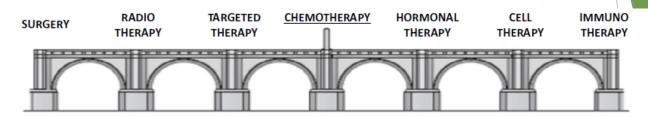
癌症治療新趨勢下的 緩和護理

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outline

- Cancer therapy
- Toxicity Management
- Nursing care
- Long-Term follow up

Cancer therapy



CHEMOTHERAPY: 80 cytotoxic drugs

Azacitidine	Capecitabine	Cladribine	Clofarabine	CPX-351	Cytarabine	Decitabine	Fludarabine	Fluorouracil	Gemcitabine
Methotrexate	Nelarabine	Pemetrexed	Pralatrexate	Raltitrexed	Trifluridine	Altretamine	Bendamustine	Busulfan	Carboplatin
Carmustine	Chlorambucil	Cisplatin	Cyclophospha mide	Dacarbazine	Estramustine	Fotemustine	Ifosfamide	Lobaplatin	Lomustine
Mechloretham ine	Melphalan	Miriplatin	Mitomycin C	Nedaplatin	Nimustine	Oxaliplatin	Procarbazine	Ranimustine	Semustine
Streptozotocin	Temozolomide	Thiotepa	Trabectedin	Treosulfan	Trofosfamide	Actinomycin D	Amsacrine	Mithramycin	Bleomycin
Peplomycin	Cabazitaxel	Docetaxel	Eribulin	lxabepilone	Nab-paclitaxel	Paclitaxel	Vinblastine	Vincristine	Vindesine
Vinflunine	Vinorelbine	Aclarubicin	Amrubicin	Belotecan	Daunorubicin	Doxil	Doxorubicin	Epirubicin	Etoposide
ldarubicin	Irinotecan	Mitoxantrone	Nal-IRI	Pirarubicin	Pixantrone	Teniposide	Topotecan	Valrubicin	Ingenol

Type of monoclonal antibodies

Types of monoclonal antibodies.

dotox-tdfk
ntansine

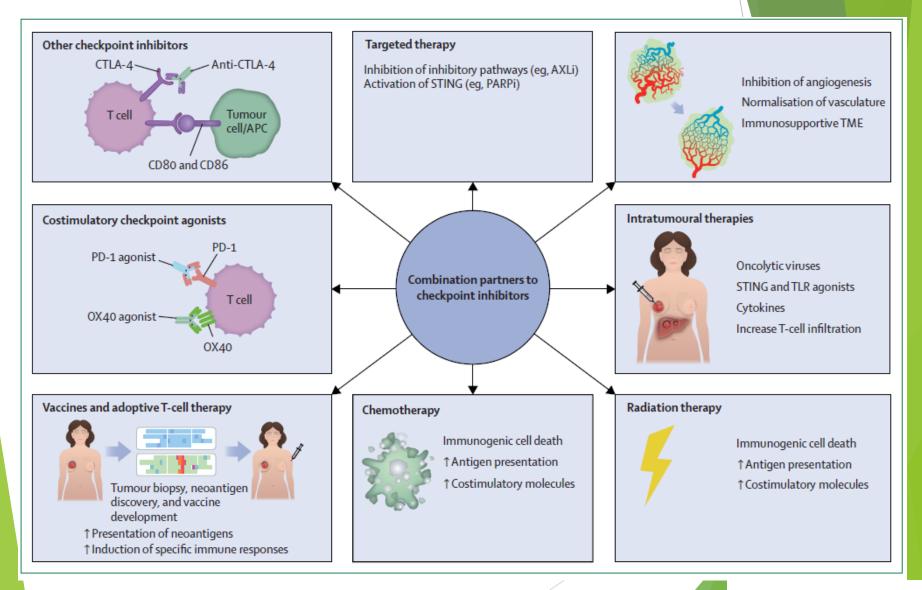
Data from Buss et al⁶ and Garcia Merino.7

Type of Checkpoints inhibitors

ICPI Monoclonal Antibody	Trade Name	Mechanism of Action
Ipilimumab	Yervoy	CTLA-4 inhibitor
Pembrolizumab	Keytruda	PD-1 inhibitor
Nivolumab	Opdivo	PD-1 inhibitor
Atezolizumab	Tecentriq	PD-L1 inhibitor
Avelumab	Bavencio	PD-L1 inhibitor
Durvalumab	Imfinzi	PD-L1 inhibitor
Cemiplimab	Libtayo	PD-1 inhibitor

CTLA-4: Cytotoxic T-lymphocyte antigen 4; ICPI: Immune checkpoint inhibitors; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1.

Combination partners for Immunotherap



Chemotherapy Side Effect

Chemotherapy Side Effect



Intravenous (IV) Chemotherapy



Patient



Fatigue Hair Loss



Kidney **Problems**



Mood Changes



Weight Changes



Increase Risk of Bleeding and Bruising



Infection



Normal



Anemia



Dry Skin



Brain Fog



Nausea



Vomiting



Constipation/ Diarrhea



Difficulty **Swallowing**



Muscle Pain



Loss of Libido



Fertility **Problems**

https://www.123rf.com/photo_115984582_stock-vector-chemotherapyside-effects-icons-depict-the-list-of-reactions-and-issues-of-chemotreatment-on-a-huma.html

Toxicities

Table 1 Different classes of new cancer drugs, frequently used agents, and main toxicities

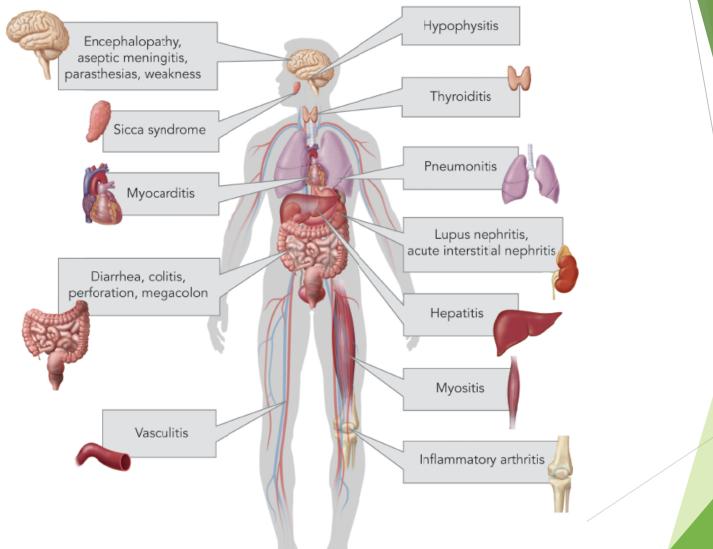
Toxicities
CRS Immunodeficiency
Cardiac disease
Diarrhea Exanthema
Hypertension GI bleeding or perforation Thromboembolism
Pleural/pericardial effusions Pulmonary hypertension
Thromboembolism
Exanthema, diarrhea GI bleeding or perforation
Pneumonitis Colitis, hepatosis
Diarrhea, edema Decrease of LVEF
Hypertension GI bleeding or perforation Thromboembolism PRES

Toxicities

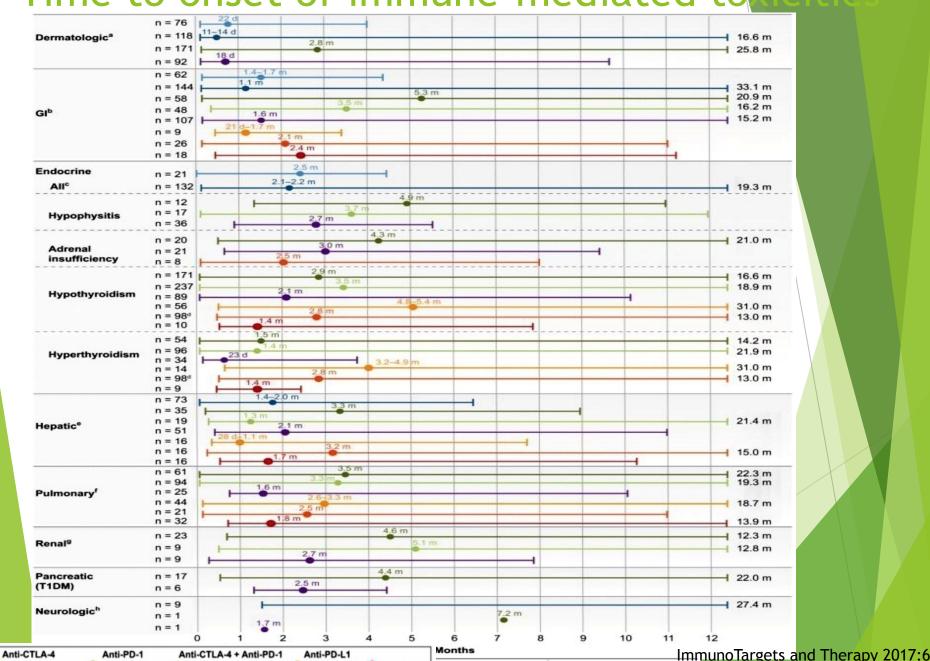
Table 1 Different classes of new cancer drugs, frequently used agents, and main toxicities

Agent	Target	Indications	Toxicities
Sorafenib Sunitinib Pazopanib Bispecific antibodies (BAB)	Multiple kinases	Renal cell cancer GIST Soft tissue sarcoma	Decrease of LVEF Hypertension
Blinatumomab	CD3/CD19	ALL B-cell lymphomas	CRS Neurotoxicity (e.g., convulsions) Liver toxicity (transaminitis)
Checkpoint inhibitors			
Ipilimumab	CTLA-4	Melanoma	IRAEs:
Nivolumab Pembrolizumab	PD-1	Melanoma NSCLC RCC Hodgkin's lymphoma	Diarrhea, colitis Hypophysitis Immunhepatitis Polyarthritis
Cellular treatments			
CAR T cells	CD19	ALL B-cell lymphomas	CRS Neurotoxicity (e.g., convulsions, encephalopathy, or ischemia)

Common Immune-Related Adverse Events



Time to onset of immune-mediated toxicities



Atezolizumah Dunyalumah

Inilimumah 3 ma/ka

Nivolumah

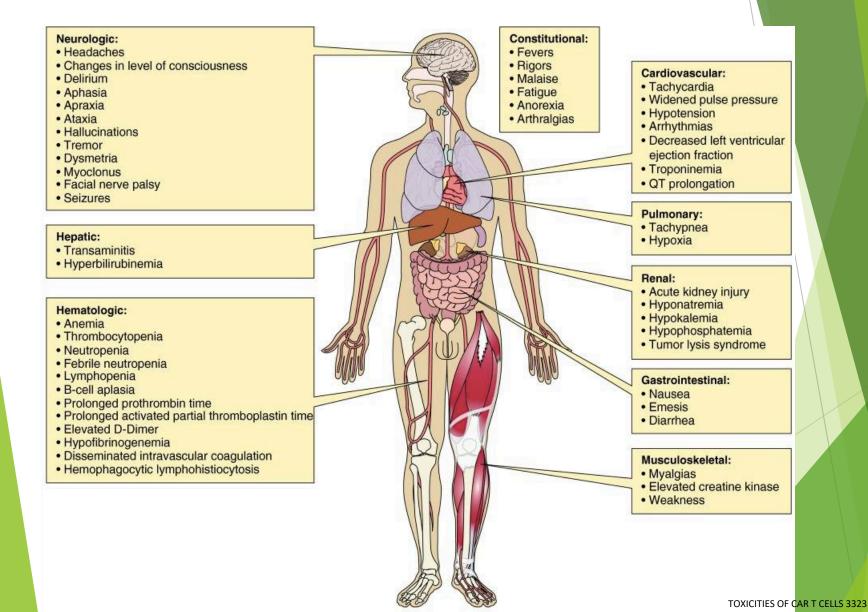
Treatment of immune checkpoint inhibitor-related toxicity

Table 2 Treatment of immune checkpoint inhibitor-related toxicity				
Type of Toxicity	First-Line Therapy ^a	Second-Line Therapy ^a		
Pneumonitis (grade 3–4)	 Methylprednisolone 1–4 mg/kg/ d (slow taper) 	 Infliximab 5 mg/kg MMF 1 g q 12 h IVIg for 5 d Cyclophosphamide 		
Cardiotoxicity- myocarditis (grade 3–4)	 Methylprednisolone 1–2 mg/kg/ d or 1 g/d 	MMFInfliximabAnti-thymocyte globulinTacrolimusIVIg		
Neurotoxicities: (Grade 3–4)				
Guillain- Barre syndrome/ Myasthenia gravis	IVIg (0.4 mg/kg/d) or plasmapheresisPyridostigmine	 Consider Methylprednisolone 1– 4 mg/kg/d^b Azathioprine Cyclosporine MMF 		
Aseptic meningitis/ encephalitis	 Methylprednisolone 1–2 mg/kg/ d 	Methylprednisolone (1 g/d)+ IVIg if no improvementRituximab		
Transverse myelitis	Methylprednisolone 2 mg/kg/ day-1 g/dIVIg	 Plasmapheresis IVIg Toxicities Associate 		

Common side effects of CRA-T therapy

Side Effect	Symptoms	Treatment	Nursing Assessment
Cytokine release syndrome	Fever, myalgia, headache, anorexia, nausea and vomiting, renal dysfunction, coagulopathy, hypotension, capillary leak, and pulmonary edema	Acetaminophen, narcotics, total parenteral nutrition, antiemetics, renal dosing of medications to dialysis, fresh frozen plasma, cryoprecipitate, platelets, vasoactives, tocilizumab, methylprednisone, oxygen support, and intubation	Take vital signs every four hours. Do daily lab tests or electrolytes, hepatic function, coagulation factors, C-reactive protein, lactate dehydrogenase, and ferritin.
Graft- versus-host disease	Rash, diarrhea, and hyperbilirubinemia	Topical triamcinolone and possible systemic treatments with calcineurin inhibitors or steroids (only in discussion with CAR T-cell therapy team)	Skin assessment and output assessment
Neurologic symptoms	Confusion, B-cell aphasia, unresponsiveness, and seizures	Supportive care (e.g., reorientation, antiepileptics)	Neurologic examinations
Tumor lysis syndrome	Hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia	Allopurinol and hydration	Daily electrolytes

CAR-T Related CRS toxicities



- ▶ 清楚各類治療的副作用及處置
- ▶治療期間密切觀察
- ▶ 衛教病人及家屬相關知識或提供衛教手冊
- ▶定期追蹤、管理

Infusion- Related Reactions

Signs, symptoms and management of infusion-related reactions.³

Signs and symptoms	Management
 Chills or shaking Urticaria Flushing Dyspnea or wheezing Hypotension Pyrexia Back pain Abdominal pain 	Avelumab can cause Grade 3* or Grade 4 infusion-related reactions. Patients should be premedicated with an antihistamine [†] and acetaminophen before the first four infusions and for subsequent doses based upon clinical judgment and presence/severity of prior infusion-related reactions. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue avelumab for Grade 3 or Grade 4 infusion-related reactions.

Data from Bavencio® prescribing information, EMD Serono, 2017.³

^{*} Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = lifethreatening.

[†] Diphenhydramine, cetirizine, loratadine, fexofenadine; choice of agent as clinically appropriate and per institution guidelines/formulary.

Cytokine-release syndrome

Table 2 Main symptoms of cytokine-release syndrome

Constitutional

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Fever, 發燒,發冷,頭痛,虛弱,肌痛,關節痛,後背痛 back or abdor 或腹痛
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Organ related

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Oligu 少尿、支氣管痙攣、呼吸困難、低血壓、心動過速, cardia, 心律不整、精神錯亂、紅斑、蕁麻疹、瘙癢 ruritus
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Lab tests

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Hypo K↓, BUN↑, 腎小球濾過率↓, 血球及凝血功能異 altere 常, CRP/PCT↑ n of C-reactive protein and/or procalcitonin
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Signs and symptoms of imAEs

Signs, symptoms and management of immune-mediated adverse events.³

imAEs	Signs and symptoms	Management
Pneumonitis	New or worsening coughShortness of breathChest pain	Monitor patients for signs and symptoms of pneumonitis and evaluate suspected cases with radiographic imaging. Administer corticosteroids for ≥ Grade 2* pneumonitis. Withhold ICI for Grade 2 and permanently discontinue for Grade 3, Grade 4, or recurrent Grade 2 pneumonitis.
Hepatitis	 Yellowing of skin or whites of eyes Dark urine Severe nausea or vomiting Pain at the right side of abdomen Drowsiness 	Monitor patients for abnormal liver tests before and periodically during treatment. Rule out other infectious etiology, administer corticosteroids for ≥ Grade 2 hepatitis. Withhold ICI for Grade 2 immune-mediated hepatitis until resolution and permanently discontinue for Grades 3 or 4 immune-mediated hepatitis.
Colitis	 Diarrhea or more bowel movements than normal Blood in stool or dark, tarry, sticky stool Severe abdominal pain or tenderness 	Monitor patients for signs and symptoms of colitis. Administer corticosteroids for ≥ Grade 2 colitis. Withhold ICI until resolution for Grade 2 or 3 colitis and permanently discontinue for Grade 4 or recurrent Grade 3 colitis upon re-initiation.
Endocrinopathies Hypophysitis	Rapid heartbeatIncreased sweating	Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency), thyroid function (before and after
Adrenal insufficiency	Worsening or severe fatigue	treatment, and periodically during treatment), and hyperglycemia.
Thyroid disorder	 Feeling more hungry or thirsty than usual 	Administer corticosteroids and hormone replacement as appropriate. Withhold
Diabetes mellitus	Hair loss	ICI for Grade 3 or Grade 4 adrenal insufficiency or thyroid dysfunction.
	 Mood or behavioral changes 	Manage hypothyroidism with hormone replacement therapy. Manage
	Feeling cold	hyperthyroidism with medical management as indicated. Anticipate patients
	Constipation	who initially present with hyperthyroidism will become hypothyroid. Withhold
	Voice gets deeper	ICI for Grade 3 or Grade 4 thyroid disorders.
	Hypotension Hypotension	Monitor patients for hyperglycemia or other signs and symptoms of diabetes.
	 Urinating more than usual Dizziness or fainting	Withhold ICI and administer anti-hyperglycemics or insulin in patients with
	Abdominal pain	Erade 3 hyperglycemia and resume treatment when metabolic control is achieved.
	Headache	achieved.
Nephritis and renal dysfunction	Urinating less than usual	Monitor for elevated serum creatinine before and periodically during treatment.
repinitis and renar dystalledon	Blood in urine	Administer corticosteroids for \geq Grade 2 nephritis. Withhold ICI for Grade 2 or
	Swelling of ankles	Grade 3 nephritis until resolution to Grade 1 or lower. Permanently discontinue
	Loss of appetite	for Grade 4 nephritis.

Supportive care guidelines for patients receiving CAR T cells

Toxicity	Preventive and supportive care interventions
Constitutional	Administer acetaminophen for symptomatic management of fevers in patients with normal hepatic function;
	Provide cooling blankets for fevers >40°C;
	Avoid corticosteroids and NSAIDs; and
	Avoid meperidine
Cardiovascular	Stop or taper antihypertensive medications prior to cell infusion;
	Monitor vital signs at least every 4 h on an inpatient unit for at least 9 d following infusion;
	Monitor vital signs every 2 h in patients with fevers and tachycardia;
	Initiate replacement IV fluids for patients with poor oral intake or high insensible losses to maintain net even fluid balance;
	Administer IV fluid boluses for patients with SBP less than their preinfusion baseline:
	Patients with a SBP <80% of their preinfusion baseline and <100 mm Hg receive a 1 liter normal saline bolus
	Patients with a SBP <85 mm Hg receive a 1 liter normal saline bolus regardless of baseline blood pressure
	Patients receiving >1 IV fluid bolus for hypotension or patients in the ICU for toxicity management have a serum troponin drawn, and an ECG and an echocardiogram performed to evaluate for cardiac toxicity; and
	Patients with hypotension are initiated on vasopressor support. Norepinephrine is the preferred first-line vasopressor
Infectious disease	Initiate prophylactic antimicrobials, such as trimethoprim-sulfamethoxazole, for <i>Pneumocystis</i> prophylaxis prior to conditioning chemotherapy;
	Initiate prophylactic antimicrobials, such as acyclovir or valacyclovir, for herpes virus prophylaxis prior to conditioning chemotherapy; and
	All patients with fevers and neutropenia have blood cultures drawn and broad-spectrum antibiotic coverage initiated
Hematologic	Initiate allopurinol for TLS prophylaxis in patients without a contraindication prior to conditioning chemotherapy;
	Transfuse packed red cells for goal hemoglobin of ≥8.0 g/dL;
	Transfuse platelets for a goal platelet count of ≥20 000/μL;
	Monitor complete blood count with differential twice daily. When ANC decreases to $<500/\mu L$, initiate filgrastim support. Continue until ANC increases to $\ge1500~\mu L$;
	Transfuse fresh frozen plasma with a goal of normalization of PTT in patients with a PTT >1.5-fold above the upper limit of normal; and
	Transfuse cryoprecipitate to maintain fibrinogen of ≥100 mg/dL. If patient is bleeding, a higher level of fibrinogen should be maintained
Neurologic	The nursing staff conducts focused neurologic examinations every 8 h in patients experiencing neurologic toxicity;
	Perform brain MRI in any patient experiencing neurologic toxicity;
	Perform lumbar puncture to evaluate for infectious pathogens, cytokine levels, and CAR T-cell levels in patients experiencing neurologic toxicity whenever feasible;
	Request a neurology consultation for any patient experiencing neurologic toxicity; and
	Standard antiepileptic medications are used for patients having active seizures. We do not use prophylactic antiepileptic medications

- Gastrointestinal Side Effects
 - diarrhea, colitis
 - ✓ lipilimumab: 32.8%
 - watery bowel movements, blood or mucus in stool, flatulence, and abdominal cramping
 - ✓ 清淡飲食;避免高纖維/乳糖、脂肪、咖啡因、酒精
 - ✓ Grade 4-> NPO
 - ✓ 止瀉劑使用
 - ✓ IVF
 - autoimmune hepatitis
 - ✓ rare
 - ✓ ALT,AST,Bil ↑, fatigue and low-grade fevers

- Pulmonary Side Effects
 - 非感染性的間質性或肺泡性炎症反應
 - ✓ PD-1 : 9%
 - ✓ dyspnea, cough, fatigue, hypoxia, chest pain, hemoptysis
 - CxR: diffuse infiltrates, lobular nodularity with air trapping, interstitial fibrosis
 - ✓ Microscopic findings: diffuse lymphocytic infiltrates(PD-1)
 - ✓ 衛教病人及家屬相關症狀(shortness of breath, coughing, chest pain, fever)
 - ✓ 氧氣給予、SpO2,、聽診呼吸音、確保充足的水分、減少呼<mark>吸道刺激</mark> 鼓勵戒菸

Dermatological Side Effects

- Pruritus ,maculopapular rash, vitiligo, Stevens-Johnson syndrome, Sweet's syndrome, toxic epidermal necrolysis, bullous pemphigoid, lichen sclerosus
- Rash ,pruritus
 - ✓ ipilimumab: 50%
 - ✓ Nivolumab, pembrolizumab : 28%-37%

Endocrine-related Side Effects

- hypophysitis(pituitary gland inflammation), thyroiditis, hypothyroidism, adrenal insufficiency
 - ✓ combination: 11%-17%
 - ✓ PD-1 monotherapy : <1%
- hypophysitis: headaches, dizziness, diplopia, loss of peripheral vision, extreme fatigue, irritability, cold intolerance, nausea, vomiting
- 監測生命徵象、心電圖、充足的水分和支持性護理

Screening and Monitor of Endocrine Toxicity

Before Immunotherapy

- Fasting venous glycemia (if anti-PD-1/PD-L1), natremia
- TSH, T4I
- 8 am cortisol (without corticosteroid intake) +/- ACTH (depending on 08:00 am cortisol level)
- LH, FSH, testosterone in males; LH, FSH, estradiol in females with irregular periods; FSH in menopausal females (gonadotropic axis activity in non-menopausal females without contraception is determined by cycle regularity)

Immunotherapy onset

Systematic biological evaluation during immunotherapy

At each course of treatment for 6 months, every 2 courses for the following 6 months, then in case of clinical alert signs

- Fasting venous glycemia (if anti-PD-1/PD-L1), natremia
- TSH, T4I
- 8 am cortisol
- Testosterone in males

- Cardiac Toxicities
 - ✓ 少見(<1%)
 - ✓ 平均發生時間: 10wk (2days~8m+)
 - ✓ mortality rate : 50%
 - ✓ 使用其他藥物也會增加心毒性風險 (ex TKI)
 - ✓ 臨床症狀:

myocarditis, pericarditis, heart failure, arrhythmias.

- ✓ The most common arrhythmias include atrial fibrillation (30%), ventricular tachycardia/fibrillation (27%), and conduction abnormalities such as heart block (17%)
- ✓ 觀察生命徵象、心電圖、戒菸

Late effects of radiotherapy and chemotherapy

Organ system	Late effects/sequelae of radiotherapy	Late effects/sequelae of chemotherapy	Chemotherapeutic drugs responsible
Bone and soft tissues	Short stature; atrophy, fibrosis, osteonecrosis	Avascular necrosis	Steroids
Cardiovascular	Pericardial effusion; pericarditis; CAD	Cardiomyopathy; CHF	Anthracylines Cyclophosphamide
Pulmonary	Pulmonary fibrosis; decreased lung volumes	Pulmonary fibrosis; interstitial pneumonitis	Bleomycin, BCNU Methotrexate, adriamycin
Central nervous system (CNS)	Neuropsychologic deficits, structural changes, hemorrhage	Neuropsychologic deficits, structural changes Hemiplegia; seizure	Methotrexate
Peripheral nervous system		Peripheral neuropathy; hearing loss	Cisplatin, vinca alkaloids
Hematologic	Cytopenia, myelodysplasia	Myelodyplastic syndromes	Alkylating agents
Renal	Decreased creatinine clearance	Decreased creatinine clearance	Cisplatin Methotrexate
	Hypertension	Increased creatinine Renal filtration Delayed renal filtration	Nitrosoureas
Genitourinary	Bladder fibrosis, contractures	Bladder fibrosis; hemorrhagic cystitis	Cyclophosphamide
Gastrointestinal	Malabsorption; stricture; abnormal LFT	Abnormal LFT; hepatic fibrosis; cirrhosis	Methotrexate, BCNU
Pituitary	Growth hormone deficiency; pituitary deficiency		
Thyroid	Hypothyroidism; nodules		
Gonadal	Men: risk of sterility, Leydig cell dysfunction.	Men: sterility	Alkylating agents
	Women: ovarian failure, early menopause	Women: sterility, premature menopause	Procarbazine
Dental/oral health	Poor enamel and root formation; dry mouth		
Opthalmologic	Cataracts; retinopathy	Cataracts	Steroids

CAD, coronary artery disease; CCF, congestive cardiac failure; LFT, liver function tests; BCNU, carmustine.

Source: Data from Ganz (1998, 2001)12,13 and Aziz (2002, 2003).2,6

Long-term side effects

Emotional difficulties

癌症倖存者經常經歷積極和消極、害怕復發、憤怒、 內心沮喪、焦慮和孤立的情緒。 倖存者、照料者、家人和 朋友也可能會經歷創傷後症候群,可能會發展為焦慮症。

- ✓ 轉介心理師或身心科門診
- Secondary or subsequent cancers

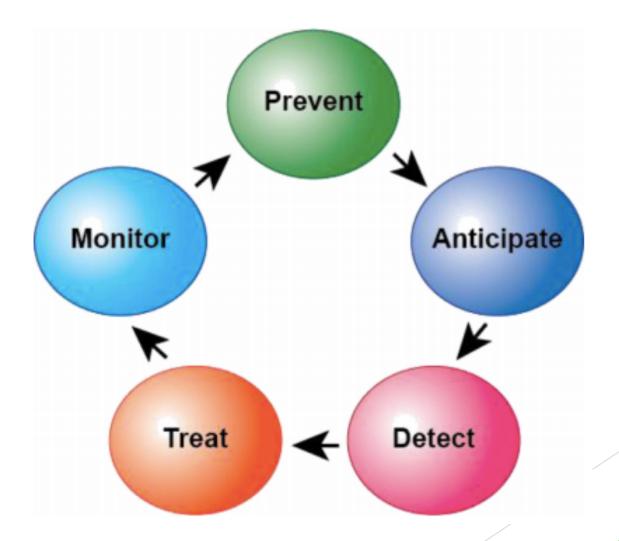
化學治療或放射線治療,抽菸、喝酒、肥胖也是一個 危險因子

- Stopping tobacco use
- Reducing alcohol intake
- Eating well

選擇吃營養,健康的飲食可以幫助癌症倖存者治療後恢復體力。

- Exercising regularly
 - ✓ 每周至少進行150分鐘的有氧運動,例如散步和阻力(力量)訓練,每週兩到三天。
 - ✓ 提高生活品質,減少焦慮、憂鬱、疲憊

Five Pillars of Immunotherapy Toxicity Management



Summary

- ▶ 護理師是照護患者的最前線,必須了解各種不同的治療方法及副作用
- 做好衛教患者及家屬
- ▶ 預防及減少患者的症狀
- ▶ 提高病人存活率及生活品質