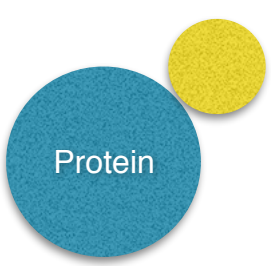
TYROSINE KINASE INHIBITORS (TKIs)



Kinases are enzymes that add a phosphate group to a protein

Phosphatase REMOVE the phosphate group from a protein

Down stream signalling

PROLIFERATION

ANGIOGENESIS

These two processes modulate protein activity. It functions as an "on" or "off" switch in many cellular functions.
Kinase enzymes that specifically phosphorylate tyrosine amino acids are termed **tyrosine kinases.**

Most tyrosine kinases are enzymes that promote cell proliferation, survival and migration. And hence mutated tyrosine kinases act as drivers of cancer or oncogenes.

The tyrosine kinases are divided into two main families:

- the transmembrane receptor-linked kinases (EGFR, HER2, VEGFR)
- those that are cytoplasmic proteins (ABL-BCR: mutated gene that encodes a cytoplasmic tyrosine kinase)

Kinase specific inhibitors can be used to inhibit this process and target cancer cell killing (when mutated kinases are the driving oncogenes) and have favourable toxicity profiles.

MOST TKIs are ORAL MEDICATIONS

Imatinib was the first TKI and change the landscape of treatment for CLL. It is now also used to treat rarer Gastrointestinal stromal tumours. Sometimes it can shrink the tumour so rapidly that can cause stomach perforation!

TKIs such as Crizotinib are first line in ALK+ (tyrosine kinase) mutated lung cancers. Patients with metastatic lung cancer treated with crizotinib have a median overall survival of >4 year (compared to 12 months on traditional chemotherapy)

Examples include:

Drug name (TKI)	**Tyrosine Kinase / Tyrosine Kinase receptors**	**Used to target this Cancer**
Imatinib	ABL-BCR	CLL, GIST
Transtuzumab	HER2 or EGFR2	Breast cancer

Erlotinib, Geftinib	EGFR1 (epidermal growth factor receptor)	Lung Cancer
Sunitinib, Sorafenib	VEGFR1 (vascular endothelial growth factor receptor)	Renal call cancer, GIST, (sorafenib for HCC)
Vemurafenib	B-RAF	Melanoma

TOXICITY: With variations from drug to drug, tyrosine kinase inhibitors cause:

Skin toxicity, including folliculitis, in more than 50% of patients.
The agents that target EGFR, erlotinib and gefitinib, display the broadest spectrum of adverse effects on skin and hair, including folliculitis, paronychia, facial hair growth, facial erythema, and varying forms of frontal alopecia.

In contrast, folliculitis is not common during administration of sorafenib and sunitinib, which target VEGFR.

Periorbital edema is a common adverse effect of imatinib.

Hypothyroidism is a common side effect of sunitinib

Cardiac toxicity is a serious concern with transtuzumab including risk of left ventricular heart failure. Other TKIs are also associated with risk of arrythmia, QTc prolongation.

Other common side effects include vomiting and diarrhoea. Fatal pneumonitis can also occur with TKIs (EGFR inhibitors)

QUESTIONS:

A. Which cardiac medication should be avoided with sunitinib?

1. Bisoprolol
2. Ramipril
3. Amiodarone
4. Aspirin

B. Transtuzumab is used as adjuvant therapy in HER2+ breast cancer. What baseline scan should be performed prior to starting treatment?

1. USS liver
2. Echocardiogram
3. Doppler US of leg/deep veins
4. CT brain

Answer A: : Amiodarone. Amidoarone can cause Qtc prolongation and hypothyroidism. Both side effects also associated with sunitib.

Answer B: Echocardiogram.
Side effects include risk of CCF 2% (severe 1%)
INFUSION RELATED REACTION 20-40% (severe 1%)

Cardiac dysfunction is NOT dose related and reversible - so good prognosis after adverse event.
Assess with echo every 3 months on treatment, and 6 monthly post Rx for 2 years post. then yearly till 5 years complete.
Does not KILL myocytes but reduces contractility. Thus Can halt drug is drop in LVEF >10-15% from baseline, and restart in 3 weeks if needed.

References:

Hartmann JT, Haap M, Kopp HG, Lipp HP. Tyrosine kinase inhibitors - a review on pharmacology, metabolism and side effects. Curr Drug Metab. 2009 Jun;10(5):470-81.