General concepts in Cancer Pharmacology:

Q1. What dose to prescribe?[1]

DOSING IN Chemotherapy:
Body Surface Area (BSA) is limited in predicting good dose Pharmacokinetics. Other factors such as genetic and environmental, can play a role in pharmacokinetics. (8 fold variation in 5FU metabolism due to DPD enzyme across populations. Racial variations also exist - Japanese populations tend to have a higher AUC for palbociclib and lower for sorafenib for the same dose).

Carboplatin is a unique drug where it's clinical efficacy and toxicity have been found to be related to renal clearance. Dosing of Carboplatin is not accordion got BSA but according to Area under the Curve. Area under the curve is the the **area under** the plot of plasma concentration of a **drug** versus **time** after dosage. It gives insight into the extent of exposure to a **drug** and its clearance rate from the body.

Carboplatin dosing (in mg) = Target AUC (mg.min/ml) x (GFR ml/min + 25 ml/min)
25 is a rounded constant that represents non renal elimination.
Thus for a target AUC of 5 and GFR of 80ml/min, Carboplatin dose would be = 5 x (80 + 25) = 525mg.

Many chemotherapy drugs are hepatically excreted and it is harder to use LFTs (compared to eGFR) for dose adjustment.

Other examples of relevance of AUC in chemotherapy:
For many alkylating agents - response is proportional to AUC. (alkylating agents directly attack DNA. Hence total extent of tumour exposure in terms of concentration AND Time is important. Note: summation of concentration x time plot of drug = AUC. Hence AUC is important.

For many antimetabolites - response is more dependent on duration of exposure than AUC. Antimetabolites interfere with DNA replication processes by inserting toxic substitutes into DNA instead of natural deoxyribose-sugar molecules. Thus the crucial element is exposure of all tumour cells to the antimetabolite during the S phase (DNA replication phase of the cell cycle). The longer the exposure time - the more chance that tumour cells will pass through an S phase. Time is much more important than the AUC.

In comparing different chemotherapy regimens you might find that different doses and different intervals are used, making direct comparison difficult. The concept of dose intensity is helpful here.
Dose Intensity - Amount of drug delivered per unit time (mg/m2/week)
Intended dose intensity as per protocol and achieved dose intensity in clinical practice can vary due to delays, dose reductions, patient's schedule. Achieving target dose intensity has shown to be important for outcomes of several cancers such as sarcoma, breast cancer

Q2. What route to prescribe by?

Most commonly used IV

Oral Chemotherapy:
Some chemotherapy can be given orally. **Bioavailability is the fraction of the administered dose of unchanged drug that reaches systemic circulation.** Bioavailability for IV medication is 100% (all dose reaches systemic circulation as it is given into the veins!)
If chemotherapy drugs are taken orally, only a fraction tends to reach systemic circulation unchanged (variability in absorption through intestines, stomach, metabolism in liver due to hepatic circulation before drug reaches systemic circulation)

Examples include:
Melphalan: Bioavailability highly variable 25-89%
Capecitabine: Bioavailability approximately 100%
Temozolamide: Bioavailability 96-100%
Etoposide: Dose dependent, absorption decreases as dose of etoposide increases. Mean bioavailability 50%
Cyclophosphamide: >75%

Regional Chemotherapy
Chemotherapy can be administered regionally. It needs low exchange between the region and systemic circulation for benefit. The idea is to deliver more of the chemotherapeutic agent directly into the region of interest.

Examples:
Intrathecal Chemotherapy
Can be given via a lumbar puncture or via a Ommaya Reservoir
Examples of drugs used in intrathecal chemo : Methotrexate, Cytarabine, Hydrocortisone
Can achieve local clearance temporarily
NEVER GIVE Vincristine INTRATHECALLY - NEVER EVENT.
Examples: Used in leukaemias with CNS spread and breast cancer with metastatic leptomeningeal disease.

Intravesical chemotherapy: BCG for early stage bladder cancer

Intraperitoneal chemotherapy: for ovarian cancer (mitomycin C and chemotherapy drug combinations)

Intraarterial chemotherapy: Can be used to treat liver tumours/mets by directly injecting the chemotherapeutic agent into the hepatic artery.

Q3 Pharmacokinetic concepts (what the body does to the drug)

Transport into Cells
Drugs can either transported into cells by two ways:

1. Active transport (required energy and carrier proteins)

Examples:
Methotrexate (reduced folate carrier)
Doxorubicin
Cisplatin
Nitrogen mustards (choline carrier, melphalan uptake by ASC carrier: alanine-serine-cysteine carrier or L-carrier : Leucine preferring carrier)

Lack or downregulation of carrier proteins can cause resistance to the chemotherapy drug

2. Passive transport: (no energy or carrier proteins required, diffuse across cell membrane)

Examples:
Carmustine, Lomustine, Busulifan

Pro Drugs in Chemotherapy:
Many chemotherapeutic agents are prodrugs and metabolised by the body to active agents. Few examples include

Examples
Cyclophosphamide ---------> phosphor amide mustard
Capecitabine, 5 FU, Gemcitabine ---------> all converted to active triphosphate form
Temozolamide, Dacarbazine ---------> MTIC (**3-methyl**-(triazen-1-yl)**imidazole**-4-carboxamide)
Irinotecan ------> SN38

Tissue Binding, Protein Binding, Volumes of Distribution and Half life:

Volume of distribution (Vd) is the apparent volume - it is a theoretical volume of fluid that would be necessary to contain the total amount of drug, homogeneously, at a concentration equal to that in plasma (or blood). This is not a real volume, but a conceptual pharmacokinetic parameter.

Drugs that are lipid soluble tend to be absorbed more readily and bind to tissues. Of the total dose administered, only a small fraction remains in plasma and large amounts of drug are bound to tissues in the body. This results in a large apparent volume of distribution.
Drugs that are more water soluble or polar, tend to remain in the intravascular space and larger fractions of the total dose administered are reflected in the plasma concentration of the drug. This results in a smaller volume of distribution.

Tissue binding increases the Vd. Hence lipid soluble drugs often have a large Vd.
Protein binding decreases the Vd. Hence highly protein bound drugs often have a small Vd.

Half life the period of time required for the concentration or amount of drug in the body to be reduced by one-**half**. We usually consider the **half life** of a drug in relation to the amount of the drug in plasma. The half life is influenced by the processes of elimination of the drug - inactivation, renal and hepatic clearance.

Examples:
Lipid soluble, with extensive tissue binding and long half life - Doxorubicin
Lipid soluble, but rapid inactivation and short half life - Carmustine

Occasionally half life is expressed as
t1/2 alpha (rate of distribution of drug from plasma into other tissues)
t1/2 beta (rate of removal of drug from body)

t 1/2 gamma (OR terminal half life. It is the time taken to halve the plasma concentration of the drug after pseudo-equilibrium has been reached and not time required to eliminate half the dose administered. Hence IF absorption is a limiting factor then, terminal half life will reflect absorption rate more than elimination!)

Q4. Cell Cycle and Chemotherapy Drugs (Washington Manual of Oncology, 3rd Edition 2018. Authors/Editor: Govindan, Ramaswamy; Morgenstern, Daniel. Publisher: Lippincott Williams & Wilkins)

	CLASS of Drug	**Examples of Drugs**
PHASE SPECIFIC (Activity depends on tumour cells being in a specific PHASE of the cell cycle)		
G1	**Tyrosine Kinase inhibitors**	**Erlotinib**
	EGFR Anitbody	Cetuximab
	Enzyme	Aspraginase
	Steroid	Corticosteroid
	Other	Octreotide
G1/S	**Purine Analogue**	**Cladribine**
S	**Purine Analogue**	**Fludarabine**
	Pyrimidine Analogue	Gemcitabine, 5FU, Ara-C
	Folic Acid Antagonist	Methotrexate
	Topoisomerase I inhibitor	Topetecan
	Other	Hydroxyurea
G2	**Antibiotic**	**Bleomycin**
	Topoisomerase II inhibitor	Etoposide
	Microtubule polymerisation/stabilisation	Paclitaxel
M	**Mitotic Inhibitor**	**Vinca alkaloid**
CELL CYCLE Specific (Activity depends on tumour cells being in the cell cycle, i.e. actively dividing but not on a specific phase of the cell cycle)		
	Alkylating Agents: Nitrogen mustards	Cyclophosphamide, Melphalan,
	Alkylating Agents: Triazenes	Dacarbazine
	Alkylating Agents: Alkyl Sulfonate	Busulfan
	Alkylating Agents: Metal salts	Cisplatin, Carboplatin
	Antibiotics	Doxorubicin, Epirubicin
CELL CYCLE NON SPECIFIC	Alkylating agents: Nitrogen Mustard	Mechlorethamine
	Alkylating agents: Nitrosurea	Carmustine, Lomustine

Q5. Dose adjustments for Chemotherapeutic Drugs
If drugs are eliminated through an organ (liver or kidney) - doses will require adjustment in corresponding hepatic or renal disease.

HEPATIC DISEASE - dose adjustment required	*(highlighted drugs require both hepatic and renal dose adjustment)*
Alkylating Agents	Cyclophosphamide, Ifosfamide
Antimetabolite	5FU, Capecitabine, Methotrexate
Anthracyclines	Doxorubicin, Epirubicin
Antibiotics	Mitomycin C
ALL Taxanes	Paclitaxel, Docetaxel, Cabazitaxel
ALL Vinca Alkaloids	Vincristine, Vinblastine, Vinorelbine
TOP I Inhibitors	Irinotecan, Topetecan
TOP II Inhibitors	Etoposide
NOT PLATINUMS, NOT PLATINUMS, NOT PLATINUMS	**NOT PLATINUMS, NOT PLATINUMS, NOT PLATINUMS**
RENAL DISEASE - dose adjustment required	
ALL Platinums	Cisplatin, Carboplatin
Antimetabolites	Pemetrexed, Methotrexate, Capecitabine
Antibiotics	Bleomycin, Mitomycin C
ALL Alkylating Agents	Cyclophosphamide, Ifosfamide, Melphalan, temozolamide etc
TOP I Inhibitor	Topetecan
TOP II Inhibitor	Etoposide
NOT TAXANES, NOT VINCA ALKALOIDS, NOT ANTHRACYLCINES (except Epirubicin)	**NOT TAXANES, NOT VINCA ALKALOIDS, NOT ANTHRACYLCINES (except Epirubicin)**

Q6. Vesicants and Extravasation of Chemotherapy

VESICANTS: Drugs that can result in tissue necrosis or formation of blisters when accidentally infused into tissue surrounding a vein
Although all vesicants can cause tissue damage upon extravasation, anthracyclines, such as daunorubicin, doxorubicin, epirubicin, and idarubicin, have the greatest vesicant potential when compared to other chemotherapeutic agents.
Examples:
Doxorubicin, Epirubicin, Idarubicin
ALL Vinca- alkaloids
Mitomycin C

Treat all extravasations with cold compress except VINCAS.
Extravasation of Vinca alkaloids treated with local heat.
Hyaluronidase, Sodium thiosulphate and DMSO also used for various extravasation management protocols.

Exfoliants (may have low vesicant potential): Drugs that can cause inflammation and shedding (peeling off) of skin without causing underlying tissue death.
Eg. Taxanes and liposomal doxorubicin.

Irritants: Drugs that can cause inflammation, pain or irritation at the extravasation site, without any blister formation
Eg. Carmustine either vesicant or irritant depending on reference, Etoposide, Topetecan

Neutrals: Drugs that neither cause inflammation nor damage upon extravasation
Eg. Cyclophosphamide, bleomycin, gemcitabine, transtuzumab, rituximab

Top tip: Remember the vesicants and the neutrals well. This will help answer MCQs which will often be designed to be unambiguous with examples from either ends of the spectrum.

REFERENCES:
1. The basic science of oncology editors, Ian F. Tannock, Richard P. Hill. - 3rd ed. **THE CHAPTERS ON PHARMACOLOGY IN Tannock and Hill are excellent.**
2. Washington Manual of Oncology, 3rd Edition 2018. Authors/Editor: Govindan, Ramaswamy; Morgenstern, Daniel. Publisher: Lippincott Williams & Wilkins
3. Notes by Dr. Oliver Coen, SpR Leeds Cancer Centre. Personal communication.