

Hematology-Oncology Orientation

高雄長庚血液腫瘤科

Learning Objectives

- Diagnosis
 - ✓ Site, pathologic diagnosis
 - ✓ Stage, treatment course & response
 - ✓ Performance status
 - ◆ ECOG
 - ◆ Karnofsky
 - ◆ WHO
 - ✓ Treatment complication

Performance Status: ECOG

Score	Definition	
0	Asymptomatic	
1	Symptomatic but totally ambulatory and self care without limitation	Eligible for IV chemotherapy
2	Symptomatic and ambulatory $\geq 50\%$ of time, partial care assist	
3	Ambulatory $\leq 50\%$ of time, need care assist	Increased risk for chemotherapy complication
4	Bedridden	

RECIST v1.1 Summary

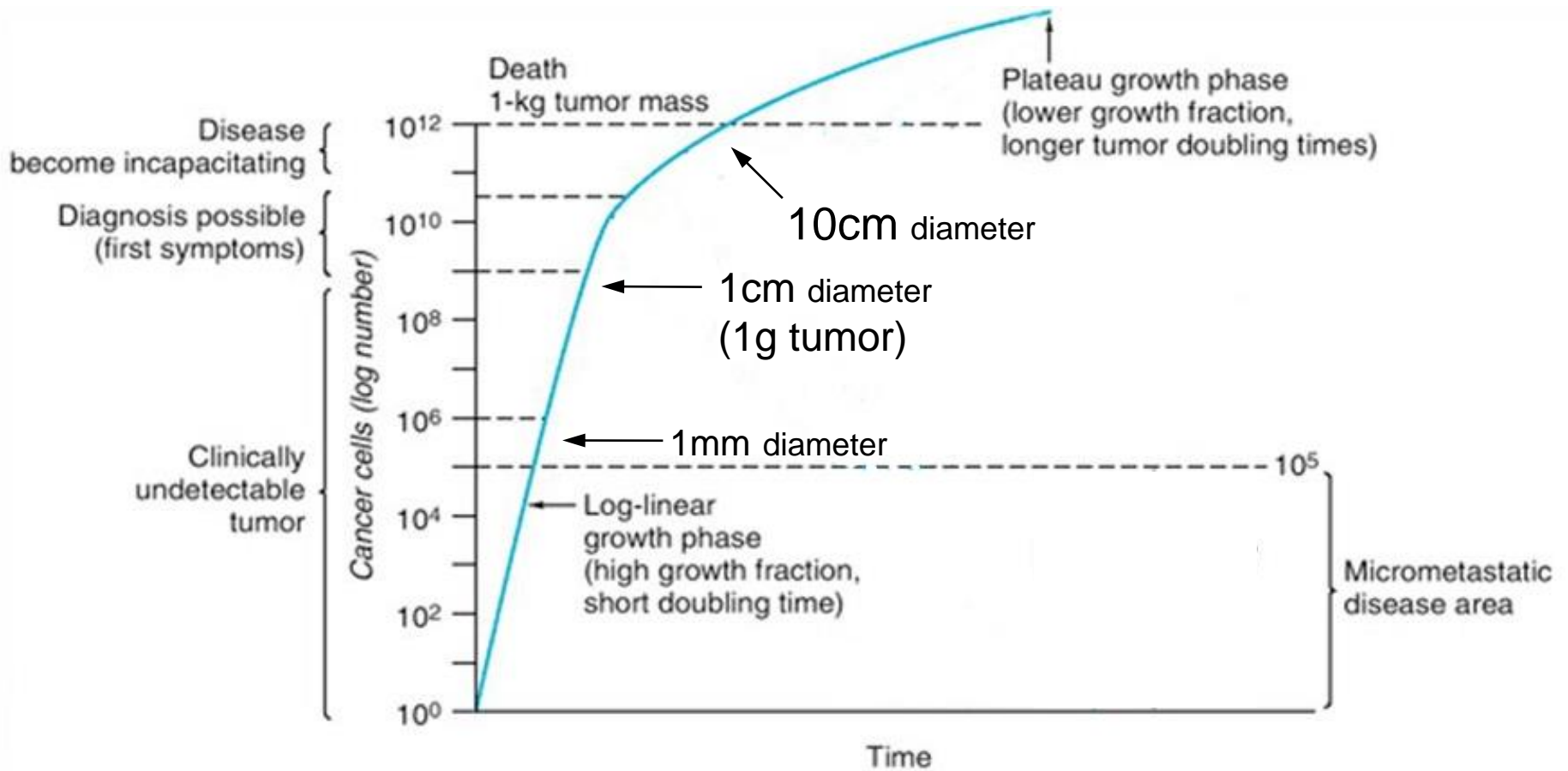
Evaluation	Definition
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

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- Chemotherapy
 - ✓ Agent, mechanism, side effect, contraindication, indication...

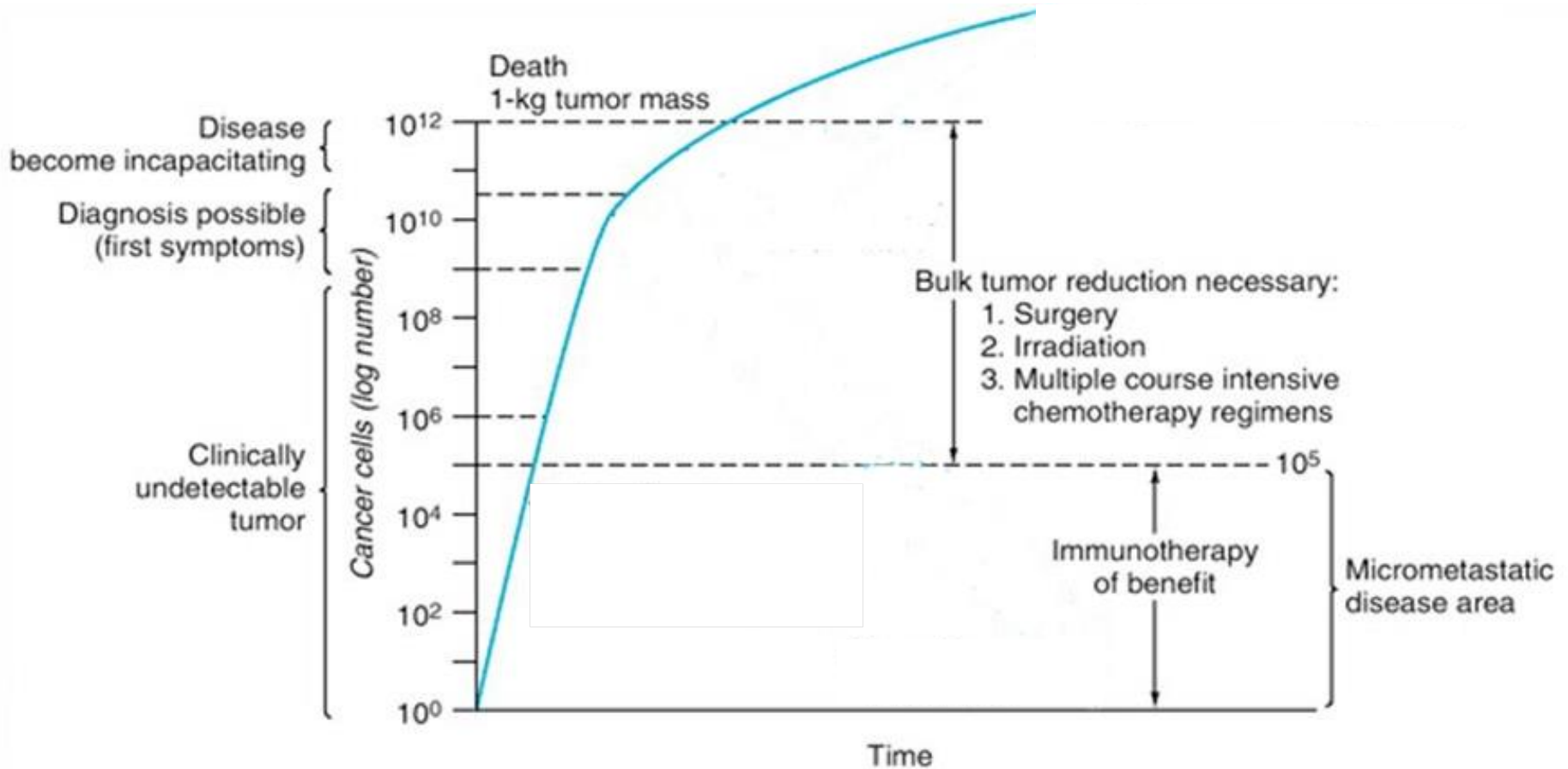
Tumor Growth Kinetics

Nature Course



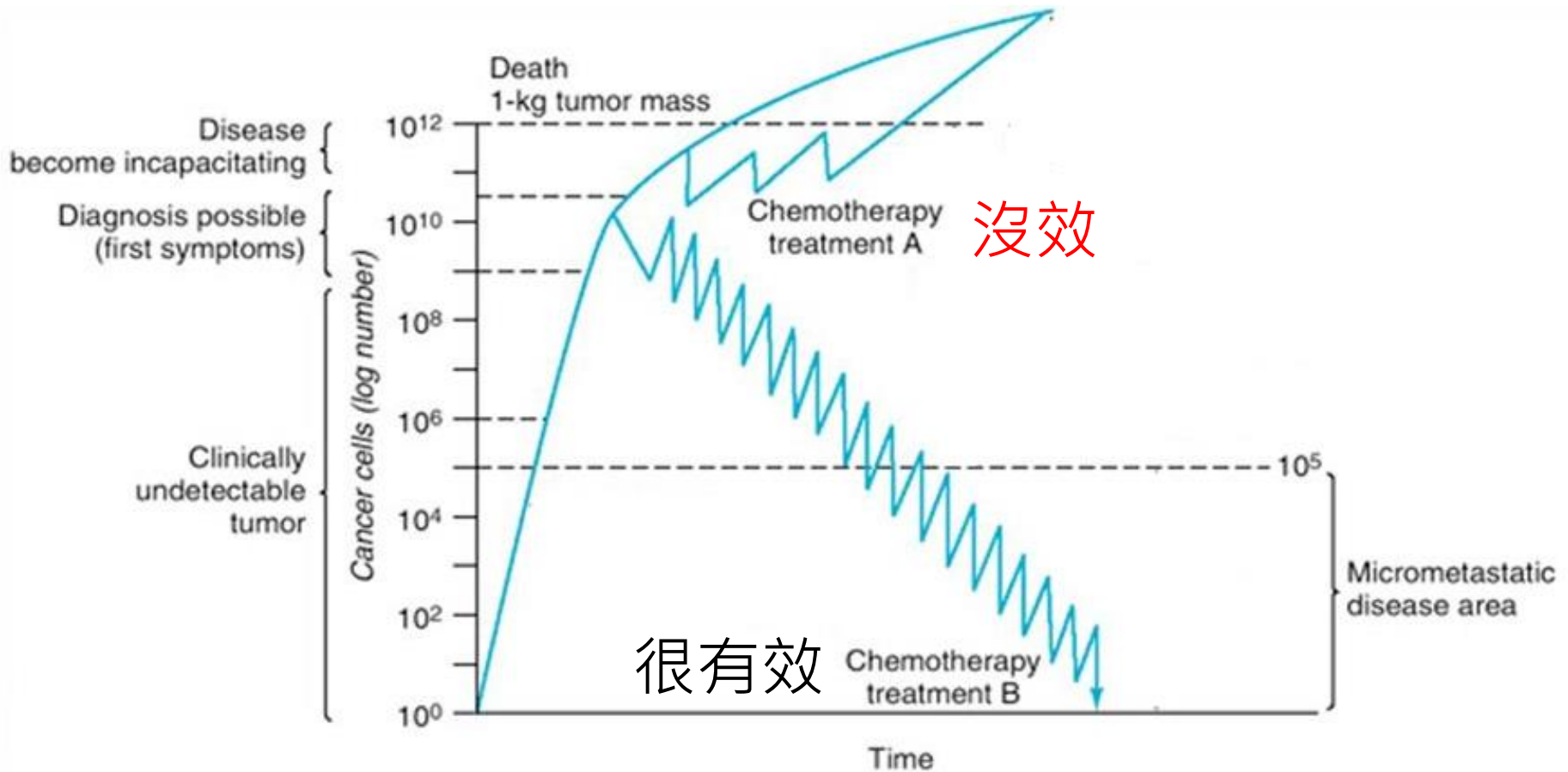
Tumor Growth Kinetics

Surgery or local ablative treatment



Tumor Growth Kinetics

Chemotherapy



Cancer treatment

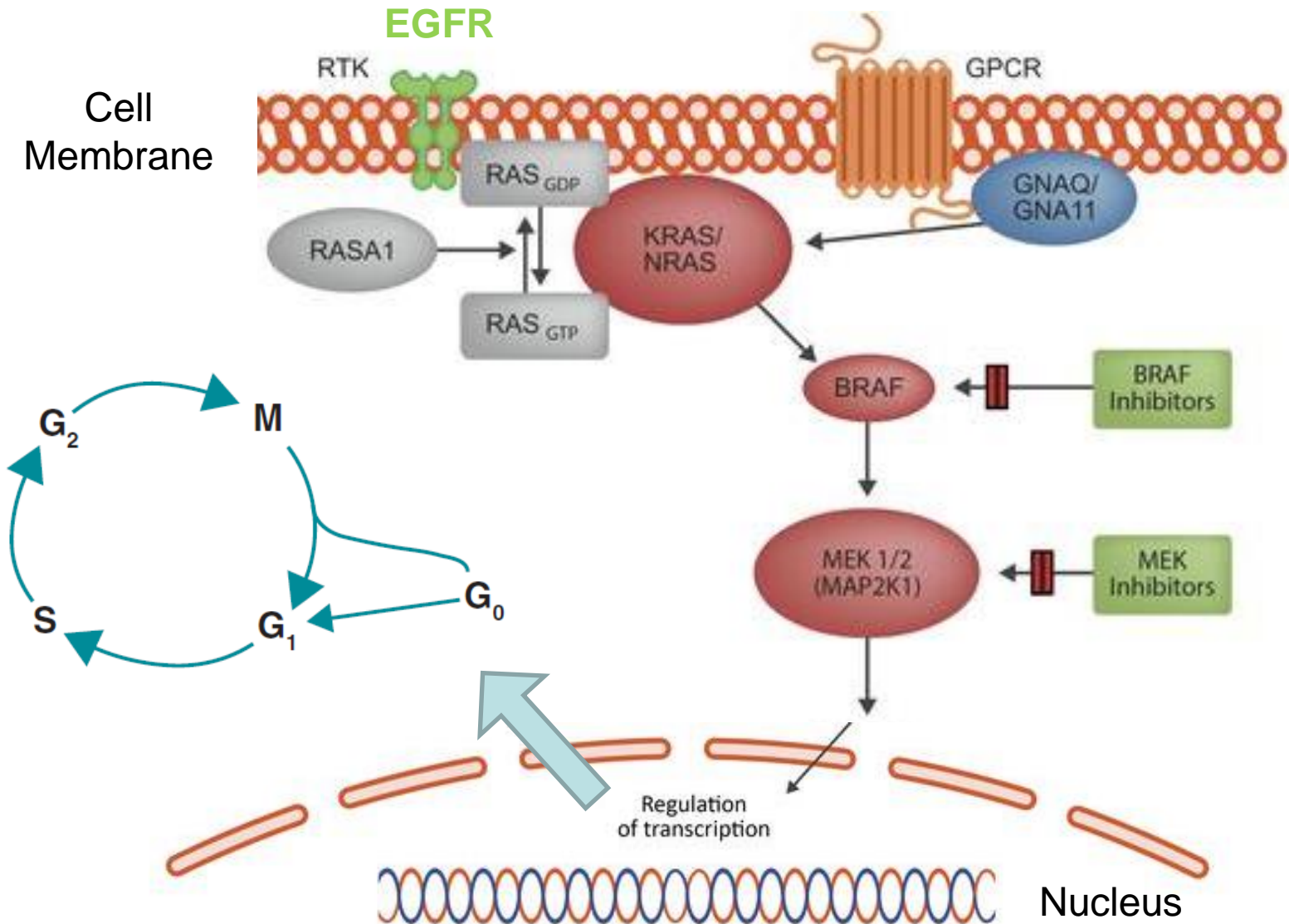
- Systemic treatment
 - Chemotherapy
 - Target therapy
 - Immunotherapy
- Local treatment
 - Surgical resection
 - Local irradiation
 - RFA, PEI or cryoablation
 - TAE or TACE
 - IA chemotherapy

Chemotherapy Terms

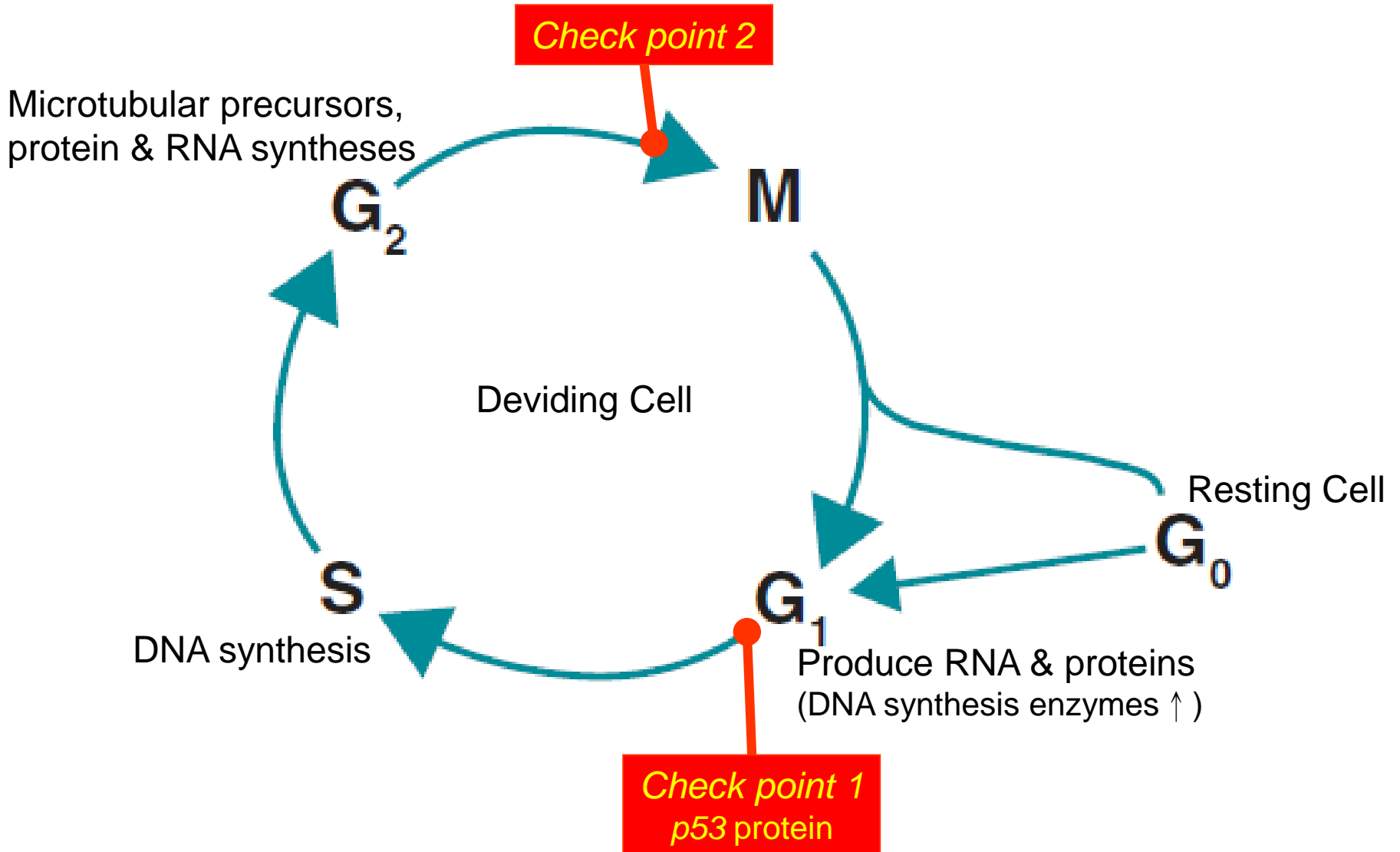
Terms	Definition/ Purpose
Induction	Initial treatment in combined modality
Neo-adjuvant	To make clinical resectable but locally advanced tumor amenable for eradication
Definitive	Intent to cure
Adjuvant	Prevent recurrence
Maintenance	Bridge to cure after induction treatment
Salvage	Intent to cure after initial definitive treatment failed
Consolidation	Sustain remission achieved after induction treatment
Palliative	Symptom relieve & prolong survival



RTK signal transduction cell cycle



Chemotherapy



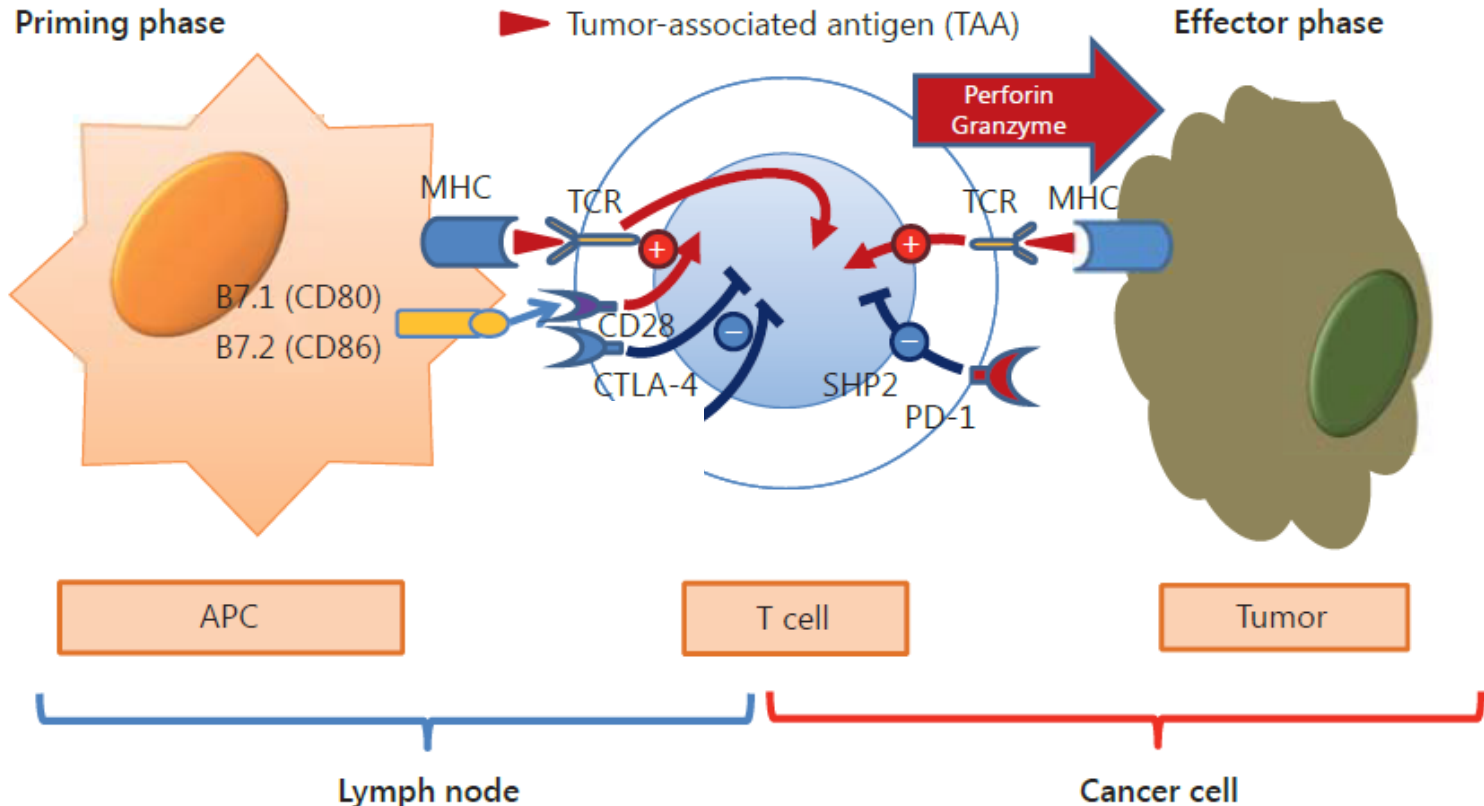
Chemotherapy

- Alkylating agent
 - Cyclophosphamide
- Platinum analogue
 - Cisplatin, Carboplatin, Oxaliplatin
- Anti-tumor antibiotics
 - Anthracycline (Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Mitoxentron)
 - Dactinomycin, Bleomycin, Mitomycin
- Miscellaneous
- Antimetabolite
 - 5-FU, MTX, Pemetrexed, Gemcitabine
- Topoisomerase inhibitors
 - Camptothecin (Etoposide)
 - Epipodophyllotoxins (Irinotecan)
 - Topotecan
- Antimicrotubule
 - Taxane (Taxol, Taxotere)
 - Vinca alkaloid (Vincristine, Vinblastine, Vinorelbine)

Immunotherapy

T cell activation by stimulatory co-signal

Attack on cancer cells by stimulatory co-signal



- Anti-CTLA4
 - Ipilimumab
- Anti-PD-1
 - Pembrolizumab
 - Nivolumab
- Anti-PD-L1
 - Durvalumab
 - Atezolizumab

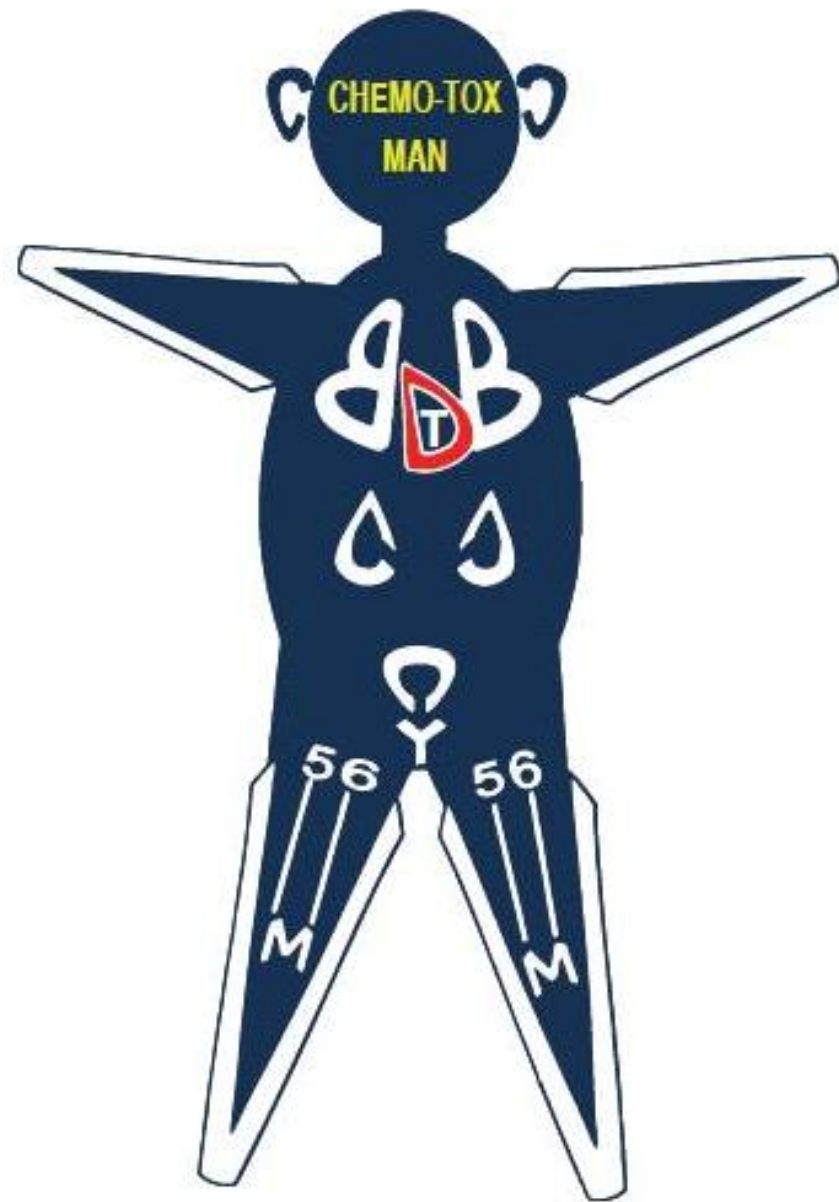


Side effect of chemotherapy



Side effect of chemotherapy

- Nausea and Vomiting
 - Emetic potency
 - Schedule & dose
- Bone marrow suppression
- Neuropathy
- Mucositis
- Diarrhea
- Electrolyte imbalance
- Renal & hepatic toxicity



Cisplatin/Carboplatin → acoustic nerve damage
(and nephrotoxicity)

Vincristine → peripheral neuropathy

Bleomycin, Busulfan → pulmonary fibrosis

Doxorubicin → cardiotoxicity

Trastuzumab → cardiotoxicity

Cisplatin/Carboplatin → nephrotoxic (and
acoustic nerve damage)

CYclophosphamide → hemorrhagic cystitis

5-FU → myelosuppression

6-MP → myelosuppression

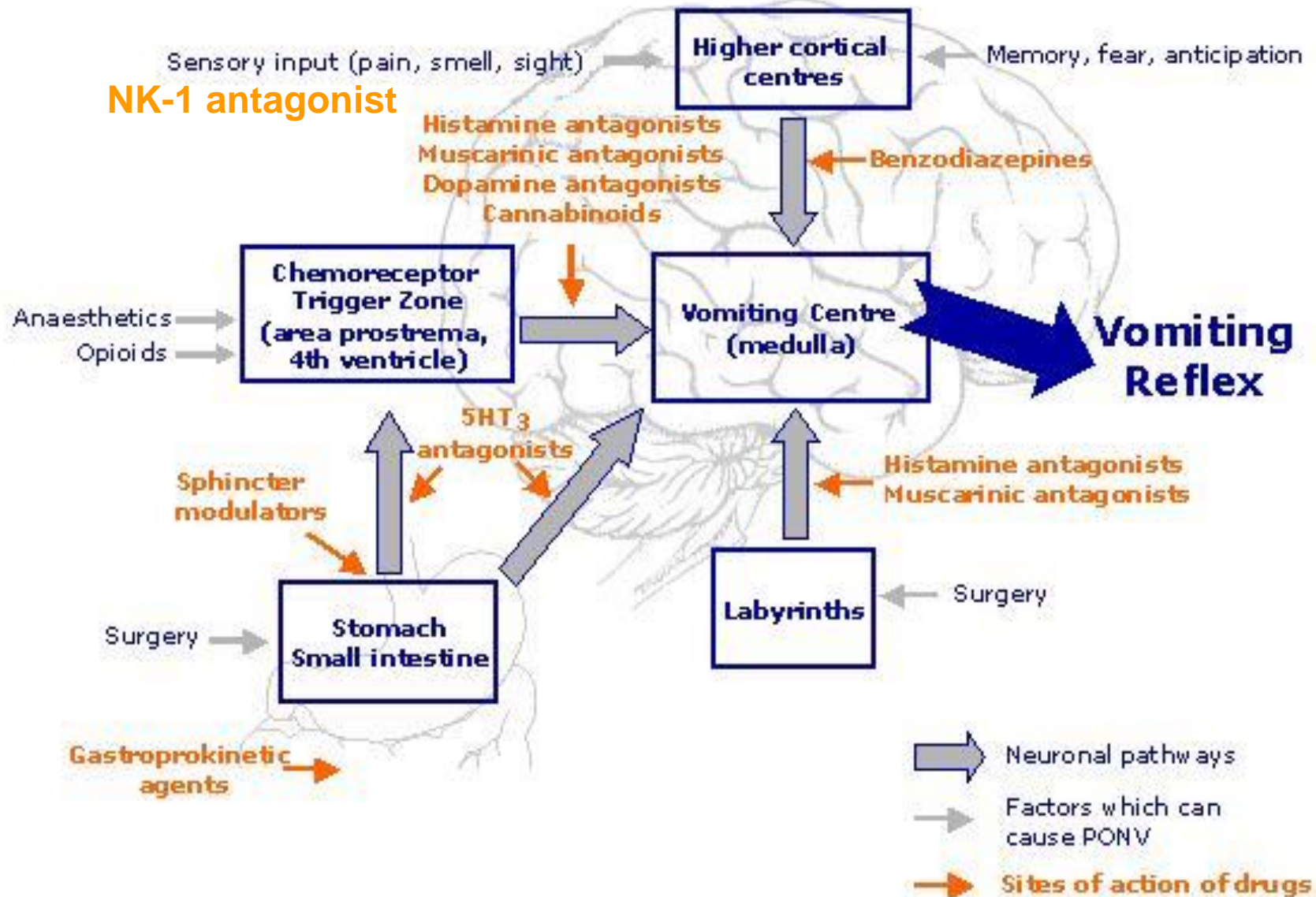
Methotrexate → myelosuppression

Chemotherapy Leakage

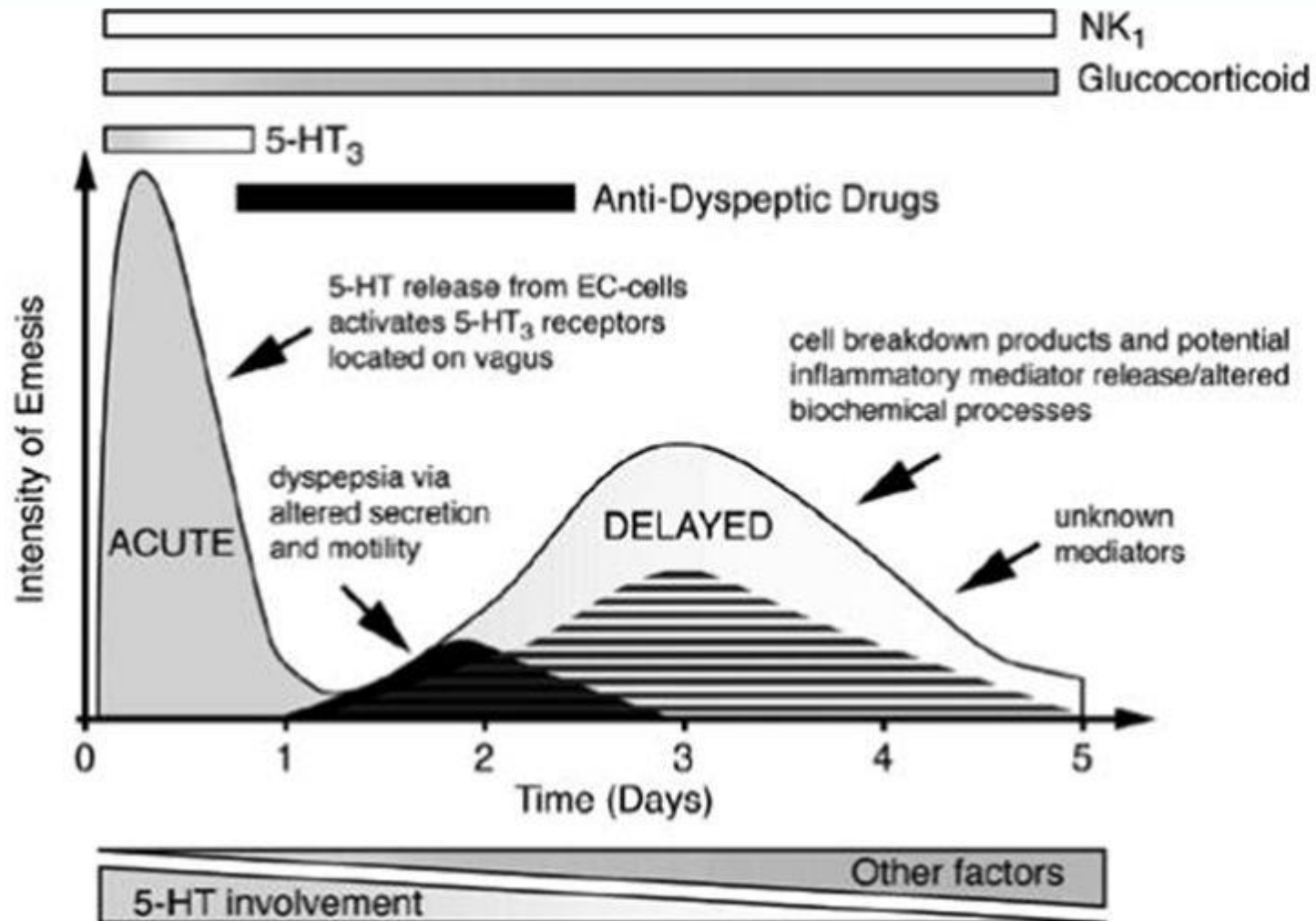
- Vesicants
 - Anti-tumor antibiotics
 - Actinomycin D
 - Dactinomycin
 - Mitomycin C
 - Doxorubicin類 (包括epirubicin, idarubicin, daunorubicin)
 - Vinca alkaloid
 - Vinblastine
 - Vincristine
 - Vinorelbine



CINV Pathophysiology



Neurotransmitter Involvement



Antiemetic agents

Chemical class	Drugs	Action sites
Corticosteroid	Dexamethasone (Dexan)	↓ neurotransmitter release
BZD	Lorazepam (Ativan) Diazepam (Valium)	Sedative & anxiolytic
Antihistamines	Diphenhydramine (Vena)	Vestibular nucleus
Dopamine antagonist	Metoclopramide (Primperan) Prochlorperazine (Novamin)	Dopamine receptor
5HT ₃ antagonist	Ondansetron (Zofran) Granisetron (Kytril) Palonosetron (Aloxi)	CTZ and peripheral 5-HT ₃
NK-1 antagonist	Aprepitant (Emend PO) Fosaprepitant (Emend IV)	CTZ substance-P

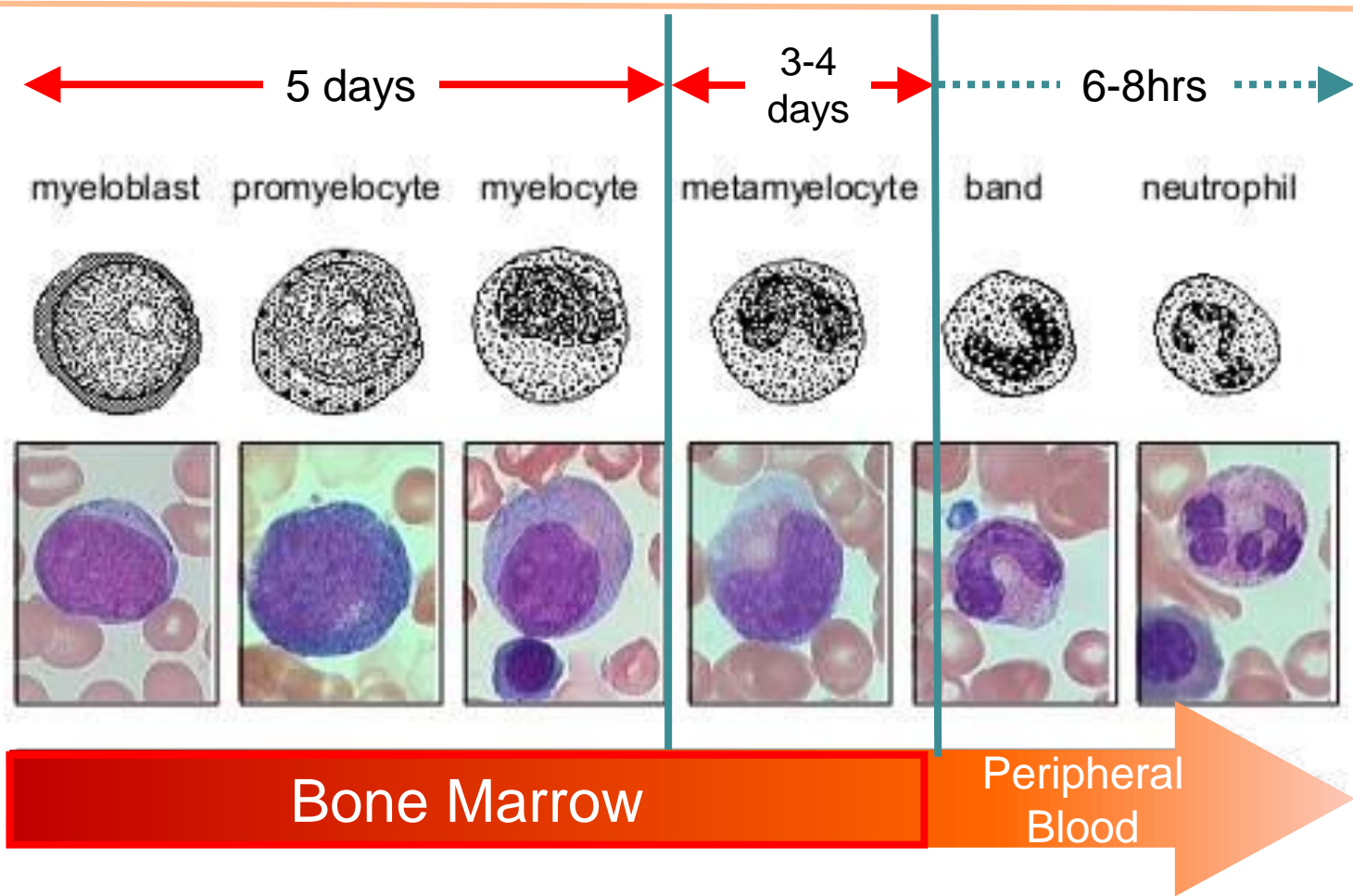
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- Diagnosis
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- **Oncologic emergency**



Febrile neutropenia definition

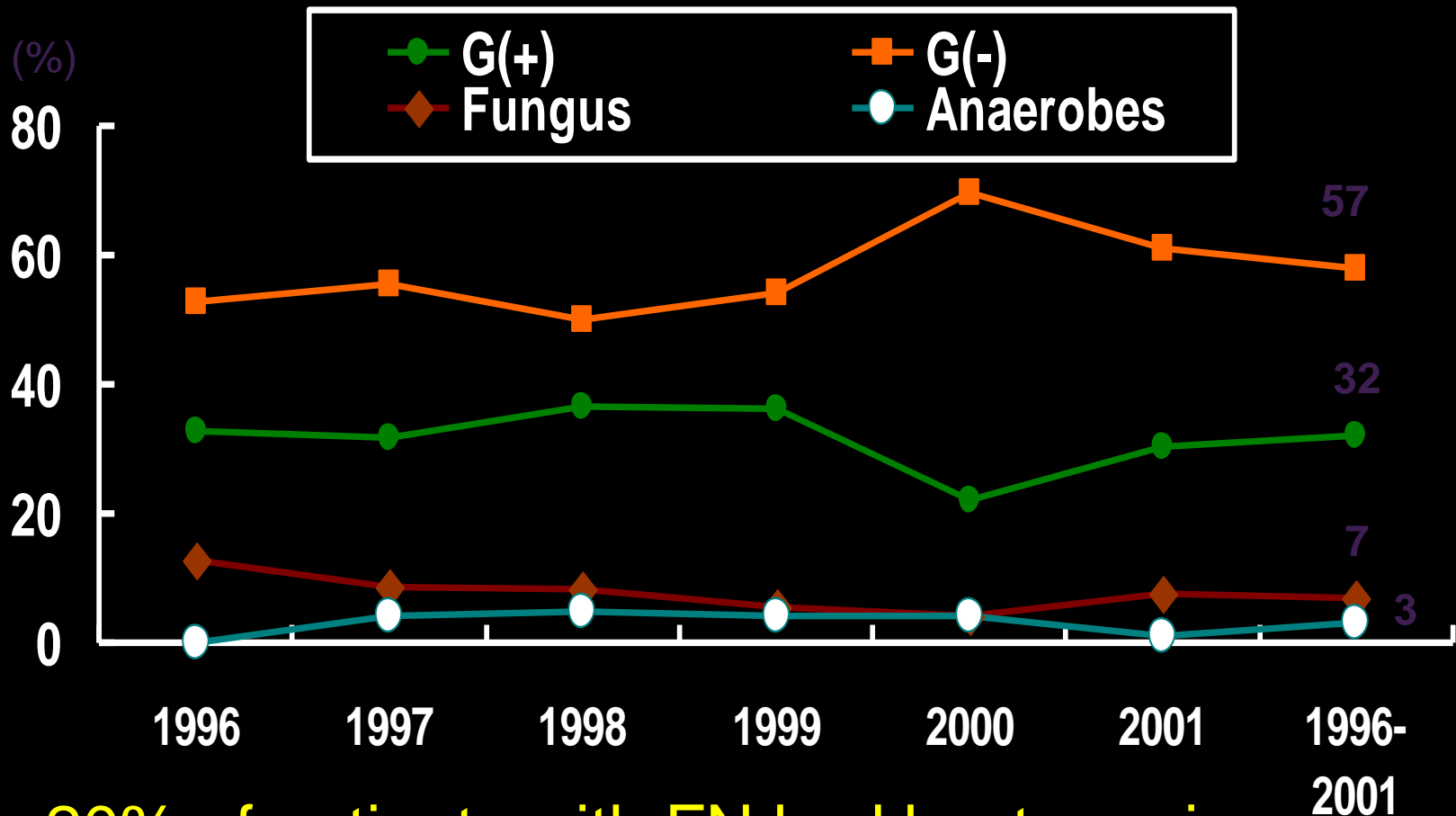
Neutropenia	Fever
<p>ANC = WBC × (Segs + Bands) ANC <500/μL or</p> <p>ANC <1000/μL and a predicted decline to \leq500/μL over the next 48 h</p>	<p>Oral BT \geq38.3°C (single reading) or \geq38.0°C (>1 h) or SOFA score > 2</p>





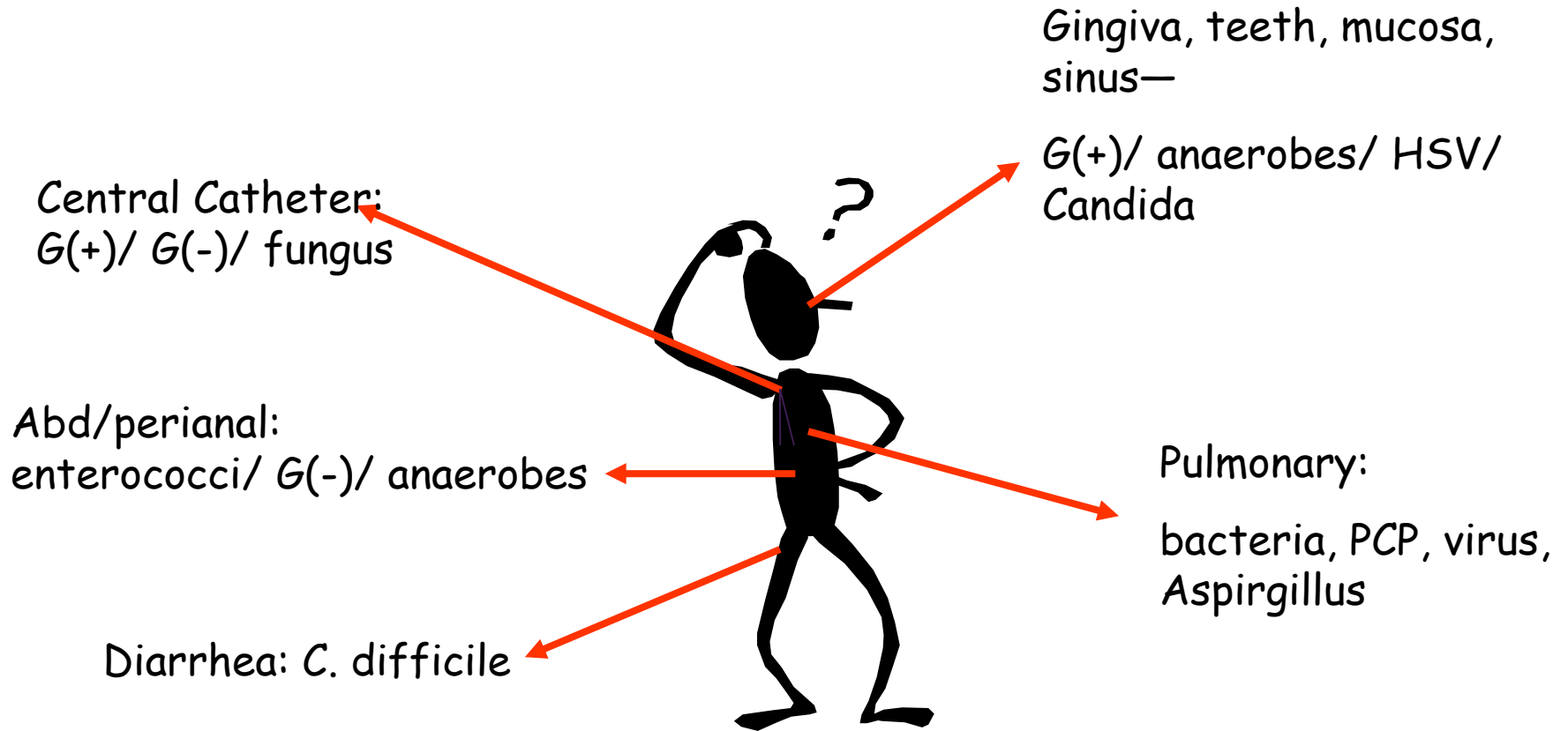
Febrile Neutropenia-- Etiology

NTUH, 1996-2001



20% of patients with FN had bacteremia

Recognition of potential pathogens



Even with a comprehensive evaluation, an infectious etiology is demonstrated in 50 to 70% of cases

Guideline for febrile neutropenia

Fever^a (temperature 38.3°C) + Neutropenia^b (<500 neutrophils/mm³)

Low risk^c

High risk

Oral

Intravenous

Glycopeptide^f
not needed

Glycopeptide^f
needed

A newer
fluoroquinolone^d
+
amoxicillin-
clavulanate or
ampicillin-sulbactam
(adults)
Cefixime (children)

A cephalosporin^e
+
an aminoglycoside

Monotherapy (A)
Cefepime,
ceftazidime,
piperacillin-
tazobactam or
a carbapenem^g

Two drug (B)
An aminoglycoside^h
+
ceftazidime, piperacillin-
tazobactam,
cefepime, ceftazidime or
a carbapenem^g

A glycopeptide^f
+
A or B

Reassess after 3-5 days

Tazocin 3.75-4.5g Q6H
Cefepime 2g Q8H

Brosym 2g Q12H
Carbapenem

(注意腎功能調整)

Hypercalcemia

Hypercalcemia

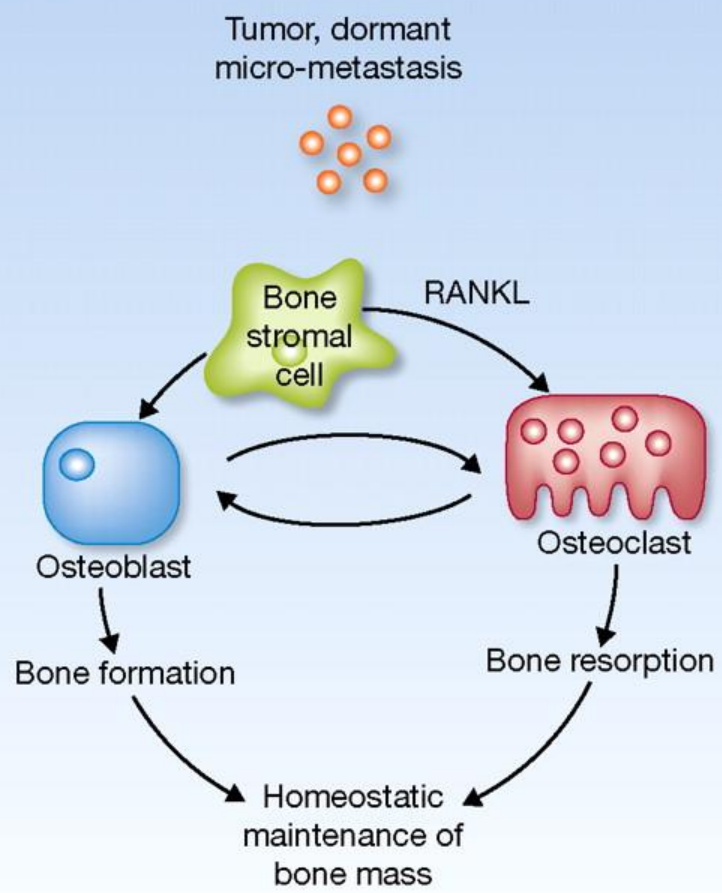
- Clinical presentation:
 - Renal impairment, dehydration, polyuria, polydipsia
 - Constipation, nausea, anorexia
 - Conscious change
- Corrected Ca
 - = measured Ca + (4.0 - alb) x 0.8
- Intact-PTH is low in cancer related hypercalcemia



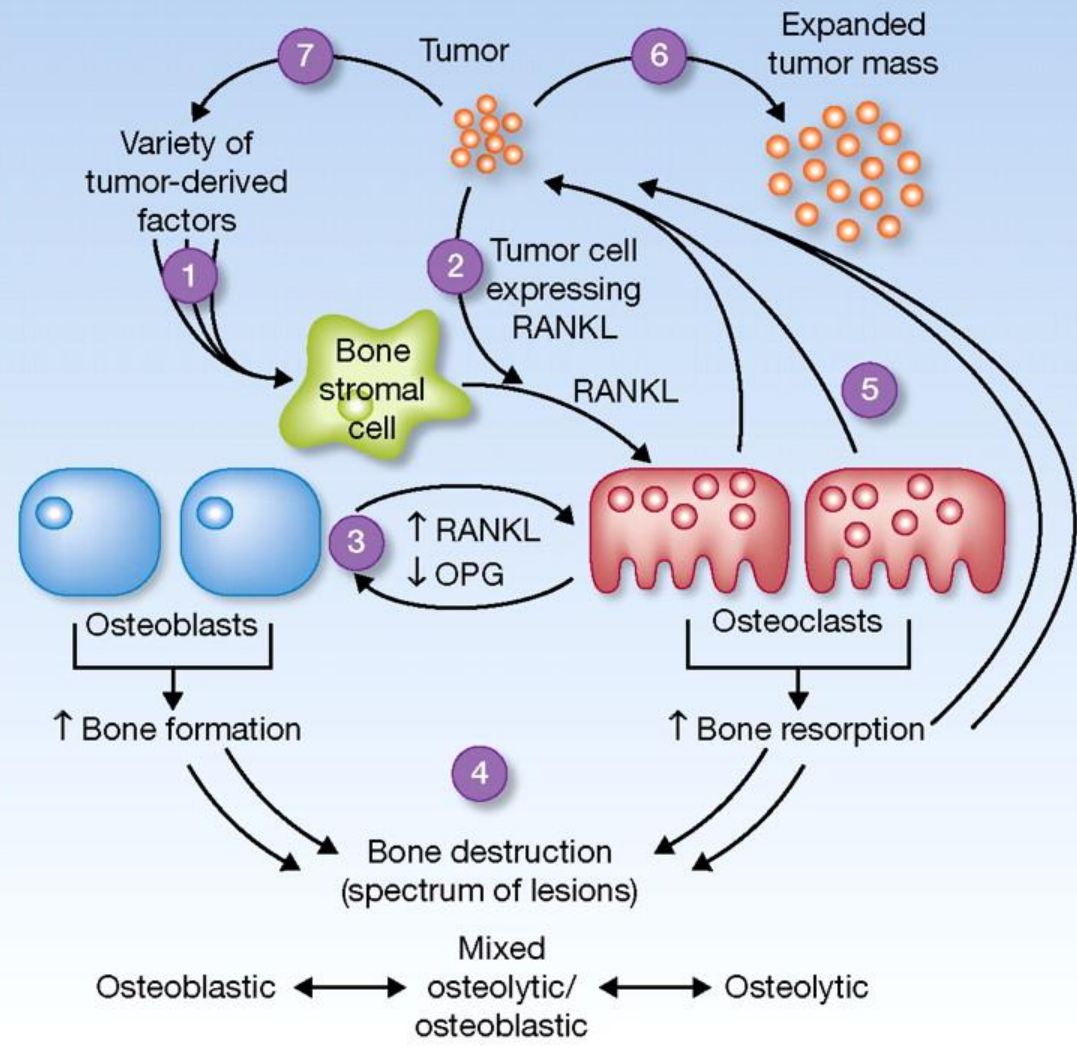
Risk Group for Hypercalcemia

- Hematological malignancy
 - Multiple myeloma
 - Lymphoma
- Solid tumor
 - Osteolytic bone metastasis (lung, breast...etc)
 - **Squamous cell carcinoma with PTHrP**
 - Atopic PTHrP secretion

A Physiological bone turnover/remodeling (normal)



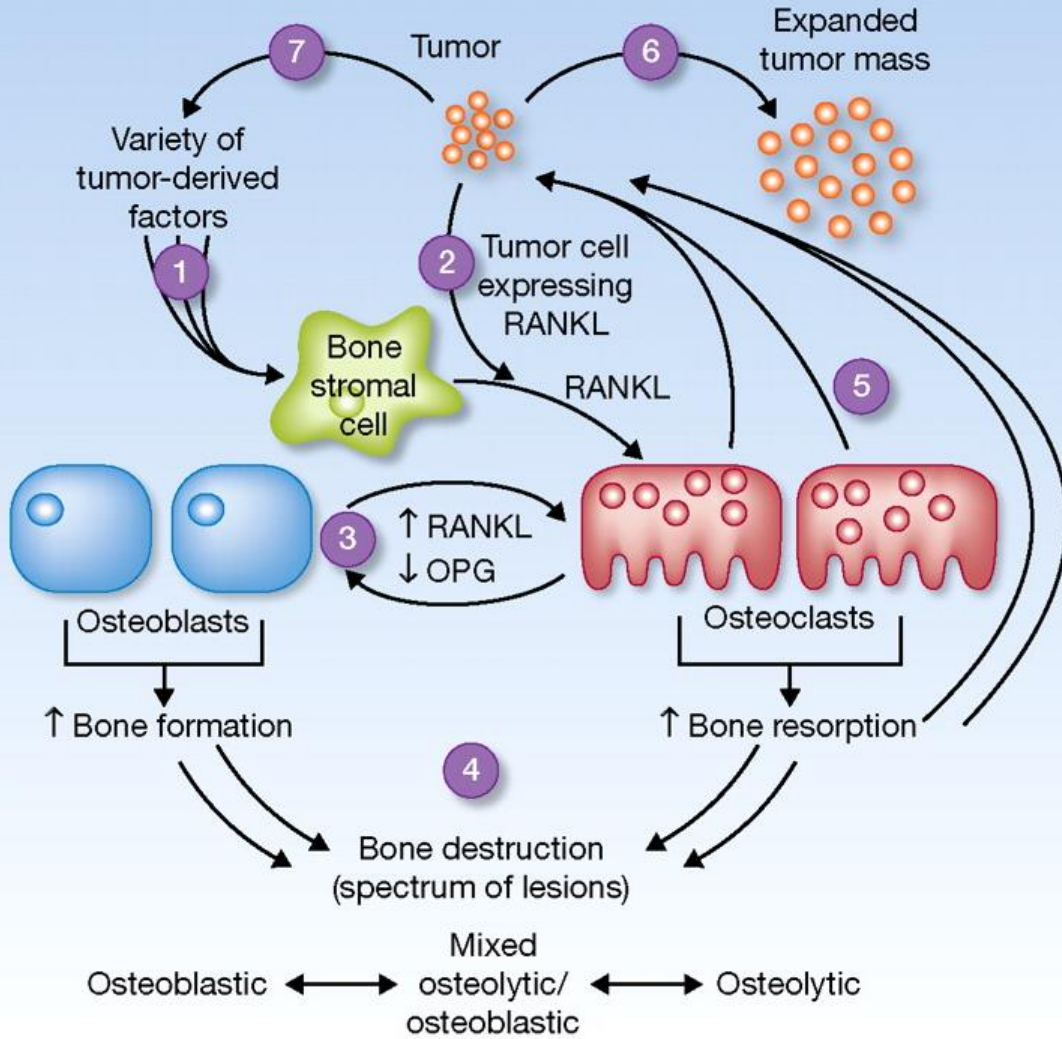
B Tumor-induced pathologic bone turnover/remodeling (high)



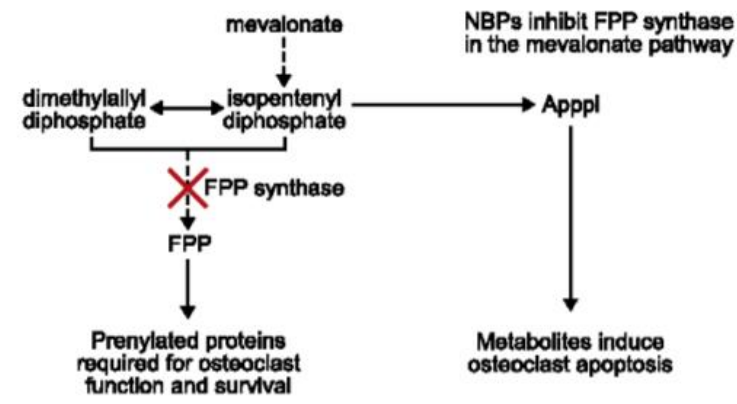
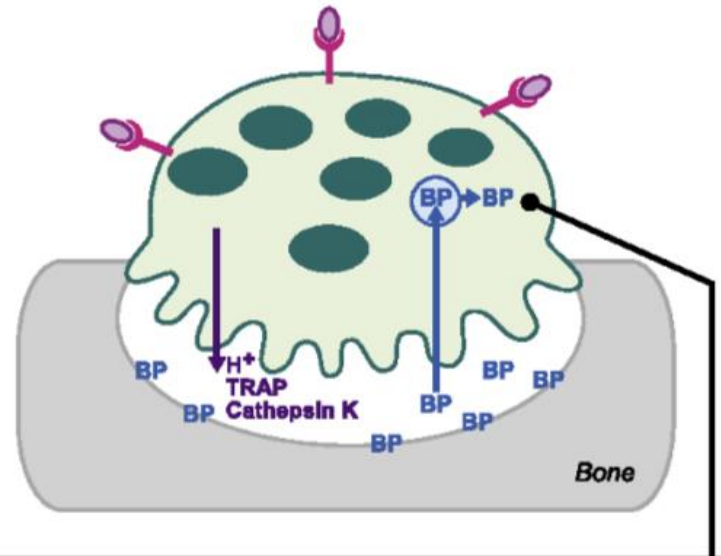
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B

Tumor-induced pathologic bone turnover/remodeling (high)



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Treatment of hypercalcemia of malignancy

Agent	Regimen	Onset	Duration
0.9% Sodium chloride	80-100cc/hr	Immediate	2-3 days
Bisphosphonates (↓ markers in 3 days; 須注意腎功能)			
Pamidronate (Aredia)	60-90 mg IV over 2-6 hours	48 hours	3-4 weeks
Zoledronic acid (Zometa)	3-4 mg IV over 15-30 minutes	48 hours	3-4 weeks
<u>RANKL monoclonal antibody</u>			
Denosumab (Xgeva) 健保：乳癌、前列腺 癌及肺癌併有蝕骨性 骨轉移之病患。	120 mg SQ weekly for 4 weeks, then monthly thereafter	7-10 days	3-4 months

Abbreviations: IV, intravenous; q, every; SQ, subcutaneous.

Spinal Cord Compression

Clinical significance

- Symptoms
 - New onset of back pain: radicular pain
 - motor symptoms: weakness
 - Sensory symptoms: paresthesia, numbness
 - Autonomic symptoms: urine & stool incontinence
 - Ataxia
- Poor prognosis
 - Complete paraplegia
 - Autonomic symptoms
 - Rapid progression
 - T1~T4 level: no man's area
 - Radioresistant tumor: melanoma, RCC, HCC

Management

- Diagnosis: Spine MRI
- Treatment
 - **Dexamethasone 20mg iv st and 5mg iv q6h**
 - Radiotherapy
 - Surgery
 - indication
 - contraindication

Management

- Surgery
 - Indication
 - Radioresistant tumor
 - Alignment change
 - Symptom progression under radiotherapy
 - Previously irradiated spine
 - Tissue proof
 - Contraindication
 - Life expectancy <3months
 - Multiple compression
 - Multiple comorbidity (recent MI, recent stroke)

Tumor Lysis Syndrome

Tumor cell lysis



Hyperkalemia

Release of DNA



Purines

Phosphorous

Allopurinol

Hypocalcemia

Hypoxanthine/Xanthine

Ca-Phos Precipitation

Ca X Phos Product ~60

Xanthine Oxidase

Uric Acid

(low urinary excretion)

Urate nephropathy

(low urine pH)

Ca-Phos nephropathy

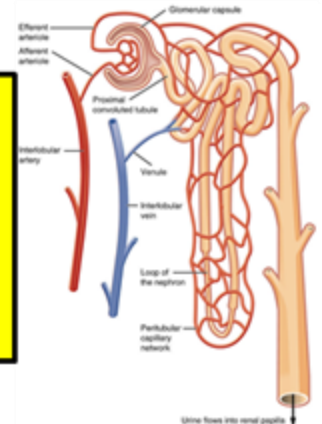
(high urine pH)

Rasburicase

Uricase

Allantoin

(High urinary excretion)



Tumor Lysis Syndrome

- Etiology
 - Acute lymphoblastic leukemia, Burkitt's lymphoma
 - Bulky tissue destroyed by chemotherapy, radiation
- Lab picture
 - Increased K, P, uric acid, LDH; decreased Ca
 - Severe metabolic acidosis
- Management
 - Hydration
 - Correct electrolyte
 - Uric acid elimination
 - Hemodialysis

SVC Syndrome



Superior Vena Cava Syndrome

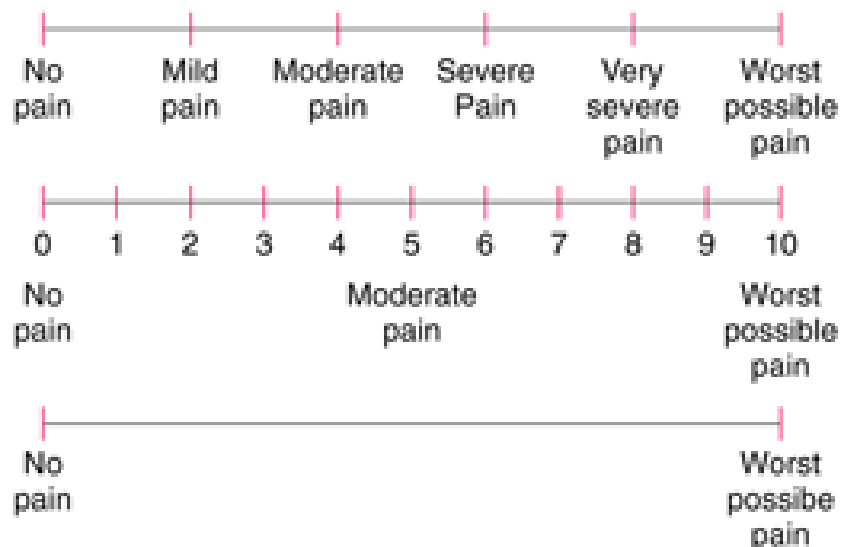
- Etiology:
 - Tumor : Lung cancer (small cell lung cancer and squamous cell carcinoma), lymphoma
 - Metastasis LN : adenocarcinoma
- Clinical symptoms:
 - Dyspnea, pain, dilated neck vein, swelling of the face, neck and upper extremities
- Treatment:
 - Dexamethasone and Radiotherapy
 - Tumor compression + thrombosis: heparin

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- Oncology emergency
- Cancer pain

Cancer pain

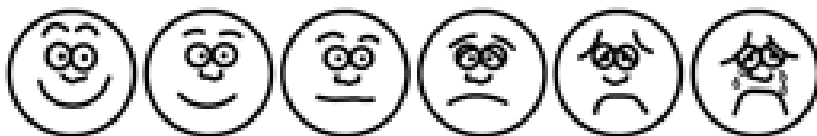
Visual Analog Scale



Word Descriptor Scale

- 0 = No pain
- 1 = Mild pain
- 2 = Distressing pain
- 3 = Severe pain
- 4 = Horrible pain
- 5 = Excruciating pain

Graphic Scale



Verbal Scale

"On a scale of 0 to 10, with 0 meaning no pain and 10 meaning the worst pain you can imagine, how much pain are you having now?"

Functional Pain Scale

- 0 = No pain
- 1 = Tolerable and pain does not prevent any activities
- 2 = Tolerable and pain prevents some activities
- 3 = Intolerable and pain does not prevent use of telephone, TV viewing, or reading.
- 4 = Intolerable and pain prevents use of telephone, TV viewing, or reading.
- 5 = Intolerable and pain prevents verbal communication

Norciceptive and Neuropathic pain

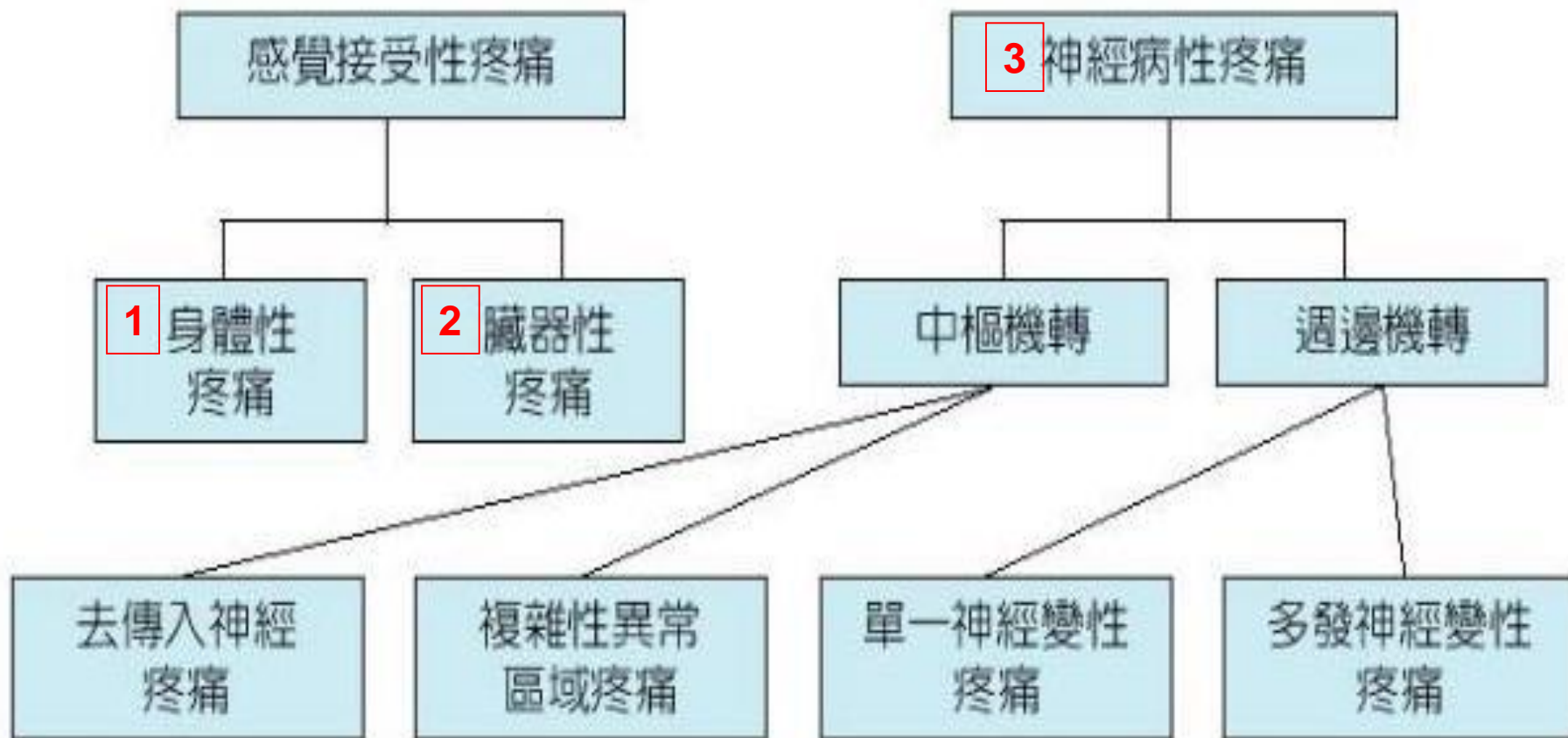


圖1 疼痛的分類

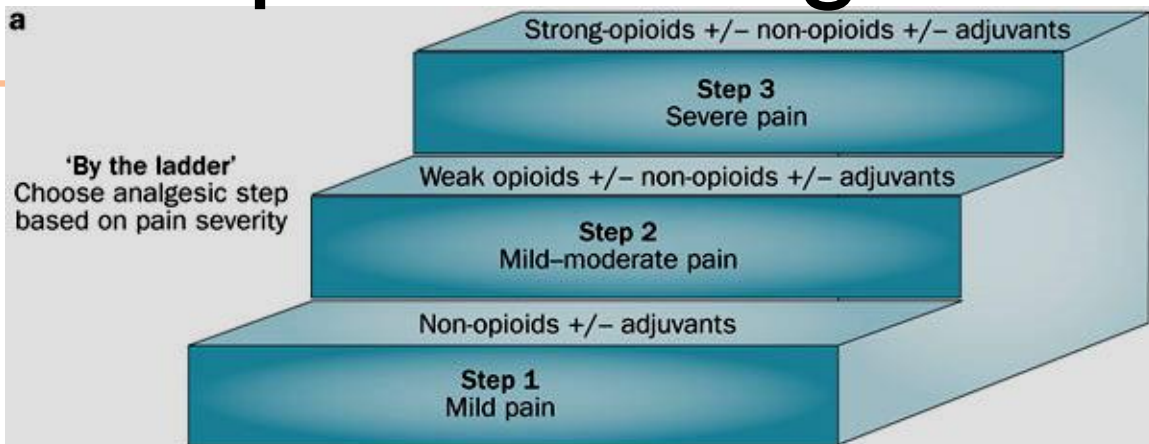
Nociceptive pain

- Somatic pain: Well localized, constant, aching or throbbing quality
- Visceral pain: Episodic, poorly localized, time limited (meaning when the tissue damage heals, the pain typically resolves)
- Respond well to treatment with opioids

Neuropathic pain

- Nerves can be infiltrated or compressed by tumors, strangulated by scar tissue, or inflamed by infection
- Symptoms: Burning, lancinating, or electric shock
- Poor response to treatment with opioids
- May respond to other drugs
 - anti-convulsant
 - antidepressant medications.

Principle of pain management



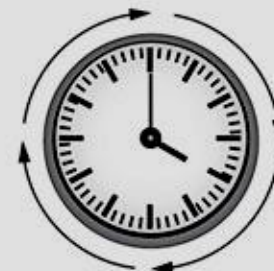
b

'By mouth'
Oral administration preferred over parenteral routes



c

'By the clock'
Around the clock dosing to prevent pain



d

'For the individual'
Tailor pain relief to individual needs and circumstances

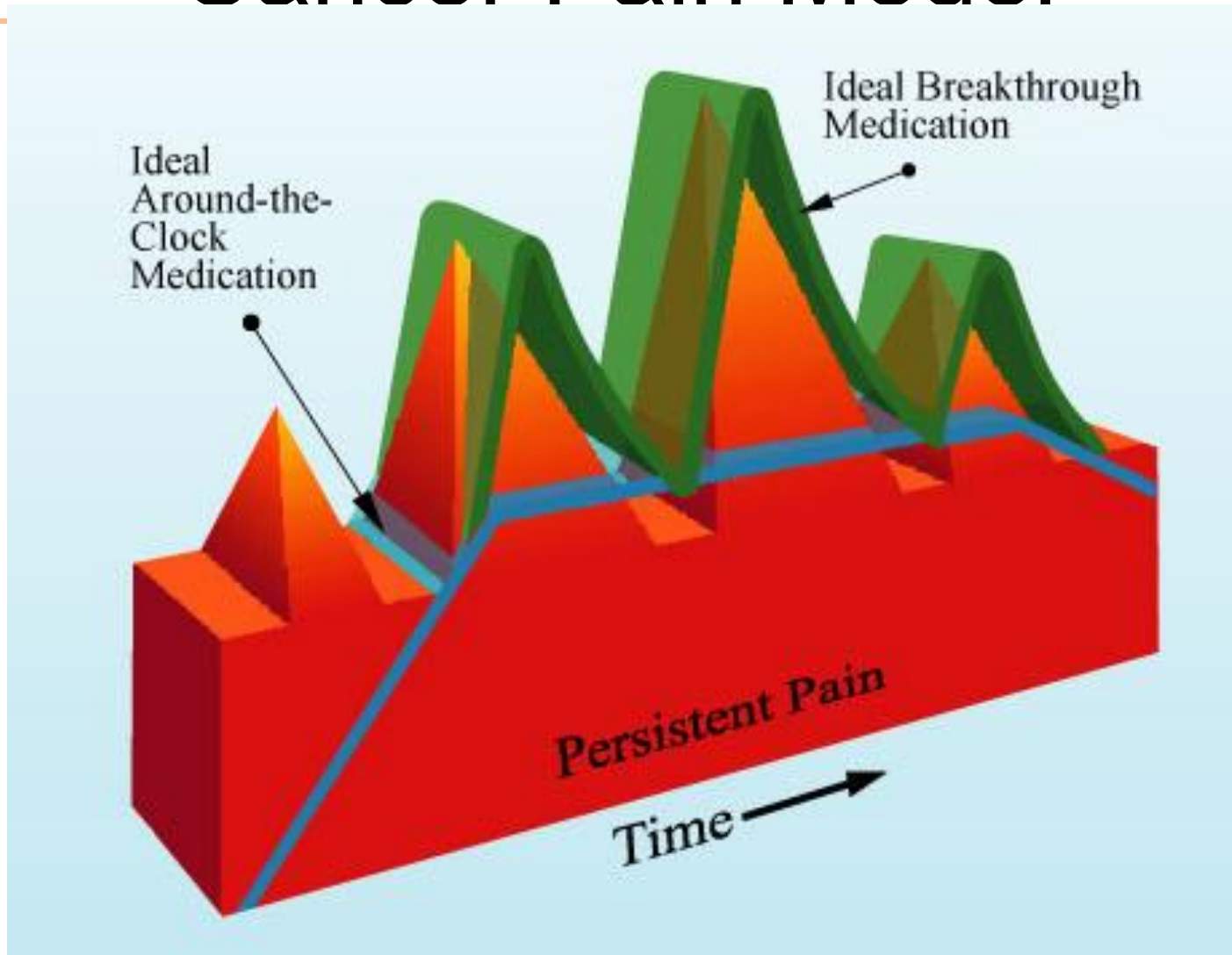


e

'Attention to detail'
Explore all sources of pain and adverse effects of treatment



Cancer Pain Model



疼痛來源	疼痛性質	藥物種類	
Bone or soft tissue	perifocal edema	Steroid	Dexamethasone
			Prednisolone
	compression or motion related	NSAID	Ibuprofen
			Sulindac
			Naproxen
Bone destruction	Bone metastasis	Bisphosphonate	Pamidronate
			Zoledronate
		RANKL inhibitor	Denosumab

Opioid receptors

- Mu receptor effect
 - analgesia, respiratory distress, constipation, euphoria, sedation, miosis, increased secretion of GH & prolactin
- Kappa receptor effect
 - analgesia, diuresis, sedation, miosis, dysphoria
- Delta receptor effect
 - analgesia

	Mu	Delta	Kappa
Morphine	agonist	Weak agonist	Weak agonist
Meperidine	agonist		
Tramadol	Weak agonist		
Fentanyl	agonist		
Nalbuphine	Antagonist		agonist
Naloxone	antagonist	antagonist	antagonist

Opioid principle

- Dose equivalent
 - Morphine 30mg po = morphine 10mg IVF
 - Morphine 20mg po = morphine 10mg IM
- Break through pain :
 - 1/6 total daily morphine dose
 - Usually, morphine 5 ~ 10 mg ivf slowly

藥物	劑型	劑量換算
Morphine (PO)	15mg	
Codeine (PO)	30mg	0.5 PC Morphine
Ultracet (Tramadol) (PO)	37.5mg	0.5 PC Morphine
Fentanyl (Q3D)	25ug/hr	4 PC Morphine

PEACE