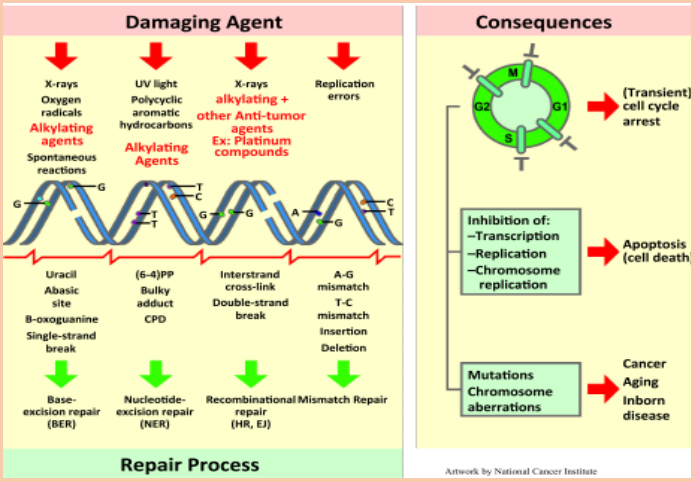
TYPES OF DNA DAMAGES AND THEIR REPAIR:



CELLULAR RESPONSES TO DNA DAMAGE:

Cell cycle arrest	• Multiple surveillance systems are employed to halt cell proliferation upon DNA damage induction • Prevent propagation of errors
DNA repair	• DNA damages on a single strand are repaired with base-excision (BER) or nucleotide-excision (NER) repair • Double-stranded DNA breaks are repaired by homologous recombination (at G2 and before cell division) or non-homologous end joining (all other cell cycle phases) mechanisms • DNA mismatches are repaired with mismatch repair pathways, correct base is determined with epigenetic marks • Cell cycle resumes when DNA repair is completed
Apoptosis	• When damage is beyond repaired, the same surveillance systems will induce program cell death

- Erroneous repair as well as the failure to induce apoptosis when repair is not possible will lead to **genomic changes** (MUTATIONS)

ALKYLATING AGENTS: cyclophosphamide, ifosfamide, chlorambucil, bulsulfan

	Cyclophosphamide	Ifosfamide
MOA	• Damage DNA by covalently attaching an alkyl group to nucleophilic sites (oxygen or nitrogen atoms) • Crosslinking activity is the major mechanism of cytotoxicity	
Notes	• Most commonly used alkylating agents in cancer chemo	• Analog of cyclophosphamide with slight differences in PK parameters
Route	• Oral or IV infusion	• IV infusion
Activation	• Pro-drug, requires activation by the CYP2B in the liver	
Toxicity	• Dose-dependent and can be severe o Myelosuppression o Cardiotoxicity with high doses o High-moderate emetogenicity	• Dose limiting toxicity similar to cyclophosphamide o Myelosuppression o Encephalopathy o Low-moderate emetogenicity
	• Hemorrhagic cystitis (due to accumulation of acrolein = active metabolite, in bladder; txt = mesna, containing sulfhydryl)	
Resistance Mechanism	• Increase metabolism by glutathione transferase • Increase metabolism by aldehyde dehydrogenase • Increase DNA repair capacity	
Inter-individual variability	• Activated by CYP2B6 (cyclosphosphamide) and CYP3A4 (ifosfamide) • Inter-patient genetic differences may affect therapeutics (activation and toxicity)	

PLATINUM COMPOUNDS:

	Cisplatin	Carboplatin	Oxaliplatin
MOA	• Act similarly to alkylating agents; target nucleophilic centers in guanine, adenine and cytosine • Cytotoxicity related to their crosslinking of DNA molecules		
Notes	• Cisplatin (prototype platinum compound) = most efficacious in the treatment of testicular and ovarian cancer	• Less reactive and exhibit reduced toxicity compared to cisplatin • Pro-drug, must be activated intra-cellularly (via hydrolysis) to reactive platinum compounds for efficacy	• Activated by hydrolysis • Synergy with 5-FU and irinotecan
Route	• IV and IP	• IV infusion	• IV and IP
Toxicity	• Myelosuppression • Nephrotoxicity = dose-limiting • Cumulative & irreversible ototoxicity • High emetogenicity	• Myelosuppression • Nephron- and oto-toxicity less severe than cisplatin • High-mod emetogenicity	• Myelosuppression • Acute nephrotoxicity • Peripheral sensory neuropathy • High moderate emetogenicity
Resistance Mechanisms	• Increase metabolism by glutathione conjugation or by sulfhydryls conjugation • Decrease intracellular concentrations (decrease uptake and increase efflux) • Increase DNA repair capacity		

	Doxorubicin	Epirubicin
MOA	• Synthesized by or derived from fungus *Streptococcus peucetius* • Cytotoxic mechanisms: (1) intercalate DNA (2) tripartite complex w/ topoisomerase II (3) generate free radicals → induce oxidative stress	
Notes	• Widely used to treat solid tumors	• Doxorubicin analog • Approved in 1999 for treatment of breast cancer
Route	• IV bolus and IP in special applications	• IV bolus
Toxicity	• Myelosuppression • High-moderate emetogenicity (dose-related) • Cardiac toxicities (dose-dependent = related to free radical production; doxorubicin >> epirubicin) → 1-10% develop irreversible CHF o Dexrazoxane (iron chelating agent) can prevent or reduce cardiac toxicities o Liposomal formulations of doxorubicin were found to be associated with fewer cardiac toxicities	
Resistance Mechanisms	• Increase expressions of p-glycoprotein • Decrease Topoisomerase II activities • Increase metabolism by glutathione peroxidase	

SIGNAL TRANSDUCTION INHIBITORS:

1. Small-molecule kinase inhibitors used to stop growth signaling
2. Small molecules are able to penetrate solid tumors, where larger antibodies might not have access
3. Cheaper and easy to manufacture than antibodies

VEMURAFENIB:

BRAF signalling	• V-Raf murine sarcoma viral oncogene homolog B1 • Serine/threonine protein kinase activated by RAS GTPase • Mutated in 40-60% melanoma cases ○ Most common: V600E (>80%)
MOA	• Reversible competitor of ATP binding in mutated BRAF • Only works in melanoma patients whose cancer has a V600E BRAF mutation • Paradoxical increase in wt-BRAF activity due to the release from auto-inhibition → development of unrelated cutaneous and non-cutaneous cancers
Route	• Orally administrated
Toxicities	• QT prolongation • Cutaneous squamous cell carcinoma & unrelated cancer with RAS mutation
Resistance Mechanisms	• Switch to other growth receptors (PDGF, IGF and others) dependent growth • Mutations in MEK and ERK • Increase in drug efflux (P-glycoprotein)

OTHER USEFUL PROTEIN KINASE INHIBITORS:

Drug	Targets	Cancer types
Erlotinib	EGFR/JAK2-V617F	NSCLC Advance pancreatic cancer
Sorafenib	VEGFR PDGFR RAF	Hepatic Renal Thyroid
Everolimus	Mtor	Breast Renal not responsive to 1st line TKIs Neuroendocrine tumors of pancreatic origin

IMATINIB :

BCR-Abl	• BCR-Abl is an abnormal tyrosine kinase (translocation gene product chr9:22 = Philadelphia chromosome) found in Chronic Myelogenous Leukemia • BCR-Abl tyrosine kinase over-activity results in the phosphorylation of proteins and activation of signal transduction pathway that leads to uncontrolled growth
MOA	• Small-molecule inhibitor of BCR-Abl tyrosine kinase ○ Binds to ATP binding site & inactivates this enzyme • Shows selective inhibition of other cancer-associated TK activities, such as PDGF and c-kit kinases
2nd gen	• Rational drug design congeners of imatinib were developed: nilotinib, dasatinib, bosutinib, ponatinib (only congener that can be used with T315I mutation) • These 2nd generation TKIs are used as successive therapy following resistance development against Imatinib
Route	• Orally administrated
Toxicities	• Myelosuppression • Hepatic disturbances • HBV reactivation
Resistance Mechanisms	• Mutation of TK (T315I renders broad drug resistance • Amplification of BCR-Abl
Inter-individual variability	• Variability of therapeutic outcomes due to CYP3A4 metabolism

GEFITINIB:

Epidermal Growth Factor Receptors	• Family of 4 human EGF receptors (HER1-4) • Membrane-bound receptor tyrosine kinase • Blocking EGFR attenuate the downstream signal transduction pathways that lead to excess growth

MOA	• Blocks the ATP binding domain of EGFR associated tyrosine kinase (also known as HER1)
	• Overall clinical responses to Gefitinib are low
	  ○ Tumors with good response have mutated EGF-R
	  ○ More than one signal transduction pathways could be high-jacked in tumorigenesis, underscoring the potential of combination chemotherapies

Route	• Orally administrated
Toxicities	• Diarrhea • Nausea and vomiting • QT prolongation
Resistance Mechanisms	• KRAS mutation • Mutation (particularly T790M) in HER1-K • Increase in drug efflux

SUMMARY: PHARMACOLOGY OF GENOTOXIC CHEMOTHERAPEUTIC AGENTS

- Specific DNA damages are resolved with different DNA repair pathways
  - In the presence of DNA damages, cells will halt growth & division for repair, or engage in program cell death to prevent propagation of genetic mistakes
- DNA damaging agents work in all phases of the cell cycle, but cells have the highest sensitivity during the replication phase
- Alkylating agents attack the nucleophilic centers of macromolecule, N9 of guanine is a common site of attachment
- Platinum compounds can be crosslinked to the same strand or opposite strands of DNA molecule, resulting in both single and double-stranded DNA breaks
- Anthracycline antibiotics induce cancer cytotoxicity with several different mechanisms of action
  - Their use is limited by dose-related cardiovascular toxicity

SUMMARY: PHARMACOLOGY OF ANTI-CANCER SIGNAL TRANSDUCTION INHIBITORS

- Signal transduction pathways are frequently altered in cancer
- Advances in targeted therapies provide tumor-specific therapy with reduced acute toxicity to normal tissues
- Targeting major controllers of signal transduction pathways, such as tyrosine kinases, generates favorable anti-cancer strategies
- Rapid development of drug resistance is a major clinical issue in kinase inhibitor therapies