopathy

Chapter 7

Haematology&Oncology Antimetabolites Cytotoxic Mechanism of action Adverse effects Methotrexate Inhibits dihydrofolate reductase and thymidylate synthesis Fluorouracil (5FU) Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase) 6mercaptopurine Purine analogue that is activated by HGPRTase, decreasing purine synthesis Cytarabine Pyrimidine antagonist. Interferes with DNA synthesis specifically at the Sphase of the cell cycle and inhibits DNA polymerase Acts on microtubules Cytotoxic Mechanism of action Adverse effects Inhibits formation of microtubules Vincristine: Peripheral neuropathy (reversible) , paralytic ileus Vinblastine: myelosuppression Vincristine, vinblastine Docetaxel Prevents microtubule depolymerisation & disassembly, decreasing free tubulin. has a further action in blocking bcl-2 Other cytotoxic drugs Cytotoxic Mechanism of action Adverse effects Cisplatin Causes cross-linking in DNA Ototoxicity, peripheral neuropathy, hypomagnesaemia Hydroxyurea (hydroxycarba mide) Inhibits ribonucleotide reductase, decreasing

DNA synthesis Notes & Notes for MRCP
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Myelosuppression, mucositis, liver fibrosis, lung fibrosis Myelosuppression, mucositis, dermatitis Myelosuppression Myelosuppression, ataxia Neutropaenia Myelosuppression

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Busulfan • alkylating antineoplastic agent, • Busulfan was the mainstay of the chemotherapeutic treatment of chronic myeloid leukemia (CML) until it was displaced by the new gold standard, imatinib • Busulfan is used in pediatrics and adults in combination with cyclophosphamide or fludarabine/clofarabine as a conditioning agent prior to bone marrow transplantation, especially in chronic myelogenous leukemia (CML) and other leukemias, lymphomas, and myeloproliferative disorders. • Busulfan lung Busulfan lung is a form of drug-induced pulmonary toxicity with an idiopathic pulmonary fibrosis-like picture. It is clinically symptomatic in 5% of patients. There are no predictors of toxicity and pulmonary function testing is not a useful “screening” test. Withdrawal of busulfan is the key step in treatment.

Combinations of chemotherapeutic agents • what is the rationale behind using combinations of chemotherapeutic agents rather than single agents? Combination therapy decreases the chances of drug resistance developing There are two main reasons for using combinations of different chemotherapy agents:

1. Different drugs will exert their effects through different mechanisms, so combining them will increase the number of tumour cells killed in each cycle.
2. It also reduces the chances therefore of drug resistance developing.

Vinblastine • Vinblastine is an M phase-specific chemotherapeutic agent that works by disrupting the assembly of microtubules via binding tubulin. • Cell death results because anaphase cannot commence without the formation of the mitotic spindle and kinetochore. • Which cellular event occurs in the same phase of the cell cycle at which vinblastine functions? Breakdown of the nuclear membrane • Breakdown of the nuclear membrane occurs during the prometaphase portion of mitosis.

Cyclophosphamide • Cyclophosphamide is an alkylating agent used in the management of cancer and autoimmune conditions. • It works by causing cross-linking of DNA • Cyclophosphamide is inactive unless metabolised by the liver to 4-hydroxyl cyclophosphamide, which decomposes into alkylating species as well as to chloroacetaldehyde and acrolein

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Haematology&Oncology Adverse effects • haemorrhagic cystitis (Acrolein causes chemical cystitis): incidence reduced by the use of hydration and mesna • myelosuppression • transitional cell carcinoma • premature ovarian failure , • infertility in both men and women. Mesna • 2-mercaptoethane sulfonate Na • a metabolite of cyclophosphamide called acrolein is toxic to urothelium • mesna binds to and inactivates acrolein helping to prevent haemorrhagic cystitis

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Cisplatin • Platinum-based antineoplastic (end with: -platin) Mechanism of action • Causes crosslinking in DNA makes it impossible for rapidly dividing cells to duplicate their DNA for mitosis. Side effects • Marrow toxicity • Ototoxicity Due to vestibulocochlear nerve damage (CNVIII) Sodium Thiosulfate Prevents Cisplatin-Induced Hearing Loss in Children With Cancer • Peripheral neuropathy • Nephrotoxicity The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species Hypocalcaemia, hypomagnesaemia and hypokalaemia may occur as a result of nephrotoxicity Amifostine is an antidote for cisplatin treatment to counteract nephrotoxicity. Adequate hydration and diuresis is used to prevent renal damage. Chloride diuresis is a renal procedure that can be performed to prevent the nephrotoxicity caused by cisplatin. • Alopecia, • Changes in taste. • Although optic neuritis is described it is not a typical side effect.

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Trastuzumab A baseline echocardiogram to assess heart function is recommended prior to starting trastuzumab. • Trastuzumab (Herceptin) is a monoclonal antibody directed against the HER2/neu receptor. • It is used mainly in metastatic breast cancer although some patients with early disease are now also given trastuzumab. Adverse effects • flu-like symptoms and diarrhoea are common • cardiotoxicity: associated with Dilated cardiomyopathy in 2% to 7% of users more common when anthracyclines have also been used(eg : Doxorubicin). Toxic to cardiac muscle itself with relative sparing of the electrical conductivity of the heart Studies have shown that activation of Erb-b2 (also known as HER-2), the receptor blocked by trastuzumab (Herceptin), is important in preventing the development of cardiomyopathy Mechanism Anthracyclines activate stress signal pathways within the heart cardiac damage HER2 activation is protective against the damage that this stress signaling induces HER2 inhibition removes this layer of protection, leading to dilated cardiomyopathy. An echo is usually performed before starting treatment Regular echocardiogram (three monthly) is the best test to assess treatment safety Reduction of greater than 10% in ejection fraction indicating the need to stop treatment. In which chemotherapeutic agents is the cumulative dose limited due to cardiotoxicity? anthracycline chemotherapeutic agents (eg: Epirubicin) Epirubicin and the other anthracycline chemotherapeutic agents are extremely potent but are limited by dose constraints. Cumulative doses of over 900 mg/m2 can lead to significant cardiac toxicity and heart failure. Trastuzumab can cause direct myocardial damage and must be monitored with regular echocardiograms but it is not limited to a maximum lifetime dose.

Erlotinib • Erlotinib specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase (which is required for the conformational change) and binds in a reversible fashion to the

adenosine triphosphate binding site. • For the signal to be transmitted, two members of the EGFR family need to come together to form a homodimer. These then use the molecule of adenosine triphosphate (ATP) to autophosphorylate each other, which causes a conformational change in their intracellular structure, exposing a further binding site for binding proteins that cause a signal cascade to

the nucleus. By inhibiting the ATP, autophosphorylation is not possible and the signal is stopped. • A key issue with EGFR-directed treatments is that after a period of 8-12 months, the cancer cells become resistant to the treatment. This most commonly occurs due to a mutation in the ATP binding pocket of the EGFR kinase domain. This prevents the binding of erlotinib (Tarceva).

Imatinib • Belong to the class of Signal transduction inhibitor • Imatinib is a tyrosine kinase inhibitor which is fairly specific for the bcr/abl protein. It blocks the active site, which has a number of downstream effects. The result is reduced cell proliferation, reduced cell motility, decreased adhesion and increased apoptosis. • Indications accelerated or blast crisis phase of CML. gastrointestinal stromal tumours.

Tamoxifen Tamoxifen is a selective estrogen receptor modulator (SERM) which acts as an oestrogen receptor antagonist and partial agonist. It is used in the management of oestrogen receptor positive breast cancer Adverse effects • menstrual disturbance: vaginal bleeding, amenorrhoea • hot flushes • venous thromboembolism Particularly during and immediately after major surgery or periods of immobility • endometrial cancer Tamoxifen is typically used for 5 years following removal of the tumour. Raloxifene is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer

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UK licensed monoclonal antibodies Name Target Licensed indication Infliximab TNF-α Refractory Crohn's, Crohn's fistulas, refractory rheumatoid arthritis Palivizumab F protein on RSV Prophylaxis, RSV in premature infants or brochopulmonary dysplasia Abciximab Platelet glycoprotein IIb/IIIa High risk coronary intervention Rituximab CD20 Refractory low grade or follicular B cell lymphoma Basiliximab IL-2 receptor α chain Prophylaxis of acute rejection in allogeneic renal transplantation Daclizumab IL-2 receptor α As Basiliximab Trastuzumab HER 2 growth receptor Relapsed HER2 (high) breast malignancy IL-2, interleukin 2; TNF-α, tumour necrosis factor α; RSV, respiratory syncitial virus.

Rituximab • Rituximab binds to CD20, an antigen located on pre-B and mature B-lymphocytes • The receptor is thought to mediate B-cell lysis and apoptosis • After rituximab therapy, levels of B-lymphocytes appear suppressed for around 6 months, with levels slowly increasing after this time • As well as for rheumatoid arthritis, rituximab is also used for the treatment of nonHodgkin's lymphoma • Infusion reactions associated with cytokine release occur in up to 15% of patients receiving rituximab, and the medicine is administered in a specialist centre for this reason

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Cetuximab • Action epidermal growth factor receptor (EGFR) inhibitor Cetuximab works by blocking the extracellular domain of EGFR preventing ligand binding and therefore preventing downstream signal transduction. • . Cetuximab is a monoclonal antibody given by intravenous infusion • The patient's tumour must express k-ras wild-type as k-ras mutated is constitutively active regardless of whether a ligand is attached or not. Which histopathological subtypes is essential for successful treatment with cetuximab? K-ras wild-type Cetuximab and other EGFR inhibitors only work on tumors in which Kras is not mutated it has no effect in colorectal tumors with a K-ras mutation (this also applied to the EGFR antibody panitumumab). genetic testing to confirm the absence of K-ras mutations (and so the presence of the K-ras wild-type gene), is now clinically routine before the start of treatment with EGFR inhibitors. • Cetuximab is licensed by NICE in metastatic colorectal cancer for k-ras wild-type proven patients who require downstaging prior to surgical resection of liver metastatic disease. 75% of patients with metastatic colorectal cancer have an EGFR-expressing tumor and are therefore considered eligible for treatment with cetuximab or panitumumab • Side effect acne type rash (the most important and serious SE).

Capecitabine • Capecitabine is the oral analog of 5-fluorouracil, a chemotherapeutic agent which is broken down, predominantly, by dihydropyrimidine dehydrogenase (DPD). • Deficiency of dihydropyrimidine dehydrogenase (DPD) is autosomal recessive and will lead to a toxin buildup which in homozygous patients is usually fatal. Capecitabine versus 5-fluorouracil (5-FU) • Advantages of capecitabine versus 5-fluorouracil (5-FU) Can be orally administered The major difference between capecitabine and 5-FU is that capecitabine is an oral prodrug of 5-FU. 5-FU is one of the most effective chemotherapeutic agents used in the treatment of advanced colorectal cancer, it is administered via IV infusion. Capecitabine is orally administered chemotherapy, it is then metabolised to 5-FU. The final step in metabolism to 5-FU is thymidine phosphorylase, higher activity of thymidine phosphorylase occurring in tumour tissues. • Evidence suggests that efficacy of capecitabine versus 5-FU is broadly similar,

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Chemotherapy side-effects: nausea and vomiting • Nausea and vomiting are common side-effects of chemotherapy. • Risk factors for the development of symptoms include: anxiety age less than 50 years old concurrent use of opioids the type of chemotherapy used • For patients at low-risk of symptoms then drugs such as metoclopramide may be used firstline. • For high-risk patients, then 5HT3 receptor antagonists such as ondansetron are often effective, especially if

combined with dexamethasone

Adverse effects of other cancer treatment Purine analogue (eg: fludarabine) for CLL Pneumocyscis jirovecii infection • This cytotoxic agent affects T-cell function. Patients are therefore prone to opportunistic infections including pneumocystis infection. • Patients therefore receiving purine analogues should also receive co-trimoxazole to reduce this risk. • All patients who receive purine analogues are at risk of transfusion-associated graftversus-host disease and therefore should receive irradiated blood products. The clinical features of transfusion associated graft-versus-host disease are: 1. pancytopaenia, 2. liver dysfunction, 3. diarrhoea and 4. rash Etoposide secondary haematological malignancy • In patients who have received Etoposide, secondary haematological malignancy may develop in as little as 1-3 years. • It is currently indicated for the treatment of small cell lung cancer and non-seminomatous testicular carcinoma.

Filgrastim • Action granulocyte colony-stimulating factor (G-CSF) • Mechanism Filgrastim is similar to naturally occurring granulocyte colony-stimulating factor (GCSF). produced by recombinant DNA technology using genetic material of Escherichia coli. stimulating the bone marrow to increase production of neutrophils. • Indications used to treat neutropenia caused by: chemotherapy, radiation poisoning, congenital neutropenia aplastic anemia also used to increase white blood cells for gathering during leukapheresis. • It is given either by injection into a vein or under the skin. • side effects The most commonly observed adverse effect is mild bone pain after repeated administration and local skin reactions at the site of injection Severe side effects include splenic rupture and allergic reactions. Other side effects include

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