

MEDICAL ONCOLOGY HANDBOOK FOR JUNIOR MEDICAL OFFICERS



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Townsville
Hospital
and Health
Service

Medical Oncology Handbook for Junior Medical Officers
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Townsville Cancer Centre is a teaching partner of the James Cook University and
research partner of the Australian Institute of Tropical Health & Medicine,
Townsville, Queensland, Australia.

INTRODUCTION:

Welcome to the Department of Medical Oncology at the Townsville Cancer Centre. By the end of the term, you should be able to identify and manage common side effects of chemotherapy and radiotherapy in the areas of general practice, emergency departments and rural hospitals and general medical wards. You will also have some understanding of treatment principles and aims of cancer therapy for common malignancies. This handbook is meant for the use of resident medical officers and basic physician trainees. It may also be useful to advanced trainees in their first few months of training. We hope that this experience will give you the skills to deal with cancer patients with positive and empathetic approach.

If you are encountering emotional difficulties when dealing with poor prognosis, please talk to one of us earlier in the term to learn ways to deal with it effectively.

Enjoy the medical oncology rotation.

Regards,

CONSULTANT MEDICAL ONCOLOGISTS

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ORIENTATION TO MEDICAL ONCOLOGY DEPARTMENT

Junior medical officers play an important role in the day-to-day care of patients in Medical Oncology Department. It is critical that you work in close collaboration with senior medical, nursing and allied health staff, along with our administrative support officers.

We have outlined some useful practice points will help you to settle into our department smoothly.

Educational and training resources

Electronic medical records

Townsville Cancer Centre uses MOSAIQ as its EMR. Please become familiar with MOSAIQ by contacting the CNC for MOSAIQ on 32888 or through our administrative support officers 44331671 prior to commencement. We assume that you are familiar with the ieMR, the THHS-wide EMR.

Chemotherapy protocol

eviQ is a very useful website to learn chemotherapy protocols and side-effects. It also contains information about managing extravasation (www.eviq.org.au).

NB: RMOs and interns are not expected to write chemotherapy orders. When writing oral chemotherapy, targeted agents and colony stimulating factors, please exercise caution and follow the advice of your registrars and consultants.

Medication prescribing

Quality of inpatient medication prescribing can be improved by adhering to the THHS guide for inpatient medication prescription.

End of life care bedside tutorial and introduction to telehealth

These two topics are available on YouTube (searchable using the titles) and are useful resources for developing mental frameworks for approaching these topics.

Basic principles of oncology

Clinical oncology for medical students is a useful resource for learning basic principles of oncology care.

[http://wiki.cancer.org.au/oncologyformedicalstudents/Clinical Oncology for Medical Students](http://wiki.cancer.org.au/oncologyformedicalstudents/Clinical_Oncology_for_Medical_Students)

Documentation

Since funding for operations of medical departments are linked to their clinical activities, it is important to use coding terminologies during documentation of patient notes.

Issues with central venous access devices

We use central lines commonly in oncology and therefore, it is prudent to be aware of managing complications. As a rule, when it is difficult to draw blood from lines or inject fluids, it is important to use imaging (including chest-Xray and linogram) for checking the position and viability before using the lines. Please seek advice when infection and thrombosis are suspected/proven. We can rarely save lines using antibiotics

Self-care

Please maintain physical, emotional, mental and spiritual health. Take regular breaks as much as possible and maintain effective work-life balance (This doesn't mean work is bad and life is good; it is about having a balance that suits your needs). Please seek help if you think you need help including emotional support and guidance.

Day unit

- Orientate with the Day-unit staff and introduce yourself to senior nursing staff and establish working relationships with them.
- You are the first point of call for any issues in day unit and therefore, please make sure that you are always available during rostered hours. Day unit relies on effective discharge of patients to maintain flow. A delay due to one issue could delay the whole day's operation and care of other patients.
- Infusion reactions are medical emergencies: You should always attend to a patient having a reaction, leaving everything else. If you are not available, please make sure another doctor can attend the patient immediately.

Clinics

- Being "On Time" is important! Clinics start on time so that patients can receive their chemotherapy in day unit without delays.
- If a patient is seen by the consultant in clinic, please ask them to sign the blue form.

Dealing with consultants and registrars

Please don't hesitate to seek help from senior medical staff. All changes in management should be discussed. Harass them even if they are busy!

Dealing with nurses and other health professionals

- Advice from nursing staff is an important resource for patient care.
- When chemotherapy changes, delays or cancellation occur, it is prudent to inform the nursing and pharmacy staff.

Dealing with patients on chemotherapy and chemotherapy orders

- When you see a patient for chemotherapy review, please prepare the care plans for the next cycle.
- Dose reduction: After consultation with senior medical staff, please document dose reductions and make changes on MOSAIQ scripts. If there is a dose increase, it is possible only from the next cycle.
- All chemotherapy bookings are done through administration officers and day unit schedulers.
- Initial chemotherapy orders should be counter-signed by a consultant.
- Please be familiar with important practice points for common medications as described in this hand book.

Admitted patients

- Make sure they are seen by consultants within 24 hours of admission and on a regular basis;
- Have an expected date of discharge and do the discharge planning, including timely completion of high-quality discharge summaries; **ideally on the day of discharge, using the national guide for discharge summaries.**
- If a patient undergoing chemotherapy is admitted with complications, inform the day-unit and the treating consultant of any changes in treatment. It will also be important to document this episode on MOSAIQ for continuity of care and future planning including dose changes and addition of GCSF.
- If any oncology patient is admitted in another department or another hospital with complications, inform the treating consultant and document on MOSAIQ.
- In-patient consults from other departments need to be seen on the same day, discussed with or seen by the consultant on call and documented on MOSAIQ.
- It is important to inform the consultant on call of any patients admitted to medical oncology.

Remember to use telehealth for appointments via our teleoncology coordinator. Telehealth is appropriate for most rural & selected metro patients

CONSULTANT MEDICAL ONCOLOGISTS/ SENIOR MEDICAL OFFICERS

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WEEKLY TIMETABLE

| Time | Monday | Tuesday | Wednesday | Thursday | Friday |
|-----------|------------------------------|---|--|-------------------------------------|--------------------------------------|
| 0745-0830 | GI MDT (0800-0900) | | Breast MDT Gynae MDT every three weeks | | Colorectal MDT (0800-0900) |
| 0900-1200 | Clinics SV, ZO, CR | Clinic SV, ZO H&N MDT | Clinic CM, SV, AJ | Clinic CM, CR, AJ, ZO | Clinic SV, ZO, AJ, |
| 1230-1330 | Grand rounds (RDA) | Clinic SS | Radiology (Weekly)/ Uro MDT (fortnightly) | Clinical Reasoning (RDA) | |
| 1330- | Clinic Spill-over | 1430-1530 Long case practice for BPT, RMO and Interns | Clinic AJ/SV | Skin MDT (1300-1400) | |
| 1400-1500 | | | | Journal Club Reg training M&M | |
| 1500-1600 | | | | | |
| 1600-1700 | | | Neuro-MDT (monthly) | Lung MDT | |

Educational aims for this rotation:

- Management of complications of systemic therapy.
- Familiarity with common systemic therapy regimens.
- Management of medical emergencies.
- Management of quality of life issues.
- Understanding of psychosocial issues related to cancer patients- discussing prognosis, breaking bad news, family meetings etc.
- Understanding of curative vs palliative intent therapy.
- Familiarity with the management of common malignancies including multidisciplinary approach.

Routine tasks:

- Managing inpatients – routine inpatient care, ward consultations, weekend roster (it is the responsibility of the registrars to do this roster).
 - Prior to consultant ward rounds, results should be available for imaging studies, histology and blood tests.
 - (For interns, all the procedures except IV cannulation need to be initially supervised by registrars or consultants).
- Review of day unit patients.
- Review of clinic patients.
- Phone consults from GPs, other staff and the patients.
- Participation in a long case practice session each Tuesdays (taking turn among BPT, RMO and Interns) and other education sessions listed in the time- table
- Participation in departmental Research and/or Quality Improvement projects

Day unit and clinic patient review:

- To assess fitness for systemic therapy.
- To assess symptoms and side effects of treatment.
- To address new concerns.
- To assess for treatment response-
 - tumour markers,
 - scans- performed after 2-3 cycles.
- To update systemic therapy scripts.

PRINCIPLES OF MANAGEMENT OF PATIENTS ON SYSTEMIC THERAPY

Assessing fitness for systemic therapy

Fitness for systemic therapy depends on many factors:

- performance status,
- the type and severity of side effects from previous cycles or doses,
- blood parameters,
- co-morbidities and
- Patient choice

If cure is the aim, it is usual to accept mild-to-moderate, non-life-threatening toxicities and continue treatment without delaying or reducing the dosage to minimise side effects. Sometimes it is prudent to use supportive therapy such as G-CSF to maintain dose intensity. However, in patients with incurable metastatic disease where quality of life is paramount, dose delays or dose reductions are necessary.

Performance status

This is graded using the Eastern Cooperative Oncology Group (ECOG) scale.

| Grade | ECOG performance status |
|--------------|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled, cannot carry on any self-care, totally confined to bed or chair |

Usually, patients with ECOG grade > 2 are not fit for chemotherapy. The exception is chemotherapy-sensitive cancers such as lymphoma and small cell lung cancers. The decision to offer chemotherapy must be individualised, depending upon factors such as age of the patient, & comorbidities. For example, a young patient with metastatic breast

cancer with poor performance status could still be offered systemic treatments. Targeted agents and endocrine therapy are usually tolerated better than chemotherapy.

Toxicity from previous cycles of systemic therapy

Clinicians must assess whether a side effect is affecting QOL, performance status or is life threatening:

First, determine the type and severity of side effects.

For example, in patients with early breast cancers undergoing taxane chemotherapy, mild peripheral neuropathy is acceptable. However, in patients undergoing fluorouracil-based therapy, ongoing or severe diarrhoea necessitates a dose delay and dose reduction of subsequent cycles.

Mid-cycle neutropenic fever usually requires dose reduction of the subsequent cycle unless the cancer is curable. If the cancer is curable or a substantial duration of remission is expected, prophylactic colony stimulating factors such as pegfilgrastim (neulasta) and/or antibiotics can reduce the risk of subsequent and opportunistic infections.

Next, determine the effects on important organs, such as:

- Fertility. Discuss semen cryopreservation with men. Options for women should also be discussed, particularly in young women of child-bearing potential and where curative intention treatment is planned. Options include preservation of egg, embryo and a piece of ovary is offered by some fertility groups. Women who wish to discuss this option should be referred to a fertility specialist.
- Renal function, liver functions.
- Cardiac function. This may affect the dosage of anthracyclines (check ejection fraction before treatment begins and after every 2–3 cycles) and trastuzumab (check ejection fraction before treatment begins and every 3 months during therapy).

Toxicity is graded according to NCI common terminology criteria for adverse events¹.

1. Blood parameters:

- a. Requires haematological and non-haematological parameters.

¹ National cancer institute common toxicity criteria (*CTCAE, version 4.03, June 2010*), *National Institutes of Health, National Cancer Institute* .
<http://ctep.cancer.gov>.

For most regimens, a neutrophil count $>1.5 \times 10^9/L$ and platelet count $> 100 \times 10^9/L$ are needed for safe administration of chemotherapy. For some regimens, lower levels may be acceptable.

Single agent bleomycin and vincristine are not myelotoxic and administration is not affected by blood counts.

Renal function is important for cisplatin and carboplatin and liver function for docetaxel, Magnesium levels especially for cisplatin and Calcium levels for denosumab.

Action - withhold treatment until recovery, then dose delay and/or dose reduction after discussion with senior staff.

b. Pregnancy test: For women of child bearing potential, perform beta HCG before initiating treatment.

2. Non-haematological toxicity

(Also see the summary of common side effects for selected drugs on page 25).

a. Diarrhoea – mainly 5FU based, Irinotecan, Oxaliplatin, docetaxel.

Action - low threshold for withholding therapy if diarrhoea the day before, or moderate diarrhoea for longer than expected duration, or nocturnal diarrhoea.

b. Mucositis/mouth care.

c. Emesis.

Action - (see anti-emetics) change class, change route, add another agent, or reduction of chemotherapy dose.

d. Skin Rash.

e. Neuropathy- Cisplatin, Oxaliplatin, Taxanes and Vinca alkaloids.

Doses are delayed, reduced or omitted if neuropathy persists or interferes with function.

f. Autotoxicity- Cisplatin.

g. Renal impairment- Cisplatin.

Action- prior to most agents, need to check creatinine especially if they are renally cleared and Carboplatin dose adjusted based on creatinine.

h. Pulmonary toxicity- bleomycin, methotrexate.

3. Physical examination-Routine exam and oral cavity, central lines and IV site infections, lymph nodes and signs of recurrence and side effects.

Symptom control

Discussion or shared care with palliative care is helpful. However, basic principles are as follows:

(Also refer to the Guide for inpatient medication prescription)

1. Pain: Always find out the cause of the pain before prescribing analgesics.

Total daily morphine requirement will guide the required daily slow release dose. When prescribing breakthrough, the dose is 1/6th of the daily dose. So, if you are increasing the daily dose, breakthrough needs to increase as well. If oral intake is difficult—patches or infusional morphine are options.

4. Dyspnoea: Again, find out the cause, for cancer related dyspnoea—nebulised morphine and anxiolytics could be helpful.

When to stop cancer treatment

A decision to stop treatment prematurely depends on the aim of the treatment.

For curable cancers, it is acceptable to continue treatment with dose modifications. However, life threatening or severe dose limiting toxicities usually necessitate cessation of treatment (eg. moderate to severe peripheral neuropathy with taxanes and oxaliplatin, severe enteritis from fluorouracil). Alternative regimens are sometimes available.

If the cancer is incurable and the toxicities severely interfere with the activities of daily living, treatment may have to be stopped.

Deteriorating performance status and organ function usually require cessation of treatment. Ongoing neutropenia or thrombocytopenia typically means the patient is not going to handle further chemotherapy.

In case of patients with metastatic disease, palliative care team referral is done even when they are on active treatment, to improve symptom management and supportive care.

Common side effects of systemic therapeutic agents

- Adriamycin/ Epirubicin

Be aware of cumulative dose, perform cardiac function every 2-3cycles.

- Bleomycin-

Lung functions every 3 weeks (consider, discuss with consultant)

- Cisplatin

Renal function, Mg levels, peripheral neuropathy, hearing loss/tinnitus.

- Carboplatin

Adjust dose based on renal function; Dose = AUC x (GFR+25).

- 5-FU

Diarrhoea-In severe cases, it can be life threatening.

Before proceeding with treatment, please make sure no diarrhoea on the day and on the previous day of chemotherapy. When diarrhoea has been moderate to severe, consider dose reduction or cessation.

5FU could also cause coronary artery spasm.

In severe 5FU enteritis, admission for bowel rest +/-TPN along with aggressive anti diarrhoeal and antibiotics may be required.

- Gemcitabine

Pneumonitis, peripheral edema.

- Irinotecan- Normal bilirubin is required.

Diarrhoea and flushing: acute symptoms related to parasympathetic system could settle with atropine with chemotherapy.

For chronic symptoms, dose reduction may necessary.

- Taxol/ Paclitaxel

Peripheral neuropathy, flu like symptoms.

- Taxotere/Docetaxel

Adequate liver function, peripheral edema, neuropathy, rash.

- Oxaliplatin

Cold induced paresthesia (acceptable), but signs of peripheral Neuropathy may be dose limiting. Laryngo spasm (cold induced) and bronchospasm are other acute side effects.

- Cyclophosphamide/ Ifosfamide

Renal function, hydration, confusion from encephalopathy.

- Capecitabine

Mucositis, hand foot syndrome, rash, angina, diarrhoea.

- Trastuzumab

Cardiac function every 3 months.

- Cetuximab/Panitumumab

Acneform rash.

- Methotrexate

Folinic acid rescue for higher doses only.

- Caelyx/ Liposomal doxorubicin

Rash, hand foot syndrome, cardiac function.

- Avastin/Bevacizumab

Hypertension and proteinuria.

- Denosumab

Prolonged hypocalcaemia (require calcium suppliments).

- Dabrafenib (b-Raf inhibitor)

Pyrexia, rash, squamous cell carcinomas of skin.

- Mekinist – MEK inhibitor

Usually combined with Dabrafenib to reduce incidence of skin squamous cell carcinoma

- Zolendronic acid

Renal function, hypocalcaemia, requires dose reduction for renal impairment.

Need calcium supplements.

- Check point inhibitors (Ipilimumab, nivolumab, Pembrolizumab)

Autoimmune complications such as colitis, pneumonitis, hepatitis and inflammation of pituitary gland leading to Addison's crisis require urgent medical attention.

- Alopecia

This does not occur with every medication.

Common with breast, ovarian, sarcoma, small cell, lung (Carbo/Taxol) cancer and testicular regimens

Common chemotherapy abbreviations

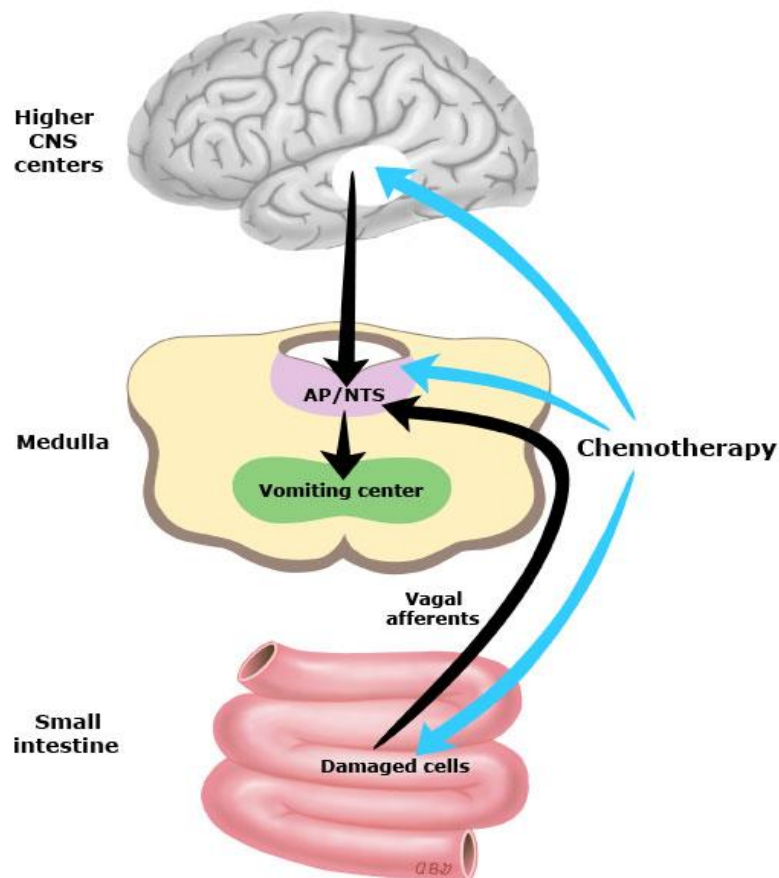
| | |
|---|---|
| <i>Breast Cancer</i> | |
| TAC | Docetaxel, Adriamycin, Cyclophosphamide |
| FEC | 5Fluorouracil, Epirubicin, Cyclophosphamide |
| AC (inc DD) | Adriamycin, Cyclophosphamide (DD for dose dense) |
| TC | Docetaxel, Cyclophosphamide |
| <i>Colo-rectal Cancer</i> | |
| FOLFOX | Oxaliplatin, Continuous infusion 5Fluorouracil and Leucovorin |
| XELOX | Oxaliplatin, Capecitabine |
| FOLFIRI | Irinotecan, Continuous infusion 5 Fluorouracil and Leucovorin |
| XELIRI | Irinotecan, Capecitabine |
| <i>Gastric/Lower Oesophageal</i> | |
| ECF | Epirubicin, Cisplatin, 5 Fluorouracil |
| EOX | Epirubicin, Oxaliplatin, Capecitabine |
| FLOT | 5FU, Leucovorin, Oxaliplatin, Docetaxel |
| <i>Head and Neck Cancer</i> | |
| TPF | Docetaxel, Cisplatin, 5 Fluorouracil |
| <i>Testicular Cancer</i> | |
| BEP | Bleomycin, Etoposide, Cisplatin |
| TIP | Paclitaxel, Ifosfamide, Cisplatin |

Chemotherapy related emesis

Causes of nausea and vomiting in patients receiving chemotherapy:

- Chemotherapy related.
- Other causes such as gastro-oesophageal reflux disease or medications related.

Pathways by which chemotherapeutic agents may produce an emetic response²



Chemotherapy-induced emesis results from stimulation of a multistep reflex pathway that is controlled by the brain and triggered by afferent impulses to the vomiting centre from the chemoreceptor trigger zone, gastrointestinal tract (by way of vagal afferent fibres), and possibly, the cerebral cortex.

² Hesketh, P. J. (2008). "Chemotherapy-induced nausea and vomiting." *New England Journal of Medicine* **358**(23): 2482-2494.

Emetogenic potential of chemotherapy agents

| High (>90%) | Moderate (60-90%) | Moderate (30-60%) | Low (10-30%) | Minimal |
|-----------------------------------|-------------------------------------|---------------------------------------|-------------------------|----------------|
| Cisplatin >50mg/m ² | Carboplatin | Cyclophos <750mg/m ² | Xeloda/5FU | Bleomycin |
| Dacarbazine | Cisplatin <50mg/m ² | cabazitaxel | Docetaxel | Herceptin |
| Cyclophos> 1.5g/m ² | Doxorubicin >60mg/m ² | Doxorubicin 20-60mg/m ² | Caelyx | Cetuximab |
| | Epirubicin >90mg/m ² | Epirubicin <90mg/m ² | Taxol | Vincristine |
| | | Irinotecan, Oxaliplatin | Gemzar, | Vinorelbine |

*Acute or early nausea and vomiting- within 24 hours of chemotherapy.

*Delayed/late – after 24 hours of chemotherapy. .

For Cisplatin, emesis reaches its maximal intensity 48-72 hours after chemotherapy and can last up to 6-7 days.

*Anticipatory nausea and vomiting- Nausea before chemotherapy

Five neurotransmitter receptor sites are of primary importance in the vomiting reflex: M1 – muscarinic, D2 – dopamine, H1 – histamine, 5-hydroxytryptamine (HT)-3 – serotonin, Neurokinin 1 (NK1) receptor – substance P

Antiemetics

- Neurokinin 1 receptor antagonist- Aprepitant (emend), fosaprepitant (Only for prophylaxis).
- 5HT₃ antagonists: ondansetron (zofran), granisetron & palonosetron (aloxi).
- Dopamine antagonists: 1. Phenothiazines- prochlorperazine, 2. Benzamides: Metoclopramide. 3. Butyrophenons-haloperidol.
- Glucocorticoids: active in early and delayed nausea.
- Anti-histamines: Promethazine.
- Benzodiazepins: Lorazepam (useful for anticipatory emesis).

High emetogenic drugs and anthracycline containing regimens for breast cancer³

- NK1 inhibitors: eg Emend (Aprepitant)

Day 1: 165 mg pre chemotherapy with no subsequent doses.

Plus

- 5HT3 antagonists: eg Aloxi (Palonosetron) 250 mcg IV on Day 1 only or Ondansetron 8mg twice daily for 2-3 days starting the night of chemotherapy.

Plus

- Dexamethasone

8-12 mg IV pre-chemo and 8mg oral mane for 2-3 days.

NB- for patients who experience sudden decline in well-being when steroids are stopped, a weaning off regimen might be useful.

- Metoclopramide

10 mg Q6H PRN.

NB: 5HT antagonists can be constipating - so warn patients about prevention of constipation. No need to prescribe take-home 5HT antagonists after Palonosetron.

Moderately emetogenic drugs or combination of drugs:

- 5HT3 antagonist: eg Aloxi (Palonosetron) 250 mcg IV on day 1**Plus.**
- Dexamethasone 8 mg IV pre-chemo and 8mg oral mane 2-3 days.

NK1 inhibitors can be added to the above regimen if the patients experience nausea & vomiting after moderately emetogenic chemotherapy.

Mildly emetogenic drugs:

Usually premedication with metoclopramide 10 mg Q6H PRN would be adequate. If nausea is not controlled, we may have to treat it like moderate drugs after excluding other causes of nausea such as gastroesophageal reflux and ulcers/gastritis.

If nausea persists, consider other causes.

Addition of lorazepam 1 mg Q6H PRN may be useful especially for anxious patients.

³ Roila, F., J. Herrstedt, et al. (2010). "Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference." *Annals of Oncology* **21 Suppl 5**: v232-243.

PRINCIPLES OF TARGETED THERAPY

If we use analogy of pesticides: empiric chemotherapy would be “Raid” while targeted therapy is “Roach Hotel”.

Dr David Gandara

It is like using a “smart” bomb versus a “cluster” bomb.

Dr Nevin Murray

The figure below depicts typical targets for anti-cancer drugs which could be pathways, processes and physiology which are uniquely disrupted in cancer cells: receptors, genes, angiogenesis, tumour pH etc.

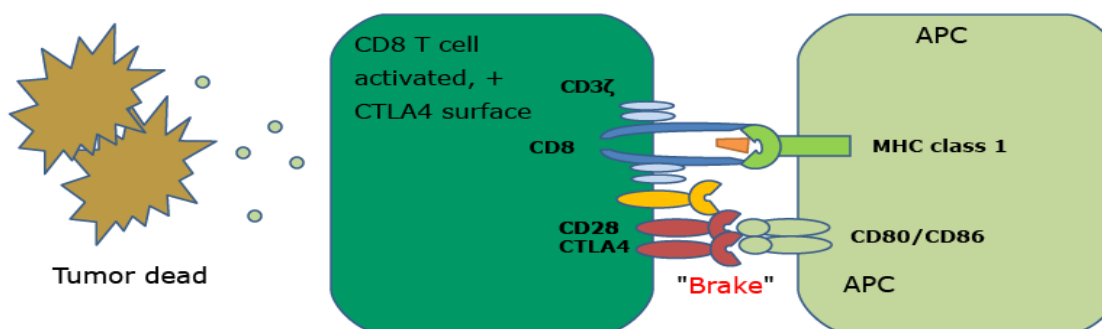


Table 1 below depicts some targets and commonly available anti-cancer drugs in common solid tumours.

Table 1 Targets and examples of treatments for common solid tumours.

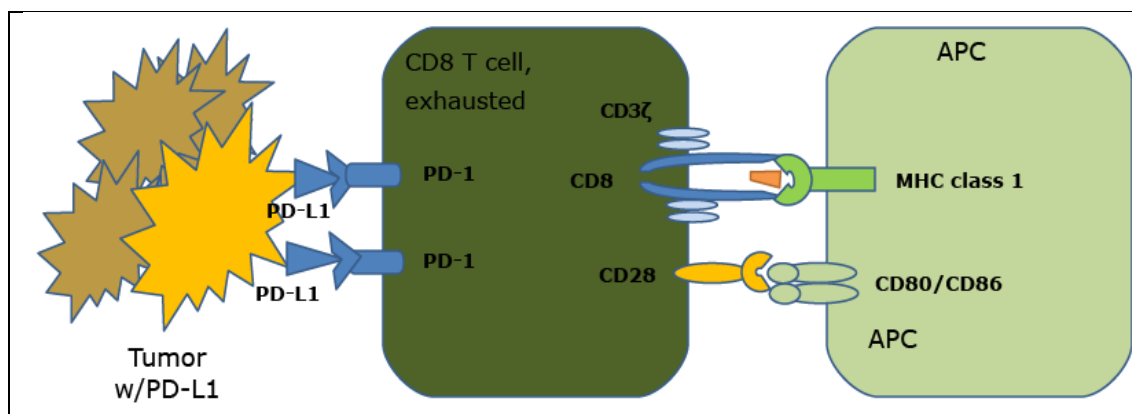
| Disease | Target | Treatment |
|------------------------|--------------------------|------------------------------------|
| Adenocarcinoma of lung | EGFR exon 9, 11 mutation | Erlotinib, Gefitinib, Afatinib |
| | T 790M | Osemertinib |
| | ALK-EML4 fusion gene | Crizotinib/Alectinib |
| Melanoma | BRAF | Dabrafenib, Vemurafinib |
| | MEK | Mekinist |
| Colon Cancer | RAS | Cetuximab, Panitimumab |
| Breast Cancer | Her 2 neu amplification | Trastuzumab, Pertuzumab, Lapatinib |
| | ER and PR | Tamoxifen, Aromatase Inhibitors |
| Prostate Cancer | AR receptor | Enzalutamide, Abiraterone |
| GIST | CD 117 (c-kit) | Imatinib Mesylate |

PRINCIPLES OF CANCER IMMUNOTHERAPY



(CTLA4 outcompetes CD28 for CD80 and CD86, and the costimulatory signal ceases as the target is eliminated, reducing the release of pro-effector cytokines such as IL-12 and cytotoxic enzymes such as perforin and granzyme B. Homeostasis is restored.)

In a state of chronic antigen presentation, such as malignancy, the chronic presence of antigen or pro-inflammatory cytokines (IL-12, IFN gamma, etc) can upregulate PD-1 expression on the T cell; tumour clones can also select for PD-L1 expression. With PD-1-PD-L1 binding, even in the presence of the costimulatory molecule, "peripheral exhaustion" can occur.



The anti-CTLA-4 antibody, [ipilimumab](#) was the first immune checkpoint inhibitor to be approved based upon its ability to prolong survival in patients with metastatic melanoma.

Programmed cell death 1 (PD-1) is a trans-membrane protein expressed on T cells, B cells, and NK cells. It is an inhibitory molecule that binds to PD-ligand 1 (PD-L1; also known as B7-H1) and PD-L2 (B7-H2). PD-L1 is expressed on the surface of multiple tissue types, including many tumour cells, as well as hematopoietic cells; The IgG4 subclass PD-1 inhibiting antibodies like [nivolumab](#) and [pembrolizumab](#) prolonged overall survival in randomized trials in various cancers, including metastatic melanoma,

clear cell renal carcinoma, bladder cancer, head and neck cancer and non-small cell lung cancer.

Immune Response Criteria: The patterns of response to treatment with these immunotherapy agents differ from those with molecularly-targeted agents or cytotoxic chemotherapy in several important respects.

Toxicities associated with checkpoint inhibitor immunotherapy

Checkpoint inhibition is associated with a unique spectrum of side effects termed immune-related adverse events (irAEs) or, occasionally, adverse events of special interest. IrAEs include dermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events⁴.

In general, treatment of moderate or severe irAEs requires interruption of the checkpoint inhibitor and the use of corticosteroid immunosuppression. Treatment is based upon the severity of the observed toxicity:

- For patients with grade 2 (moderate) immune-mediated toxicities, treatment with the checkpoint inhibitor should be withheld and should not be resumed until symptoms or toxicity is grade 1 or less. Corticosteroids should be started if symptoms do not resolve quickly.
- For patients experiencing grade 3 or 4 (severe or life-threatening) immune-mediated toxicities, treatment with the checkpoint inhibitor should be permanently discontinued. High doses of corticosteroids ([prednisone](#) 1 to 2 mg/kg/day or equivalent) should be given. When symptoms subside to grade 1 or less, steroids can be gradually tapered over at least one month.
- Patients who will benefit from corticosteroids generally do so within days. If symptoms do not clearly improve, particularly after approximately three days with intravenous steroids, our approach is to administer [infliximab](#) (5 mg/kg) rather than continue with a prolonged course of high-dose IV corticosteroids. If symptoms persist after the first infliximab dose, a second dose of infliximab (5 mg/kg) can be repeated two weeks after the initial dose.

Detailed management of various toxicities is covered by Cancer Institute of NSW's eviQ:Cancer Treatments Online site. Free registration is required for login.

⁴ Naidoo J et al.(2015) Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Annals of Oncology* 2015;26(12):2375

Common side effects of oncology medications

| | Myelosuppression | Mucositis | Enteritis | Alopecia | Cardiac | Renal | Neuropathy | Liver | Rash | Lung |
|-------------------------|------------------|-----------|-----------|----------|---------|-------|------------|-------|------|------|
| Anthracyclines | ++ | + | | ++ | + | | | + | | |
| Capecitabine | + | ++ | ++ | | angina | | | | +HFS | |
| Carboplatin | ++ | | | | | | + | | | |
| Cisplatin | + | | | | | ++ | ++ | | | |
| Cyclophosphamide | + | | | + | | + | | + | | |
| 5FU | | ++ | ++ | | angina | | | | + | |
| Gemcitabine | + | | + | | | | | | | + |
| Irinotecan | + | | ++ | + | | | | + | | |
| Oxaliplatin | + | + | + | | | | ++ | | | |
| Paclitaxel | + | | | ++ | | | ++ | | | |
| Docetaxel | + | | + | ++ | | | ++ | + | + | |
| Permetexed | + | | + | | | | | | | |

Examples of Monoclonal antibodies and small molecules

| | Infusion reactions | cardiac | rash | thyroid | Proteinuria | diarrhea | Hypertension |
|----------------------------|--------------------|---------|------|---------|-------------|----------|--------------|
| Trastuzumab | + | + | | | | | |
| Bevacuzumab | + | | | | + | | ++ |
| Cetuximab/panitumab | + | | ++ | | | | |
| Sunitinib | | | ++ | + | + | + | + |

FEBRILE NEUTROPENIA

***Neutropenic Fever*^{5 6}**

It is a medical emergency. It is the responsibility of the MO to ensure prompt antibiotic administration.

With diarrhoea and neutropenia, even if afebrile, it is advisable to use the same protocol.

Definitions

- A single oral temperature of 38.3 C.
- A temperature ≥ 38 C on two occasions over 1 hour.
- ANC ≤ 500 or less $\leq 1000/\mu\text{l}$ with predicted rapid decline to less than $500/\mu\text{l}$.

Septic Work-Up

- Physical examination.
- Blood cultures x 2 sets (venipuncture and indwelling venous catheter if present), urine C&S, cultures from any suspected sites, CXR).

***Treatment of Neutropenic Fever*⁷**

Antibiotics (early involvement of anti-microbial stewardship service is beneficial).

- Anti pseudomonal penicillins (Piperacillin/tazobactam & Ticarcillin) and cephalosporins (Cefepime) are used as single agents.

In patients with hypersensitivity to penicillins, seek expert advice.

Modifications

- Aminoglycosides may be added if patient is unstable to cover resistant pseudomonal bacteremia.

⁵ Freifeld, A. G., E. J. Bow, et al. (2011). "Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America." *Clinical Infectious Diseases* 52(4): 427-431.

⁶ National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Prevention and treatment of cancer-related infections, Version 2.2011. www.nccn.org.

⁷ Therapeutic guidelines. online-tg-org-au.cknservices.dotsec.com

- Add Vancomycin if clinically unstable, gram positive blood cultures before antibiotics, severe mucositis present, already on Quinolone prophylaxis, a catheter associated cellulitis or tunnel infection, past history, high prevalence or carrier of Methicillin-resistant staph aureus.
- Metronidazole for abdominal symptoms or suspected C. difficile infection.
- Persistent neutropenic fever on D5 – add antifungal therapy (Amphotericin B 0.5mg/kg/day or Fluconazole 400mg/day).

Discuss with consultants first.

Duration of Antibiotics (variable)

- Low risk patient (clinically well, stable signs, no mucositis, ANC >100/ μ L, rising ANC, afebrile within 2-3 days of starting antibiotics, negative cultures) consider early discharge on oral Ciprofloxacin and Augmentin for 5 days or cease antibiotics altogether when ANC >500/ μ L.
- High risk patients, who become afebrile within 3 days, should continue parenteral antibiotics, targeted to the specific pathogen, until resolution of neutropenia.
- Specific pathogens need to be treated according to therapeutic guidelines while continuing broad coverage.

Patients with any of the following characteristics are considered to be at high risk for serious complications during episodes of neutropenic fever

- Neutropenia (absolute neutrophil count <500 cells/microL) anticipated to last >7 days*

Presence of any comorbid medical problems, including, but not limited to:

- Hemodynamic instability
- Oral or gastrointestinal mucositis that interferes with swallowing or causes severe diarrhoea
- Gastrointestinal symptoms, including abdominal pain, nausea and vomiting, or diarrhoea
- Neurologic or mental status changes of new onset
- Intravascular catheter infection, especially catheter tunnel infection
- New pulmonary infiltrate or hypoxemia
- Underlying chronic lung disease
- Complex infection at the time of presentation:

Inpatient status at the time of development of fever

Uncontrolled or progressive cancer

Evidence of hepatic insufficiency (defined as aminotransferase levels >5 times normal values) or renal insufficiency (defined as a creatinine clearance of <30 mL/min)

Multinational Association for Supportive Care in Cancer (MASCC) risk index score <21

Guide to Febrile Neutropenia

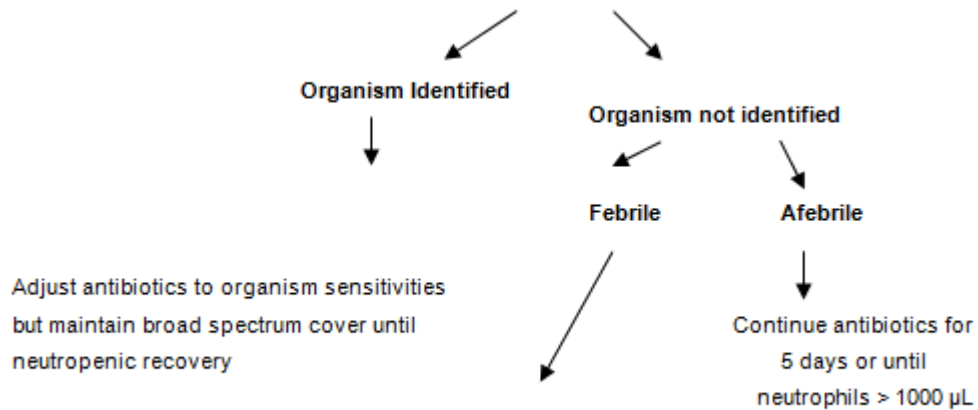
Guide to Febrile Neutropenia

Temperature $> 38.3^{\circ} \times 2$ over 1 hour + Neutrophil count $< 500 \mu\text{L}$

Broad spectrum antibiotics

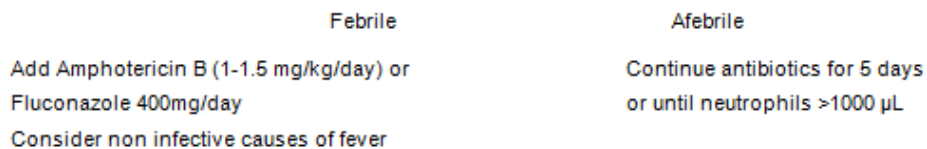
[Cefepime 2 g BD*] or anti pseudomonal penicillin +/- Gentamicin)

Re-evaluate on Day 3



Add Vancomycin 1 g 12 hourly

Re-evaluate on Day 5



Colony stimulating factors (GCSF) are generally not recommended in management of febrile neutropaenia, with some exceptions.

Catheter-related infections

Catheter removal is recommended in addition to antibiotic therapy for at least 14 days. But, if the infection is caused by coagulase-negative staphylococci and is important to save the line, catheter could be retained using systemic antibiotics.

Extravasation of Chemotherapy Drugs ⁸

If it does occur, proper documentation should include the time, site of line insertion, needle size, estimated amount of extravasated medication, technique used to manage the extravasation, appearance of site, photograph, patient's comments, and notification of physician.

Management

Stop infusion. Before removing cannula attempt to aspirate some of extravasated fluid. If antidote exists give it both IV through cannula and by SC infiltration see Table 2 below.

Intermittent local cooling is recommended, except for vinca alkaloids (warming packs). Rest and elevate the affected site for 48 hours. Telephone contact daily and assess need for plastic surgery.

Day unit nurses have protocols for managing extravasation and their input will be important for developing management plans.

⁸ Albanell, Joan, and Jose Baselga. "Systemic therapy emergencies." *Seminars in oncology*. Vol. 27. No. 3. 2000.

Table 2 Example of Antidotes for Vesicant and Irritant Drugs

| Chemotherapy agent | Pharmacologic antidote | Nonpharmacologic Antidote | Method of Administration |
|---|-------------------------------|---|--|
| <ul style="list-style-type: none"> • Mechlorethamine (nitrogen mustard) • Cisplatin (large extravasation) | Sodium thiosulfate | None | <p>Prepare 1/6 molar solution: if 10% Na thiosulfate solution, mix 4 mL with 6 mL sterile water for injection.</p> <p>Through existing IV line, inject 2 mL for every 1 mg extravasated. Inject SC if needle is removed.</p> |
| <ul style="list-style-type: none"> • Vincristine • Vinblastine • Vindesine • Etoposide • Vinorelbine | Hyaluronidase | Warm packs. 15-20 minutes at least four times/day for the first 24-48 hours and elevate | <p>Prepare hyaluronidase, 150 units/mL with 1-3 mL saline. Inject through existing IV line, 1 mL for each 1 mL infiltrated. Inject SC if needle is removed.</p> |
| <ul style="list-style-type: none"> • Doxorubicin (Adriamycin) • Daunorubicin • Idarubicin • Mitomycin C | DMSO | Ice packs | <p>Apply cold pad with circulating ice water pack or cryogel pack for 15-20 minutes at least four times/day for first 24-48 hours. Some benefit of 99% dimethyl sulfoxide (DMSO) 1-2 mL applied to site every 6 hours.</p> |
| <ul style="list-style-type: none"> • Paclitaxel • Docetaxel | Hyaluronidase | Ice packs | As for Vinca alkaloids. |
| <ul style="list-style-type: none"> • Mechlorethamine (nitrogen mustard) • Cisplatin (large extravasation) | Sodium thiosulfate | None | <p>Prepare 1/6 molar solution: if 10% Na thiosulfate solution, mix 4 mL with 6 mL sterile water for injection.</p> <p>Through existing IV line, inject 2 mL for every 1 mg extravasated. Inject SC if needle is removed.</p> |
| <ul style="list-style-type: none"> • Paclitaxel • Docetaxel | Hyaluronidase | Ice packs | As for Vinca alkaloids. |

PREMEDICATIONS TO PREVENT ALLERGIC REACTIONS

Paclitaxel Premedications

- Recommended schedule:

Dexamethasone 20 mg oral, 12 hours and 6 hours before Paclitaxel (in practice the night before and the morning of treatment).

Promethazine 25 mg IV 30-60 minutes before therapy.

Ranitidine 50 mg IV 30-60 minutes before therapy.

Additional Dexamethasone IV as antiemetic depending if Paclitaxel given alone (4mg IV) or in combination with other drugs.

- Modified regimen (in cases where the patient forgets to take premedication, or 2nd and subsequent cycles where no hypersensitivity reaction occurred with 1st treatment and steroids are not appropriate). ^{9 10 11}
 - Dexamethasone IV 20 mg 30 minutes before Paclitaxel.
 - Promethazine IV 25 mg IV 30-60 minutes before therapy.
 - Ranitidine 50 mg IV 30-60 minutes before therapy.
- Modified schedule for weekly regimen (where steroids are not appropriate):
 - 1st Treatment
 - Dexamethasone 12 mg IV.
 - Promethazine 25mg IV.
 - Ranitidine 50mg IV.

If no hypersensitivity reaction, subsequent treatments may be given without premedications.¹²

Docetaxel Premedications¹³

- Recommended schedule for 3 weekly regimen. ¹⁴

Dexamethasone 8mg BD oral x 6 doses (starting night before treatment).

⁹ Product Information, 2001

¹⁰ Markman M. *J Clin Oncol* 15(12): 3517, 1997

¹¹ Kintzel PE. *Ann Pharmacother* 35:1114-7, 2001

¹² Quock J. *Proc ASCO* 18 abstr 635, 1999

¹³ Product Information, 2001

¹⁴ Jackisch C. *Proc ASCO* 19 abstr 417, 2000

Additional Dexamethasone IV as antiemetic depending if Docetaxel used alone (4mg IV) or in combination with other drugs.

- Schedule for weekly regimen:

Dexamethasone 8mg oral BD x 3 doses (starting night before treatment).

Monoclonal Antibodies

- Trastuzumab (Herceptin) may cause fever and chills, chest tightness and tachycardia with 1st infusion.
- Rituximab (Mabthera) may cause asthenia, chills, bronchospasm, hypotension, angioedema. Premedicate with Paracetamol 1 g QID, Promethazine 25 mg IV and Hydrocortisone 200 mg IV 30-60 minutes prior to drug.
- Cetuximab requires phenergan 12.5mg or 25 mg prior to infusion.

Medical Oncology Emergencies

(Management of Neutropaenic fever is discussed above.)

Spinal Cord-compression

Neurological symptoms and signs consistent with spinal cord compression necessitates.

- Urgent review and MRI of spine.
- Urgent neurosurgical and or radiotherapy referral.
- Start Dexamethasone 8mg IV stat, followed by 16-24 mg daily in divided doses.

SVC Obstruction:

- If the patient presents with stridor or respiratory compromise, emergency treatment with endovascular stent and Radiotherapy is required.
- In other cases: a histological diagnosis is required prior to initiating specific treatment.
- In chemotherapy-sensitive malignancies like small –cell lung cancer, germ cell tumour or lymphoma, systemic chemotherapy is usually the treatment. In most other tumours, including non-small cell lung cancer, Radiotherapy is the preferred treatment.
- Endovascular stenting could achieve rapid relief of symptoms.

Hypercalcemia:

- Saline hydration, IV zoledronic acid, IV furosemide after adequate hydration.
- Steroids useful in hypercalcaemia due to lymphoma.
- s/c calcitonin may be useful in resistant hypercalcemia.

Infusion reactions and other acute reactions

- Mild to moderate infusion reactions with no features of anaphylaxis-
- IV hydrocortisone and phenergan. Stop infusion till reaction subsides and restart at a lower rate, with close monitoring.

Severe infusion reactions and anaphylaxis (hypotension, angioedema, bronchospasm, generalised urticaria) - Resuscitation with epinephrine, hydrocortisone, phenergan ranitidine and fluids.

DO NOT RE-CHALLENGE.

SUMMARY OF MANAGEMENT OF COMMON CANCERS ^{15 16}

This section outlines the principles behind the management of common cancers.

For metastatic cancers, enrolment into a clinical trial is the best treatment option.

Summaries provided below are developed using eviQ and NCCN guidelines as practical guidance.

BREAST CANCER

Early breast cancers:

(Includes axillary node positive disease.)

- Mostly curative intent therapy.

Post-operative systemic treatment depends on oestrogen and/ or progestogen receptor status, Her 2 status and the estimated risk of systemic relapse.

- Prognostic factors.

Size, age, grade, axillary nodes, receptor status and lympho-vascular invasion.

| | Low risk | Average risk | High risk |
|-------|-----------------|---------------------|------------------|
| Size | <1cm | 1-2 cm | >2 cm |
| Age | | | <35 |
| Nodes | Negative | | Positive |
| Grade | Grade 1 | Grade2 | Grade3 |
| ER/PR | Positive | | Negative |
| Her2 | Negative | | Positive |
| LVI | Absent | present | |

- Low risk - Hormonal manipulation or nil.
- Average - Hormonal +/- chemotherapy for ER/PR positive disease,

¹⁵ www.nccn.org.

¹⁶ www.eviq.org.au

Chemotherapy for ER/PR negative disease.

- High risk- Chemotherapy + hormonal manipulation for ER positive disease.

Chemotherapy for ER/PR negative disease.

- For **Her-2 positive disease**, Herceptin is given with chemotherapy for total of 52 weeks (3 weekly).
- Hormonal manipulation-

In premenopausal women; Tamoxifen alone may be an option. In patients who remain premenopausal after chemotherapy and have high risk disease, ovarian suppression with LHRH agonists or bilateral oophorectomy with exemestane or Tamoxifen is better than Tamoxifen alone. Aromatase Inhibitors are not used alone in premenopausal women.

Consider 10 years of tamoxifen over 5 years of treatment, particularly for patients at highest baseline risk eg where chemotherapy was indicated.

In post-menopausal women - Aromatase inhibitors are the preferred endocrine treatment unless contraindicated. In patients who cannot tolerate AI or where it is contraindicated, Tamoxifen is used.

In post-menopausal patients who start treatment with tamoxifen, switching to AI after 2-3 years is recommended.

5-10 additional years of aromatase inhibitors after 5 years of tamoxifen improves survival in high-risk patients.

For patients on AIs and documented osteopaenia addition of bisphosphonates decreases the risk of decline in bone density. They are also encouraged to take regular calcium and vitamin D tablets. DEXA scans are done yearly to two yearly for monitoring bone health in patients on aromatase inhibitors.

Chemotherapy regimens-

- Lower risk/Average risk- 4x TC,
- High risk- 3x FEC- 3x D OR AC-weekly Taxol OR AC- dd Taxol. AC may be given in dose dense fashion (preferred if possible).
- In **Her-2 positive disease**, Trastuzumab is combined with Taxanes and not with anthracyclines because of risk of cardiac toxicity. Eg FEC-D Herceptin or AC-Taxol Trastuzumab. Pertuzumab may be added in treatment given neoadjuvantly.
- In Her2 positive disease, a non-anthracycline regimen, eg TCarboH is an alternative.¹⁷

¹⁷ Slamon, D., W. Eiermann, et al. (2011). "Adjuvant trastuzumab in HER2-positive breast cancer." *New England Journal of Medicine* 365(14): 1273-1283

- **G-CSF prophylaxis-** If severe neutropenia, cycles delayed because of neutropenia or complicated by neutropenic fever, add neutlasta (most of these protocols now have upfront G-CSF)

Neoadjuvant chemotherapy:

- Chemotherapy regimens are similar to adjuvant regimens.
- More effective in triple negative or Her-2 positive disease.
- May be used to achieve breast conservation in some cases, large primary tumour sizes, clinical nodal involvement (locally advanced disease) or if surgical concerns for upfront surgery.
- Patients with residual cancer after neoadjuvant chemotherapy may require further chemotherapy treatment or a change in agent (eg capecitabine if triple negative, TDMI (trastuzumab emtansine) if HER2 positive).

Post-operative radiotherapy:

- After lumpectomy, radiotherapy decreases local recurrence rates.
- After mastectomy, indications include (but not limited to):
 - close or positive margins
 - ≥ 4 axillary nodes involved
 - tumour size >5 cm
- Extensive lymphovascular invasion.

Radiotherapy is given after the chemotherapy is completed, but can occur concurrently with Herceptin in Her2 positive disease

Locally advanced and inflammatory breast cancers

- The cure rate is lower than with early breast cancers.
- Chemotherapy is given before surgery to reduce the size of the primary and eradicate micrometastases (see above for regimens).
- Radiotherapy is given after surgery.

Metastatic breast cancer

- First line ER/PR+ HER2 - bone only metastases- Endocrine therapy +/- CDK 4/6 inhibitor (eg palbociclib or ribociclib).
- Patients with bone metastases also benefit from monthly Bisphosphonates or Denosumab to reduce pain, skeletal events and hypercalcemia.
- First line chemotherapy is usually Taxane or Anthracycline based (depending upon chemotherapy exposure in adjuvant setting) with combination therapies

generally reserved for patients with high volume disease (including visceral disease) or suggestion of aggressive clinical course.

Later lines of therapy can include taxanes, gemcitabine, capecitabine, vinorelbine and eribulin. Choices may be influenced by patient and physician preferences, previous chemotherapy exposure and patient fitness. For further detailed information on these protocols, visit [eviQ website](#).

- In Her 2 positive disease, Taxanes can be combined with Trastuzumab and Pertuzumab as initial treatment.

Second line treatment may include TDM1 (Trastuzumab emtansine). If progression on TDM-1, use Lapatanib/capecitabine and Herceptin/chemotherapy.

Cancers of the Gastro-Intestinal Tract

Anal Cancer

Majority of patients are treated with concurrent chemo-radiation. This requires PICC insertion and CADD pump for delivery of continuous infusion 5- Fluorouracil.

Regimen:

Mitomycin C on Day 1 and 5-Fluorouracil on Days 1 to 4 and 29 to 32 along with radiation for 5-6 weeks (standard of care).

Mitomycin C can be substituted with Cisplatin (if patient has hypersensitivity to mitomycin or has any coagulation or bleeding disorders or thrombocytopenia). If patient cannot have PICC for some reason 5-Fluorouracil can be substituted with Capecitabine.

Metastatic Anal Cancer: Different chemotherapies can be used such as, Carboplatin & Paclitaxel (weekly/three weekly), 5Fu & Cisplatin, FOLCIS (5Fu, leucovorin & Cisplatin), mFOLFOX, mDCF.

Gastro-Oesophageal and Gastric Cancer

Definitive Concurrent Chemo-Radiation

For those not suitable for surgery:

Cisplatin and 5-Fluorouracil along with radiation (2 cycles)

Neo-adjuvant chemoradiation:

Weekly Carboplatin and Taxol

Alternatively, Cisplatin and 5-Fluorouracil with radiation.

Peri-operative chemotherapy:

For adenocarcinoma of lower oesophagus, gastro-oesophageal junction and stomach.

4 cycles FLOT pre and post resection.

or, 3 cycles of ECF/ EOX pre and post resection.

or 2 x cis/5fu pre & post resection.

Advanced or Metastatic Carcinoma of Gastro-oesophageal Junction/Stomach:

Different single agent/combination regimens can be used depending on existing co-morbidities. Many regimens can be used for both adenocarcinoma and squamous cell carcinoma.

Combination: FOLFOX 6 or XELOX

Single agents: Docetaxel, paclitaxel, irinotecan

For HER-2 positive adenocarcinoma – Add Trastuzumab (Herceptin).

Biliary and Gall Bladder

Outcome is usually poor in patients with multiple co-morbidities and poor performance status. In these cases, omitting chemotherapy from management plans may be prudent.

- Adjuvant therapy for node positive disease– fluoropyrimidine or Gemcitabine based chemotherapy (eg: Cisplatin or Carboplatin/Gemcitabine).

Consider chemoradiation for margin-positive or node positive cancer.

- Metastatic/inoperable – Same regimens as adjuvant therapy.

Hepatocellular carcinoma

- Limited disease: Operable or locoregional therapy available
- Inoperable or not suitable for locoregional therapy: Lenvatinib or Sorafenib in Child-Pugh A patients). Role of systemic chemotherapy is not established.

Metastatic Neuro-endocrine Tumours of Gastro-intestinal Tract

- Grade I/II – Sandostatin/Lanreotide. On progression capecitabine and temozolomide.
Everolimus or sunitinib can be used for pancreatic Grade I/II tumours.
- Grade III – Carboplatin and etoposide or cisplatin and etoposide.

Adeno-carcinoma of Pancreas

Role of neoadjuvant therapy continues to evolve, and this is usually not standard practice outside of clinical trial settings except where an MDT strongly recommends this approach. Outcome is usually poor in patients with multiple co-morbidities and poor performance status. In these cases, omitting chemotherapy from management plans may be prudent.

- Adjuvant – modified FOLFIRINOX x 6 months or Capecitabine + Gemcitabine.
- Advanced/metastatic – If disease recurrence occurs after 6 months of completing adjuvant therapy, same regimen could be considered. In good performance patients with minimal co-morbidities, m FOLFIRINOX or Gemcitabine and nab-Paclitaxel. After 4-6 months, less intensive components could be maintained.

In poor performance patients, BSC alone or single agent regimens such as gemcitabine may be appropriate.

Colon Cancer

Stage I and II surgery alone.

Stage II with adverse features is treated as stage III with adjuvant chemotherapy. Adverse features are – poorly differentiated histology, lympho-vascular invasion, bowel obstruction, perforation, fewer than 12 lymph nodes in the resected specimen, perineural invasion, close or positive margins.

Adjuvant chemotherapy is for six months. However, in low risk patients (T1-3 N1) shorter duration (three months) of adjuvant XELOX (CAPOX) is equivalent to six months of XELOX in efficacy with less neurotoxicity. If using mFOLFOX recommendation is for six months of treatment. For High risk features, recommendation is for six months of treatment.

Regimens: Different schedules of calcium leucovorin and 5fluorouracil, Capecitabine, FOLFOX & XELOX.

Metastatic cancer: Any adjuvant regimen can be used in metastatic setting. Other regimens are Irinotecan, FOLFIRI, FOLFOXIRI, XELIRI.

Assess patients with imaging after 3 cycles of chemotherapy for respectability of lesions. Discuss in GI multi-disciplinary meetings. Some of the patients with few metastases may eventually be curable.

Bevacizumab is usually combined to different chemotherapy regimens in metastatic setting unless contra-indicated.

Patients with KRAS wild type tumours have additional option of having Cetuximab/Panitumumab added to chemotherapy regimen.

Rectal Cancer

Most of the patients are treated with neo-adjuvant concurrent chemo-radiotherapy.

Chemotherapy consists of continuous infusion 5-Fluorouracil through PICC line or oral capecitabine. If the patient did not receive neo-adjuvant treatment it may be given post-operatively for T3/T4 or node positive tumours.

For those who had neo-adjuvant treatment further adjuvant chemotherapy is offered post-operatively in the form of leucovorin-5-Fluorouracil/capecitabine to complete six months of perioperative chemotherapy.

FOLFOX is currently not approved for rectal cancer.

Metastatic rectal cancer

All the regimens used in colonic cancer can be used in metastatic rectal cancer including Bevacizumab, cetuximab and panitumumab.

Assess patients with imaging after 3 cycles of chemotherapy for resectability of lesions. Discuss in GI multi-disciplinary meetings. Some of the patients with few metastases may eventually be curable.

Gastro-Intestinal Stromal Tumours (GIST)

- **Adjuvant** – for those with high risk features – Imatinib for 3 years.

High Risk Features are: Primary GIST greater than 5 cm with a mitotic count of greater than 5/50 high power fields (HPF); or

Primary GIST greater than 10 cm with any mitotic rate; or

Primary GIST with a mitotic count of greater than 10/50 HPF

- **Metastatic** - Imatinib. Sunitinib can be used when progress on Imatinib.

GBM

- Surgery is for resectable disease.
- For resected GBM, Temazolamide with RT and 4 weeks later, 5 days per month for 6 months of Temazolamide improves survival.

Temazolamide:

- With RT- 75mg/m²/day M-F.
- After RT or on its own for palliation- 150-200 mg/m²/day for 5 days a month.

Check platelets mid cycle as a caution.

Unresectable and incurable GBM- options include Temazolamide & Avastin based combinations.

GERM CELL TUMOURS

Stage 1-

- Normally for **stage 1 seminoma** (make sure serum AFP normal) - Single dose carboplatin AUC 7. Check counts every week for 2 weeks post chemotherapy.

Discuss sperm banking with patient prior to giving chemotherapy. However, fertility is unlikely to be affected with one cycle of carboplatin.

- For **stage 1 non-seminoma**- wait and watch (6 weekly markers and 3 monthly CTs first 2 years and later relax to 6 monthly scans and 3 monthly bloods for another 3 years).

or 2 cycles of BEP for patients who are not reliable **for follow up** or who move around **different towns**.

Stage 2 onwards-

This includes patients with normal scans but have the markers elevated few weeks post orchidectomy.

Seminoma:

- Stage 2 or stage 3:
Good prognosis- 3-cycles of BEP.
Intermediate prognosis- 4x cycles of BEP (only first 3 cycles are with Bleomycin).
- Non seminoma
Good prognosis- 3 x cycles of BEP,

Intermediate or poor prognosis- 4x cycles of BEP.

Residual disease/mass after optimal chemotherapy needs to be resected.

Pre BEP treatment:

- History of renal, auditory, neuropathy and vascular issues,
- Lung function test- DLCO and lung volumes,
- Sperm banking (Semen cryopreservation: In Townsville, this is performed by QFG), ELFTS, FBC, LDH and markers.

(Please discourage smoking).

- Recurrent GCTs can still be cured by TIP or VIP chemotherapy.

Prognostic groups: Seminoma:

| | Good prognosis | Intermediate prognosis |
|--------------------------------------|-----------------------|-------------------------------|
| Primary site | any | any |
| Presence of non pulmonary metastasis | no | yes |
| Markers (not AFP) | any | any |

If serum AFP is elevated, it is treated as non-seminoma.

Non-Seminoma:

| | Good | Intermediate | Poor |
|--------------------------|-----------------|---------------------|-------------|
| Primary site | Non mediastinal | Non mediastinal | mediastinal |
| Non pulmonary metastasis | no | no | yes |
| Markers | | | |
| AFP | <1000 | 1000-10000 | >10000 |
| B HCG | <5000 | 5000-50000 | >50000 |
| LDH | <1.5 x ULN | 1.5-10 x ULN | >10 x ULN |

HEAD AND NECK CANCER

- **Resectable disease-** Surgery.

For high risk disease, post op radiotherapy with chemotherapy improves survival.

- **Unresectable** disease or organ preservation-

Induction chemotherapy followed by chemoradiotherapy.

Induction chemotherapy- 2 -3 cycles of TPF.

Chemoradiotherapy- weekly cisplatin 40mg/m².

- ***If not fit for weekly cisplatin**, abnormal renal function or cardiac issues-

Cetuximab (Erbix) Loading dose 400mg/m² one week prior to RT and then weekly 250mg/m² weekly (*Discuss with Radiation oncologists for their preference*).

They need Phenergan 12.5mg or 25mg as premedications.

- Metastatic H&N cancer- (Cisplatin or Carboplatin) and 5FU/ Capecitabine
Second-line -PDL1 antibody Nivolumab.

LUNG CANCER

- Non Small Cell Lung cancers:

*Stage I to III- Surgical resection offers the best chance of cure.

- For resected stage 1b, II or III -

Adjuvant chemotherapy with cisplatin & vinorelbine x 4 cycles to improve survival in fit and <70 years. Carboplatin & paclitaxel is other alternative.

- *Stage III -

For patients who are unresectable, chemo-radiation can improve survival.

- concurrent with radiation-

Cisplatin with Etoposide is the preferred regimen. Other alternatives are used in patients who are unfit for Cisplatin (elderly, renal impairment etc).

Eg - Carboplatin (AUC 2) and Paclitaxel (50mg.m²) weekly with radiation.

Post CRT immunotherapy improves outcomes.

Non metastatic pan coast tumours - chemo-radiotherapy followed by surgery.

- *Stage IV or incurable stage IIIb-

Always test for oncogenic mutations like EGFR, ALK and ROS-1 in Non Squamous NSCLC. If either is positive, treat with EGFR inhibitor (Afatinib is

preferred or Erlotinib or Gefitinib) or ALK inhibitor (Alectinib is preferred or Crizotinib).

- All NSCLCs (non squamous or squamous) should also be tested for PDL-1 by IHC (to check for eligibility of using immunotherapy alone as first line treatment). If PDL-1 expression >50% and there is no actionable mutation, then single agent Pembrolizumab (anti PDL-1) can be offered as upfront treatment (without chemotherapy).
- For NSCLC patients with PDL-1 expression less than 50% and with no actionable mutation, consider offering combination of immunotherapy (anti PDL-1) along with platinum doublet chemotherapy if performance status is reasonable (ECOG ≤2).
- Maintenance Pemetrexed chemotherapy can be considered in patients with Non Squamous NSCLC who have not progressed after first line combination treatment.
- All these patients with incurable disease should be considered for clinical trial if one is available.
- In select patient groups (e.g elderly with good PS, or patients who have contraindication for immunotherapy like significant autoimmune disorder), single agent chemotherapy alone is a reasonable option

Once first line treatment with chemotherapy fails – consider treatment with anti PDL-1 antibody (e.g Nivolumab) for 2nd line treatment.

- Palliative best supportive care is reasonable for patients with poor (ECOG>2) PS. Consider early referral to palliative care for all stage IV lung cancer patients undergoing active treatment as this has shown to improve survival.

Small cell lung cancer

- Limited stage-

Cisplatin and etoposide x 4 cycles and radiation as early as possible or Carboplatin and etoposide for 6 cycles and radiation.

At the end of the treatment, if no brain mets- Prophylactic cranial irradiation to add another 5% survival benefit.

- Extensive stage-

Carboplatin and etoposide with immunotherapy for 6 cycles. If complete response that last for 6-12 months, could have re treated.

- Urgent chemotherapy (with or without tumour lysis prophylaxis) for patients presenting with bulky disease and oncology emergency (e.g SVC obstruction).

Mesothelioma

Surgical decortication can be useful in selected patients.

Otherwise, Carbo AUC 5 or Cisplatin and Pemetrexed every 3 weeks.

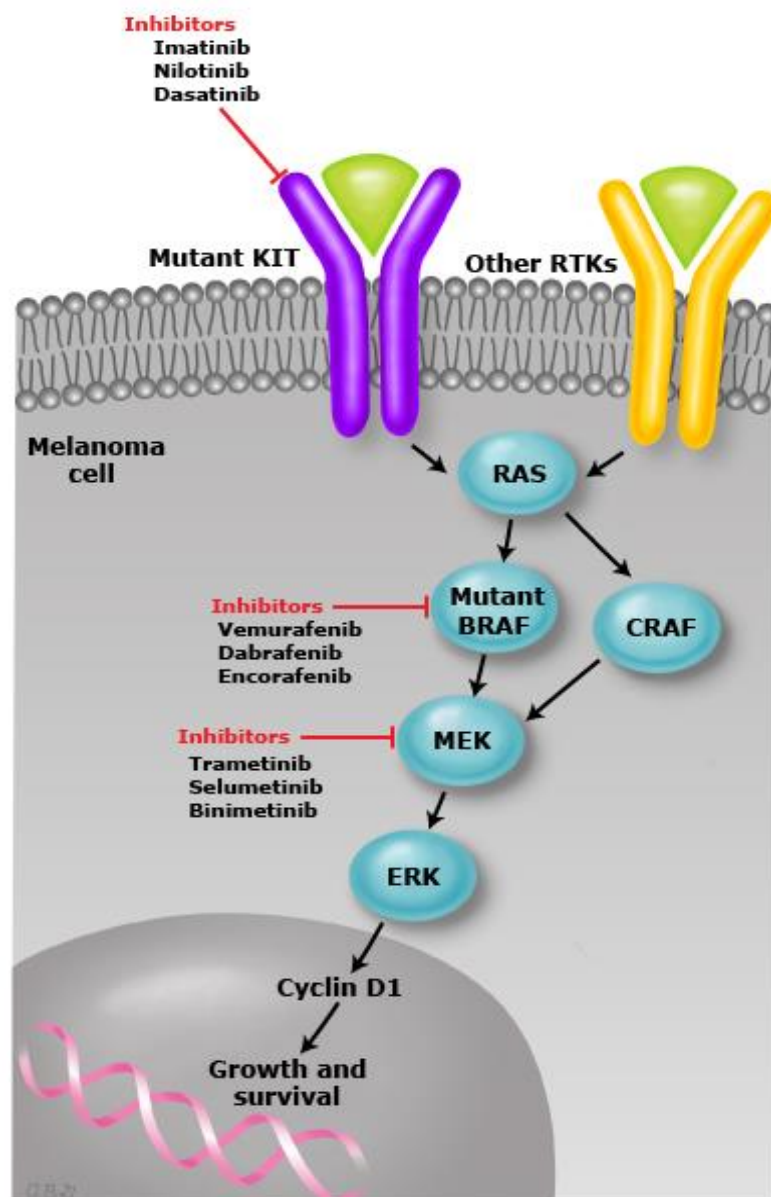
Important- 1 week before Pemetrexed - start VitB12 1000mcg IM every 9 weeks and folic acid 0.5 mg daily until Pemetrexed is stopped.

Consider Clinical trial for these patients if available.

MELANOMA

- Stage I to III - resection of the primary +/- sentinel node biopsy and node dissection for node positive disease.
 - Stage IB or II can be considered for clinical trial with adjuvant treatment if available otherwise ongoing surveillance.
- For stage III disease:
 - Stage IIIA disease: consider imaging and BRAF mutation testing. Consider systemic treatment on clinical trial, otherwise surveillance.
 - Resected stage IIIB/C/D disease: imaging to confirm staging and BRAF mutation testing. Immunotherapy (anti PD-1) for BRAF WT disease, or Dabrafenib (BRAFi) and Trametinib (MEKi) for patients with BRAF V600 mutation. Observation is also an option. Treatment subject to ECOG 1 or less.
 - Unresectable stage III disease: treat as unresectable stage IV disease.
 - Consider adjuvant radiotherapy in patients with involved surgical margins.
- Stage IV disease
 - Limited/oligometastatic (resectable) disease. Imaging to confirm staging. BRAF mutation testing. LDH. Systemic treatment followed by imaging and resection OR resection followed by systemic treatment.
 - Systemic treatment depending on BRAF and performance status.
 - Systemic options are the same as resected stage III disease

- Disseminated (unresectable) disease.
 - In patients without brain metastasis: systemic therapy as above, intralesional T-VEC, palliative resection or RT. Best supportive care.
 - With brain metastasis: Primary RT, Palliative resection with or without adjuvant RT, Followed by systemic therapy as above or combination immunotherapy in low volume cases.



GYNAECOLOGICAL CANCER

- **Ovarian cancer**

Stage 1- Surgery (adjuvant chemotherapy for high risk patients such as with tumour rupture or positive peritoneal washings).

Stage \geq 2 Debulking surgery, BSO/TAH.

Post debulking surgery- Carbo AUC 5/6 and Taxol weekly or three weekly (three weekly generally preferred).

Patients who are unfit for surgery can be given neo adjuvant chemotherapy first and receive surgery after several cycles of chemotherapy (interval debulking) with subsequent adjuvant chemotherapy. This approach may reduce surgical morbidity of debulking procedures without compromising outcomes.

Intraperitoneal chemotherapy may be used in selected stage3 disease, after optimal debulking surgery.

In patients who have metastatic disease (stage 4) or those who do not achieve optimal debulking (residual disease $>1\text{cm}$), bevacizumab for one year may be used on the PBS.

- **Relapsed Disease**

Choice of agent may depend upon interval since last exposure to platinum (ie platinum sensitive versus resistant).

Newer agents such as PARP inhibitors may be used depending upon BRCA mutation status.

Protocols include carboplatin/caelyx, carboplatin/gemcitabine and topotecan.

Cervical cancer

- Early disease- surgery
- Locally advanced- chemoradiotherapy with weekly cisplatin,
- Metastatic- Platinum/ Taxol/ Bevacizumab, Taxol/Topotecan, Gemcitabine.

CANCERS OF GENITO URINARY SYSTEM

PROSTATE CANCER

Treatment depends on disease stage and hormone sensitivity.

- **Early stage disease** is treated with surgery, radiotherapy (external beam and/or brachytherapy) or observation. Treatment modality is individualised based on several factors: age and co morbidities of the patient, serum PSA level, Gleason score, clinical stage and patient preference based on benefits and side effects of therapy.

For example, a patient with clinically non apparent tumour with Gleason score of <6 who has a life expectancy of <10 years could be actively observed without any impact on survival.

For locally advanced inoperable disease, radical radiotherapy could lead to cure. Androgen deprivation therapy is sometimes used for short periods (4-6 months) before/concomitantly/ after radiotherapy in selected high-risk patients.

Metastatic disease is incurable and the aims are to prolong survival and improve quality of life.

Hormone Sensitive disease:

- All Hormone sensitive tumours are treated with a GnRH agonist (eg- goserelin, leuprorelin). To prevent flare, antiandrogens (eg- flutamide, are started 1-2 weeks before the injection and continued for a total of 3-4 weeks). Whether anti- androgens are continued beyond that is controversial.
- Chemotherapy with Docetaxel 75 mg/m² x 6 doses, can be added to hormonal therapy in fit patients with high volume (presence of visceral mets or ≥ 4 bony mets) metastatic disease, as it improves survival significantly (CHAARTED, STAMPEDE trials).

Hormone Refractory disease:

- Hormone refractory disease includes patients where the disease has progressed despite hormonal manipulation. GnRH agonists are usually continued.
- Chemotherapy improves median survival by up to 3 months and maintains improvement in quality of life.
- Bone metastases are treated with intravenous bisphosphonates (eg-zoledronic acid) or RANK-ligand inhibitor Denosumab monthly. For asymptomatic and low volume disease, chemotherapy is usually delayed.

- Symptomatic metastases or rapid rise in PSA (doubling time of <3 months) may be treated with docetaxel (75mg/m²) and prednisone 5 mg BD. On progression after docetaxel, newer androgen inhibitors (below) are effective. Palliative care is another option.
- Localised bone pain responds to external beam radiotherapy very well. Men with multifocal painful bone metastases and those with persistent or recurrent pain despite receiving EBRT to maximal normal tissue tolerance may achieve palliation of their symptoms by treatment with bone-targeted radioisotopes such as strontium-89.

Disease progression after chemotherapy: Abiraterone, an androgen biosynthesis inhibitor or Enzalutamide an androgen receptor signalling inhibitor are effective. Median progression free survival and overall survival are better compared to placebo.

Renal Cell Carcinoma

- Metastatic renal cell carcinoma with clear cell histology is treated based on risk stratification (example IMDC criteria).
- Low risk disease can be treated with tyrosine kinase inhibitors Sunitinib or Pazopanib. Cabozantinib or Sorafenib can be used after failure of these. Sorafenib can also be used for papillary carcinoma. Everolimus and axitinib are other second line options available.
- Intermediate and high-risk disease is treated with combination immunotherapy Ipilimumab (anti CTLA4) and Nivolumab (anti PDL-1).
- Once progressed on first line VEGF TKI, immunotherapy is drug of choice for second line treatment. Vice versa if disease progresses on immunotherapy then VEGF TKI such as Cabozantinib or Sunitinib or Pazopanib can be used.

Urinary Bladder Cancer

- Non-muscle invasive disease is treated with surgery and adjuvant intravesical therapies (eg. BCG or Mitomycin).
- Muscle invasive disease is treated with surgery. Pre-op Cisplatin based (neo-adjuvant) chemotherapy improves survival.
- Adjuvant Cisplatin based Chemotherapy is considered for those at high risk of recurrence such as T3/T4 tumours, lympho-vascular invasion or positive nodes if neo-adjuvant therapy was not given.

Inoperable disease may be managed with:

- Radiotherapy with or without radio-sensitising chemotherapy with weekly cisplatin or mitomycin and infusional 5-Fluorouracil.

- Chemotherapy alone (platinum and gemcitabine), or a
- Palliative care alone.

Metastatic disease is managed with chemotherapy, immunotherapy or palliative care alone.

Platinum based chemotherapy is usually the first line palliative treatment. One such regimen is Carboplatin and Gemcitabine.

Immunotherapy with Pembrolizumab is used as second line treatment after failure of platinum-based chemotherapy.