ΠΑΡΕΝΕΡΓΕΙΕΣ ΑΝΤΙΝΕΟΠΛΑΣΜΑΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ

Αριστοτέλης Μπάμιας
Καθηγητής Θεραπευτικής-Παθολογίας-Ογκολογίας ΕΚΠΑ
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ΘΕΡΑΠΕΙΑ ΚΑΚΟΗΘΩΝ ΝΕΟΠΛΑΣΜΑΤΩΝ

Τοπικοπεριοχική

- Χειρουργική
- Ακτινοθεραπεία

Συστηματική

- Χημειοθεραπεία
- Ορμονοθεραπεία
- Στοχευμένη θεραπεία
- Ανοσοθεραπεία
- Συμπτωματική αγωγή

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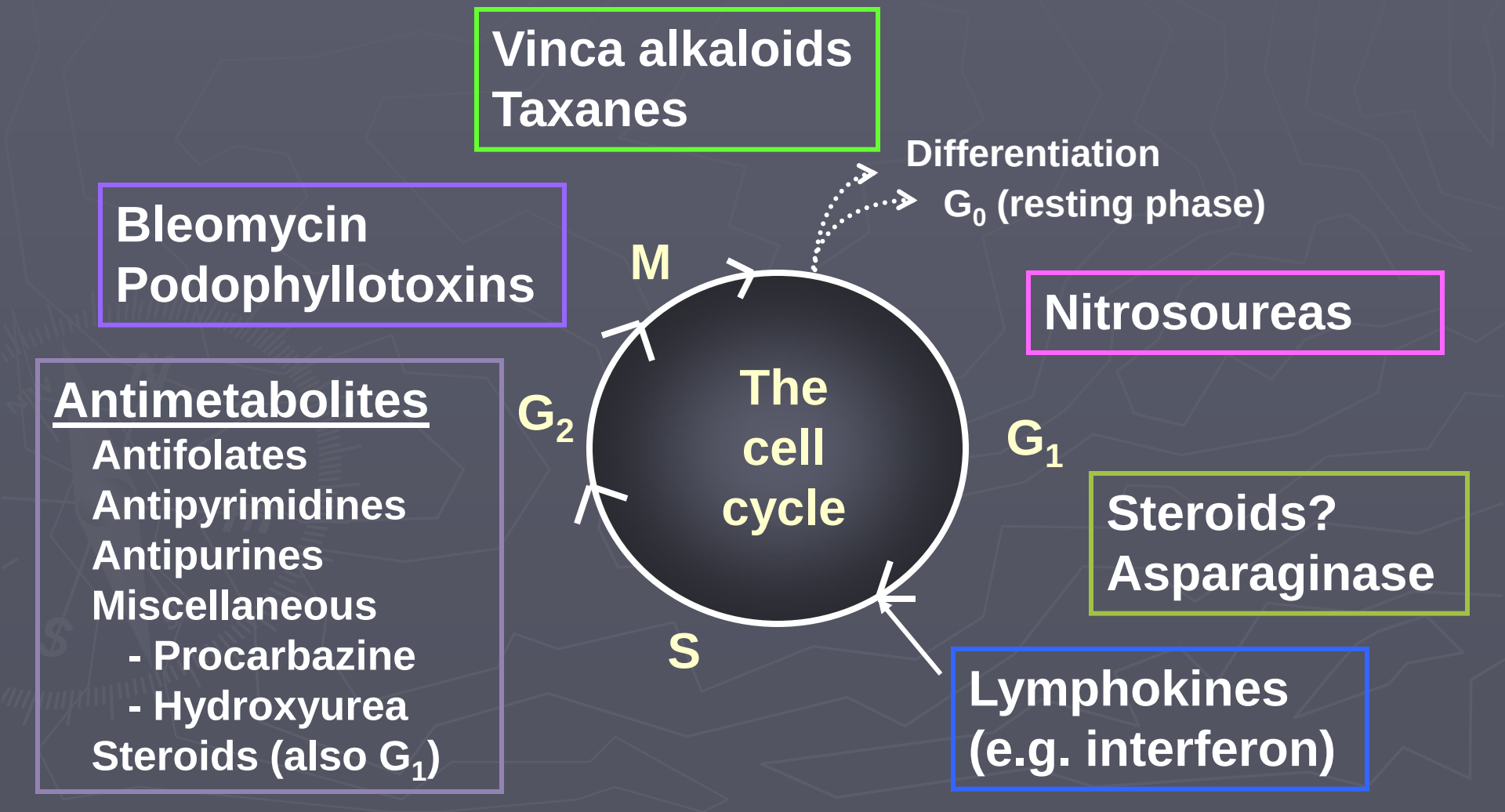
Κυτταροτοξικά αντινεοπλασματικά φάρμακα



Αρχές χορήγησης χημειοθεραπείας

- Ο συνδυασμός φαρμάκων πρέπει να έχει τη μεγαλύτερη δυνατή αποτελεσματικότητα με κλινικά παραδεκτή τοξικότητα
- Η θεραπεία θα πρέπει να επαναλαμβάνεται μετά την αποδρομή των τοξικών φαινομένων
  1-3 εβδομάδες
- Το μεσοδιάστημα των θεραπειών πρέπει να είναι μικρότερο από το χρόνο διπλασιασμού των κυττάρων του όγκου

Οξείες παρενέργειες κυτταροτοξικών φαρμάκων

- Αλωπεκία
- Ναυτία-έμετος
- Μυελοτοξικότητα
  Ναδιρ λευκών: 7-14 ημέρες
- Γαστρεντερική τοξικότητα
- Νευροτοξικότητα
- Δερματική τοξικότητα
- Σπανιες τοξικότητες
  - Αιμορραγική κυστίτις (κυκλοφωσφαμίδη, ιφωσφαμίδη)
  - Πνευμονική ίνωση (μπλεομυκίνη, χλωραμβουκίλη)
  - Αιμολυτικο-ουραιμικό σύνδρομο (μιτομυκίνη)
  - Καρδιοτοξικότητα (ανθρακυκλίνες)

Ουδετεροπενικό εμπύρετο

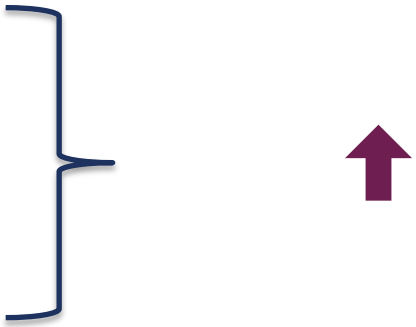
- Ορισμός
  - Ουδετεροπενία < 500 ουδετεροφιλα
  - Πυρετός 38.3 η 38 που διαρκεί τουλάχιστον 1 ώρα
- Διαλογή ασθενών για εξωνοσοκομειακή αντιμετώπιση
- Θεραπεία
  - Ενδονοσοκομειακή
    - iv αντι-ψευδομοναδική αγωγή
  - Εξωνοσοκομειακή
    - po φθοριοκινολόνη+αμοξυκιλλίνη/κλαβουλανικό

COMBO VS. MONO

Loehlrer et al. 1992

M-VAC vs. CDDP

- leukopenia
- mucositis
- neutropenic fever
- drug-related mortality



...VS GC

Toxicity	World Health Organization Toxicity Grades			
	GC (% of patients)		MVAC (% of patients)	
	3	4	3	4
Hematologic				
[illegible]mia	23.5	3.5	15.5	2.1
[illegible]	28.5	28.5	7.7	
[illegible]	[illegible]	29.9		[illegible].2
[illegible]				
Mucositis			[illegible].7	4.2
Nausea/vomiting				
Alopecia	10.5			
[illegible]	2.0	0.5	[illegible].7	
[illegible]iarrhea	3.0	0	7.8	[illegible].5
Pulmonary	2.5	0.5	2.6	3.1
Hematuria	4.5	0	2.3	0
Constipation	1.5	0	2.6	0.5
Hemorrhage	2.0	0	2.1	0
State of consciousness	0.5	0	3.1	0.5
Fever	0	0	3.1	0

Negative superiority trial!

GC became a standard due to favorable toxicity profile

Both reg[illegible] nt visits!

von der Maase H, et al. *J Clin Oncol* 2000; 18: 3068–3077

....VS DD MVAC

Hematologic Toxicity	MVAC (n = 129) No. of Patients	%	HD-MVAC (n = 134) No. of Patients	%	P(trend)
WBC	2	2	4	3	
0	8	6	46	34	
1	11	8	29	21	< .001
2	28	22	28	21	
3	59	46	16	12	
4	21	16	11	8	
Platelets	2	2	4	3	
0	80	62	48	43	.02
1	10	8	22		
2	15	12			
3	14				
4				11	
Mucositis			10	8	.034
0		24	43	323	
	43	33	44	33	
	26	20	24	18	
	18	14	12	9	
4	4	3	1	1	
Creatinine	2	2	5	4	.815
0	113	88	118	88	
1	7	5	4	3	
2	3	2	2	2	
3	4	3	5	4	
Nausea and/ or vomiting	4	3	7	5	.025
0	9	7	3	2	
1	27	21	20	15	
2	52	40	55	41	
3	32	25	42	31	
4	5	4	7	5	

Less frequent visits!

Sternberg CN, et al. *J Clin Oncol* 2001; 19: 2638–2646.

	DD-MVAC ($n = 61$)			DD-GC ($n = 59$)	
Toxicity	3 *n* (%)	4 *n* (%)	5 *n* (%)	3 *n* (%)	4 *n* (%)
Anemia	7 (11)	0		5 (8)	1 (2)
Neutropenia	7 (11)	5 (8)		5 (8)	3 (5)
Thrombocytopenia	2 (3)	3 (5)		5 (8)	0
Renal	2 (3)	0		1 (2)	0
Nausea	1 (2)	0		2 (3)	0
Vomiting	1 (2)	0		1 (2)	0
Neuropathy	0	0		1 (2)	0
Stomatitis	1 (2)	0		0	0
Hearing	0	0		1 (2)	0
Fatigue	5 (8)	0		3 (5)	0
Vascular	0	0		1 (2)	0
Febrile neutropenia	2 (3)	1 (2)		0	0
Infection [normal absolute neutrophil count (ANC)]	3 (5)	0	2 (3)	3 (5)	0

NO ALOPECIA

DOSE DENSE REGIMES

……. VS CARBOPLATIN

	M-VAC (*n* = 43)					CP arm (*n* = 41)					
Toxicity grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	***P* value**
Neutropenia	0	4	8	31	0	5	3	9	12	0	< 0.0001
Neutropenic fever	0	0	6	0	1	0	0	5	0	0	0.57
Thrombocytopenia	16	8	8	1	0	11	3	4	0	0	0.20
Sensory neuropathy	3	4	1	0	0	14	8	6	0	0	0.055
Stomatitis	3	13	4	0	0	4	2	0	0	0	0.12
Creatinine	19	4	0	0	0	8	2	0	0	0	1.00

VASCULAR THROMBOEMBOLIC EVENTS

VTE AND CANCER

Venous thromboembolism (VTE) is a frequent complication of cancer or its treatment

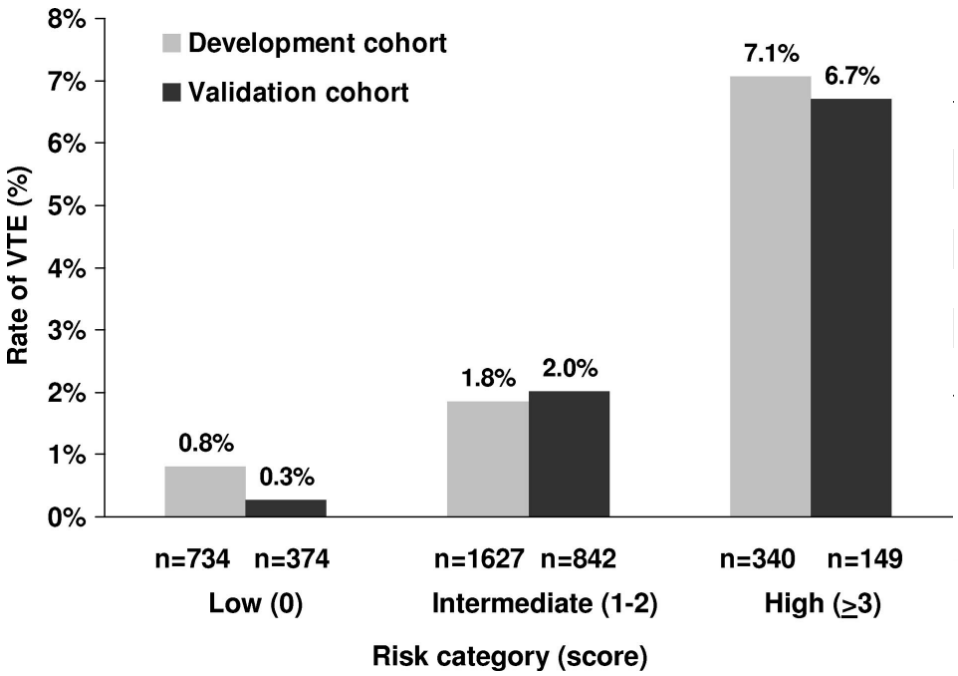
Compared to the general population, cancer patients are at a 4 to 7-fold increased risk of developing a VTE[1]

The development of VTE deteriorates both quality of life and life expectancy[2].

1. Timp JF, et al. *Blood* 2013;122:1712-1723 2. Hettiarachchi RJ, et al. Cancer 1998;83:180–5.

CANCER-ASSOCIATED THROMBOSIS (CAT) RISK-ASSESSMENT MODELS (RAMS)

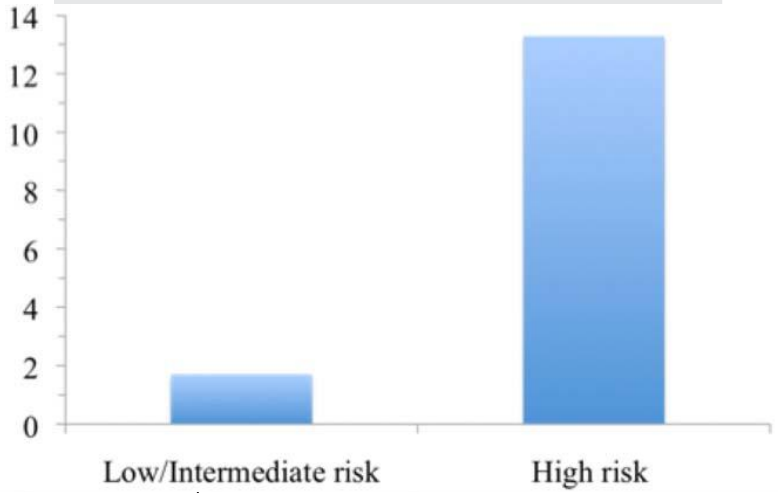
Khorana[1]



COMPASS[2]

Predictors for VTE	Score[a]
Cancer-related risk factors	
acute medical illness	
Personal history of VTE	1
Biomarkers	
Platelets count $\geq 350 \times 10^9$/L	2

[a]Low/Intermediate risk: 0–6; high risk: ≥7.



1. Khorana S et al. Blood. 2008;111:4902-4907
2. Gerotziafas G et al. The Oncologist 2017;22:1222–1231

Απώτερη τοξικότητα

- Φαινόμενα Raynaud
- Πνευμονική ίνωση
  - Αποφυγή καπνίσματος
- Υπογονιμότητα
  - Αποταμίευση σπέρματος
- Καρδιαγγειακά συμβάματα
  - Μεταβολικό σύνδρομο
  - Υπέρταση
  - Στεφανιαία νόσος
- Δεύτεροι καρκίνοι
- Ψυχολογικές διαταραχές

ΘΕΡΑΠΕΙΑ ΚΑΚΟΗΘΩΝ ΝΕΟΠΛΑΣΜΑΤΩΝ

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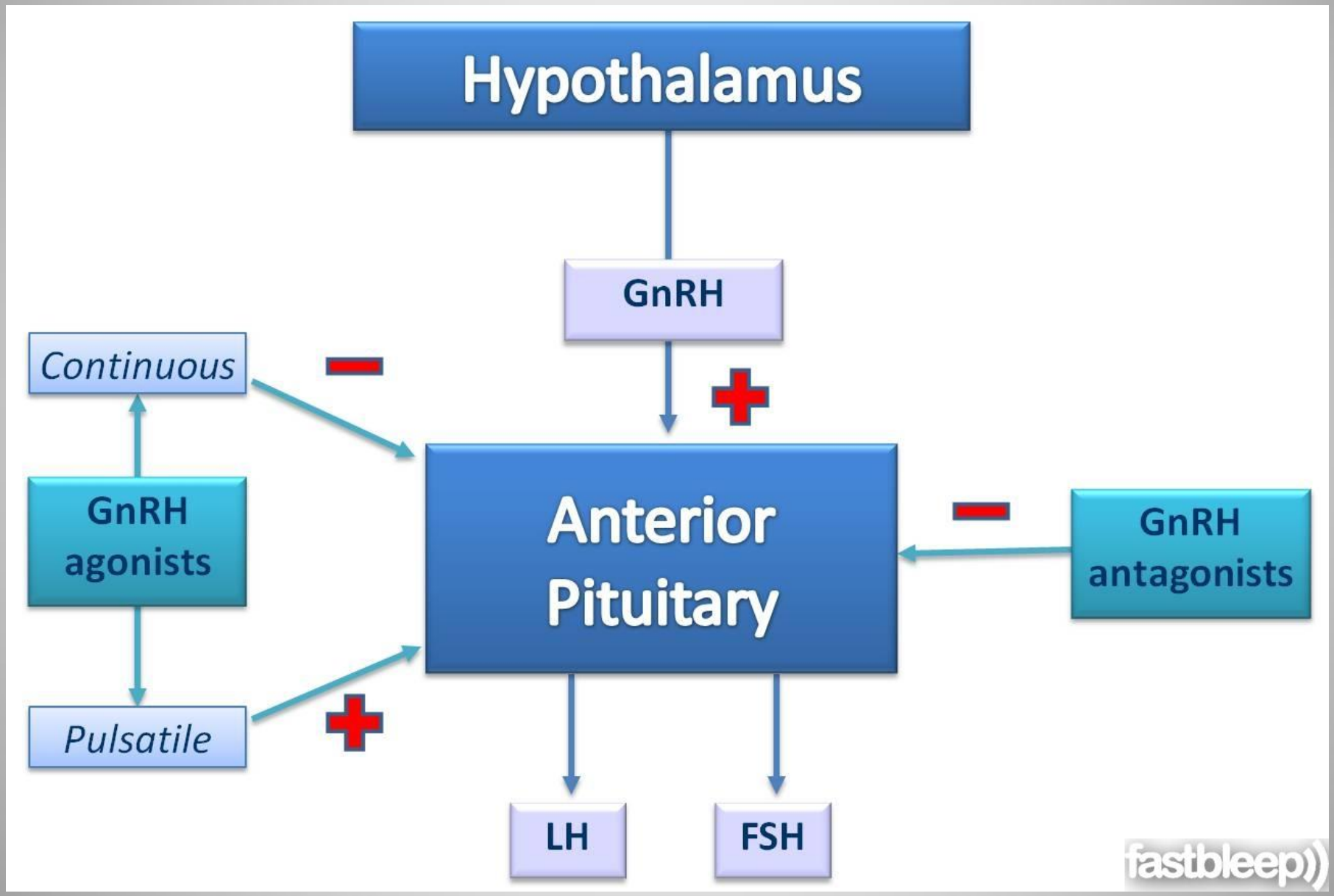
Φαρμακευτικός ευνουχισμός



Παρενέργειες ανδρογονικού αποκλεισμού

- Στυτική δυσλειτουργία
- Απώλεια libido
- Εξάψεις
- Γυναικομαστία
  - Κυρίως με αντιανδρογόνα
- Οστεοπόρωση
- Αναιμία
- Κόπωση
- Έκπτωση νοητικών λειτουργιών
- Ψυχιατρικές διαταραχές

ΘΕΡΑΠΕΙΑ ΚΑΚΟΗΘΩΝ ΝΕΟΠΛΑΣΜΑΤΩΝ

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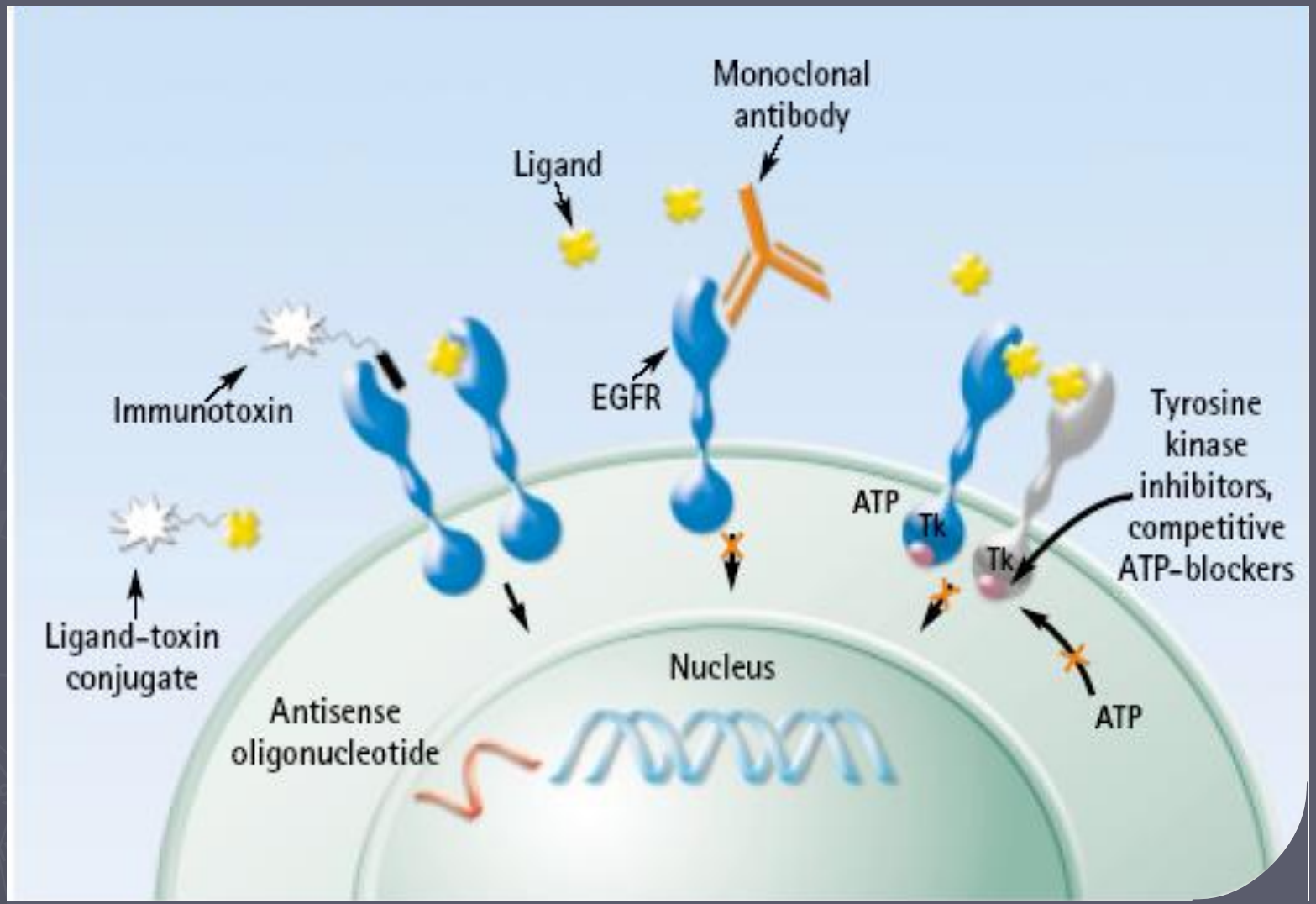
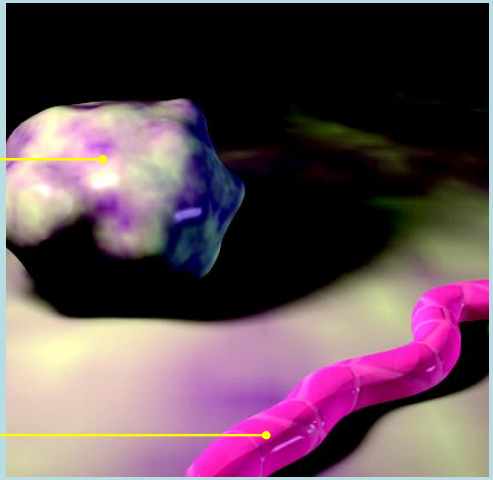
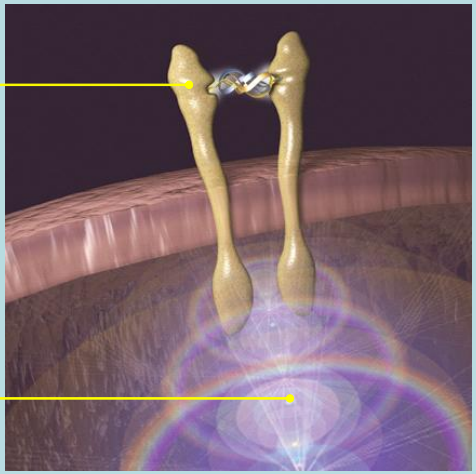
TKI-targeting approaches



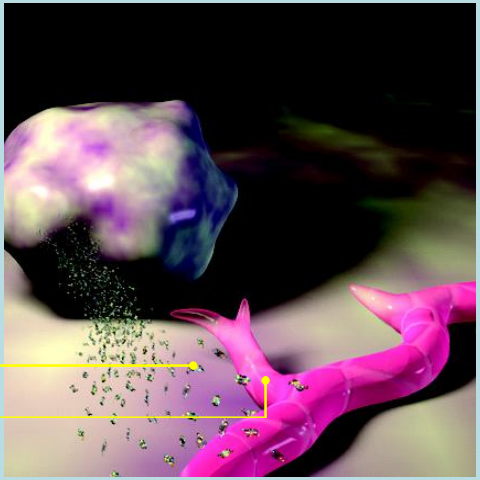
MALIGNANT TUMORS NEED A BLOOD SUPPLY TO GROW



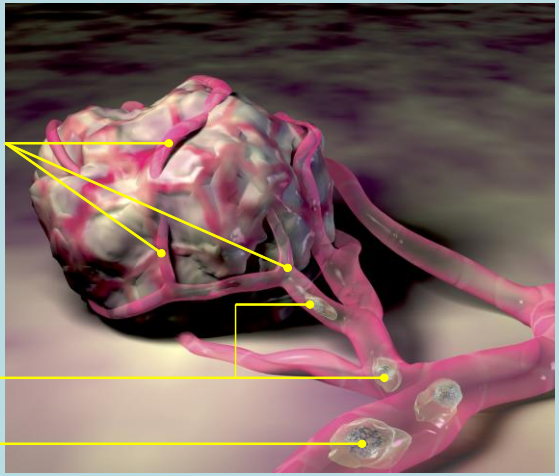
VEGF TRIGGERS MULTIPLE DOWNSTREAM SIGNALS THAT PROMOTE ANGIOGENESIS



THE ANGIOGENIC SWITCH TRIGGERS GROWTH OF NEW VESSELS



ANGIOGENESIS AND VASCULARIZATION SUPPORT TUMOR GROWTH AND METASTASIS



AXIS: Grade ≥3 AEs and Laboratory Abnormalities

AE, %	Axitinib (n = 359)	Sorafenib (n = 355)
Hypertension	16	11
Diarrhea	11	7
Fatigue	11	5
Hand-foot syndrome	5	16
Decreased appetite	5	4
Asthenia	5	3
Rash	<1	4
Laboratory Abnormality, %		
Lipase elevation	5	15
Lymphopenia	3	4
Hypophosphatemia	2	16

Rini BI, et al. *Lancet*. 2011;378(9807):1931-1939.

RECORD-1: Grade 3/4 AEs and Laboratory Abnormalities[1]

AE, %	Everolimus + BSC (n = 274)	
	Grade 3	Grade 4
Infection	7	3
Dyspnea	6	1
Fatigue	5	0
Stomatitis	4	<1
Asthenia	3	<1
Pneumonitis	4	0
Laboratory Abnormality, %		
Lymphocytes decreased	16	2
Glucose increased	15	<1
Hemoglobin decreased	12	1
Phosphate decreased	6	0

No difference in toxicity when given after 1 or 2 previous VEGFr-TKIs[2]

AE, adverse event

1. Motzer RJ, et al. *Cancer.* 2010;116:4256-4265; 2. Calvo E, et al. *Eur J Cancer*. 2012;48:333-339.

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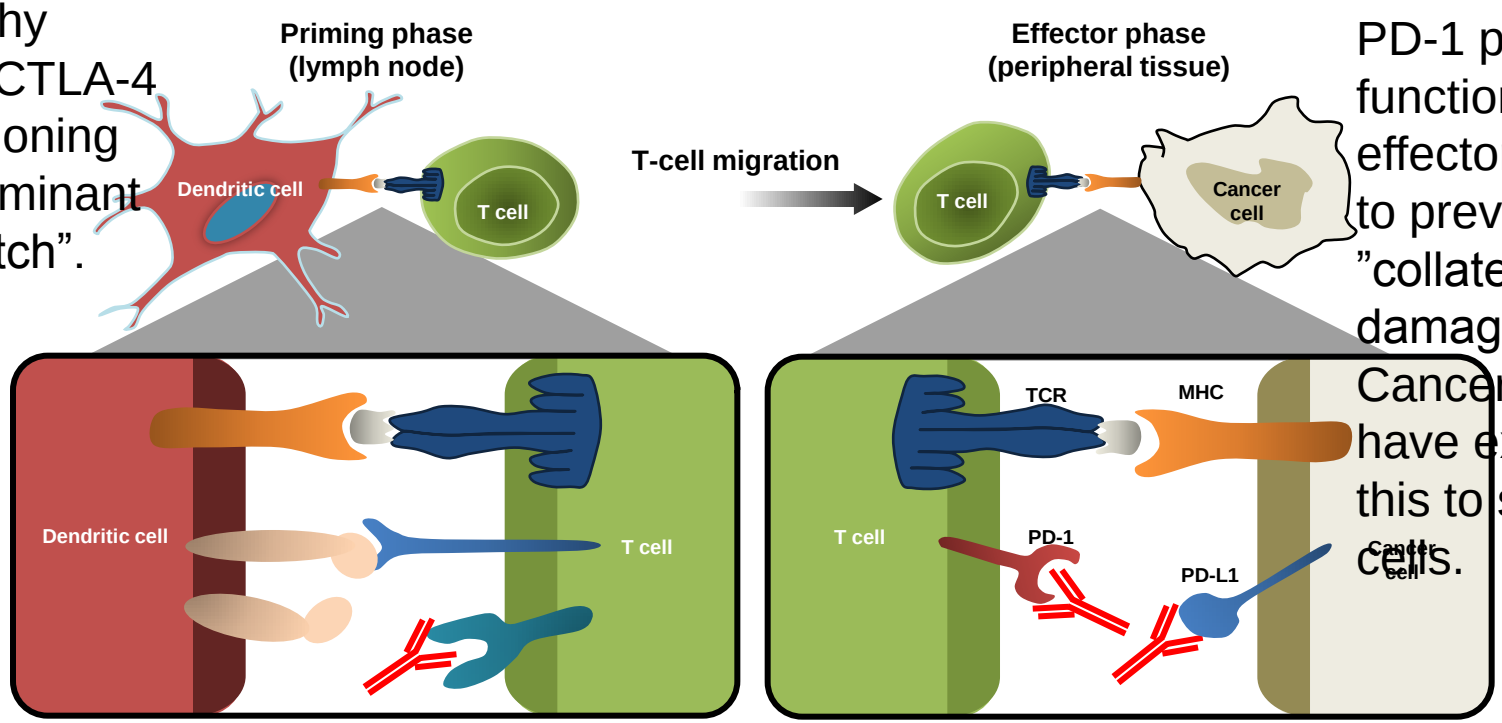
CTLA-4 and PD-1/L1 Checkpoint Blockade

In healthy tissue, CTLA-4 is functioning as a dominant ”off-switch”.



PD-1 pathway functions in the effector phase, to prevent ”collateral damage.” Cancer cells have exploited this to shut off T cells.

Ribas A. *N Engl J Med.* 2012;366(26):2517-2519.

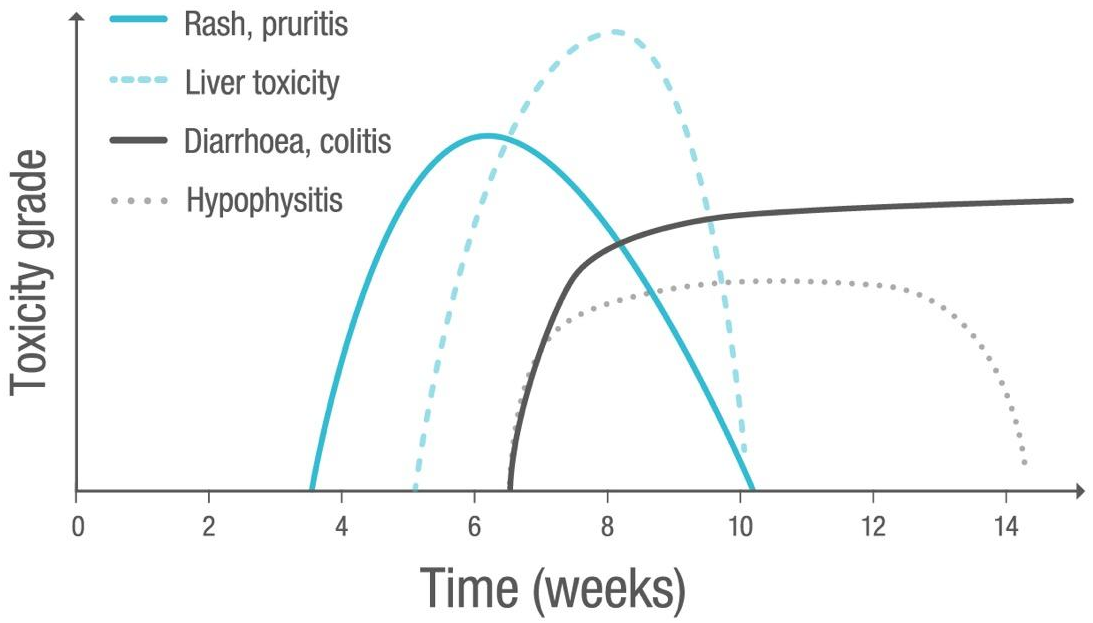
Τοξικότητες (αυτο) ανοσολογικής αρχής

- Δερματικές
- Διαρροια/Κολίτιδα
- Ενδοκρινοπάθειες
  - Υποφυσίτιδα
  - Θυρεοειδοπάθειες
  - Επινεφριδιακή ανεπάρκεια
- Ηπατοτοξικότητα
- Πνευμονίτιδα

CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Time to onset and resolution of occurrence of immuno-related adverse events following Ipilimumab treatment



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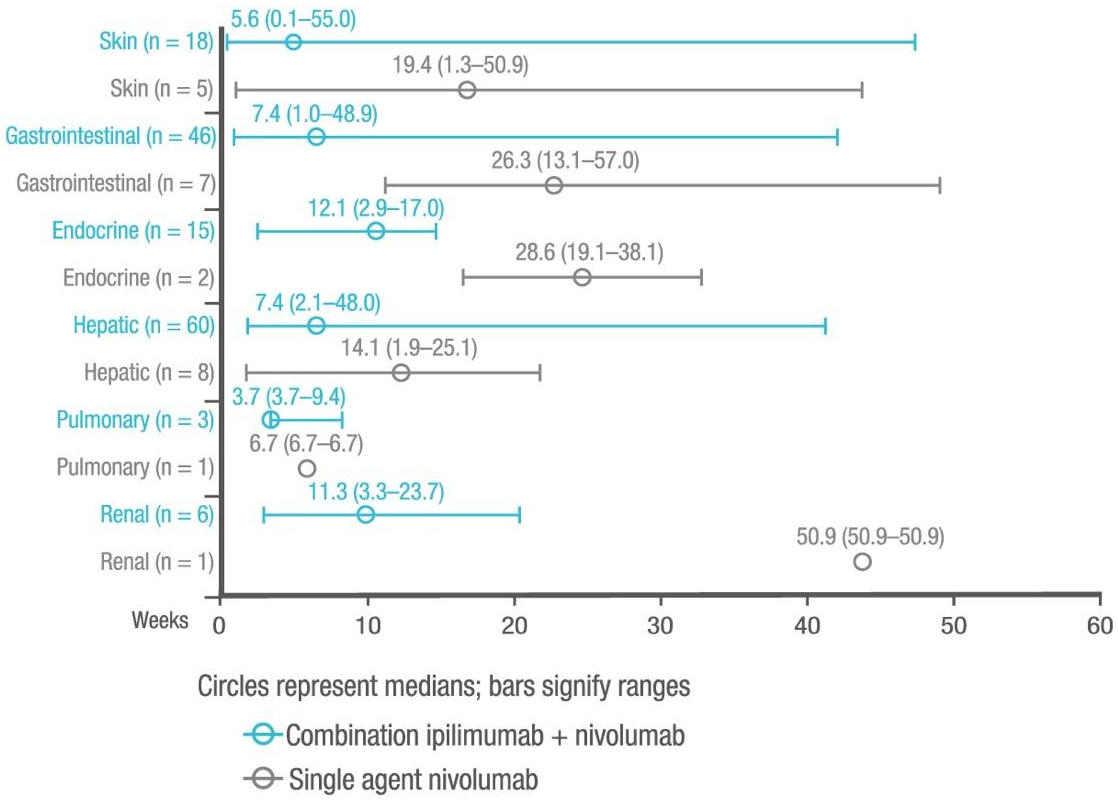
CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Time to onset of grade 3-4 treatment-related select adverse events



Larkin J et al. Presented at ECC 2015;Abs330.
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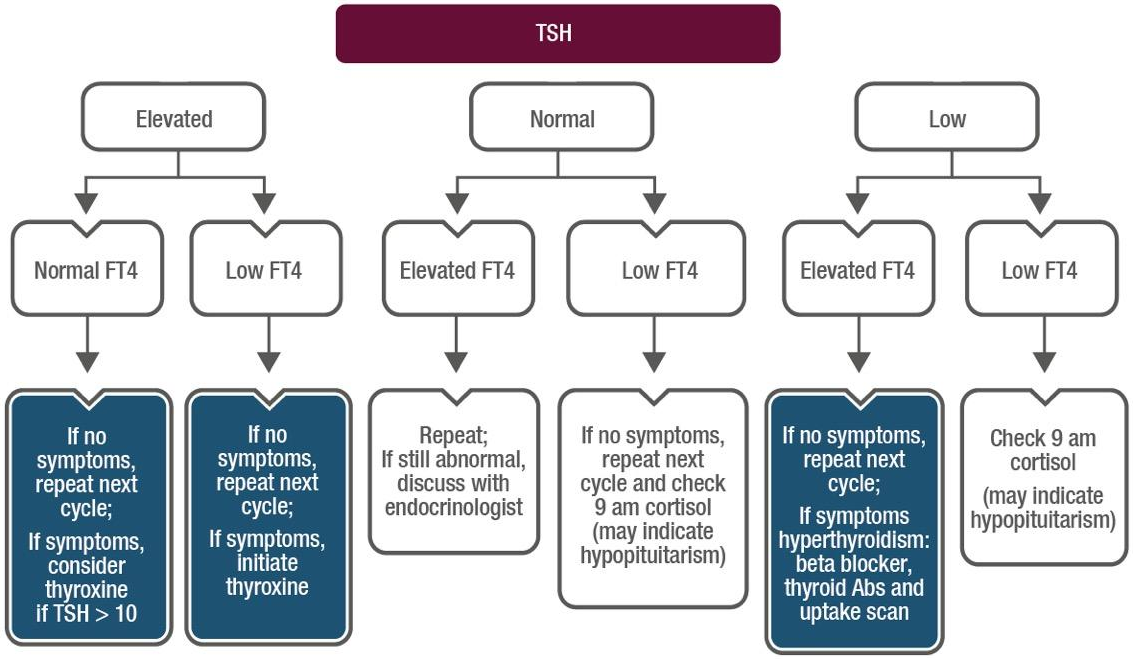
CLINICAL PRACTICE GUIDELINES

Immune related toxicities - endocrinopathies

ICPi monitoring and management: Thyroid function (cont'd)



Withhold ICPi if patient is unwell with symptomatic hyperthyroidism

Subclinical hyperthyroidism (low TSH, normal FT4) often precedes overt hypothyroidism

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CLINICAL PRACTICE GUIDELINES

Immune related toxicities - endocrinopathies

ICPi related toxicity: Management of hypophysitis

*Pituitary axis bloods: 9 am cortisol (or random if unwell and treatment cannot be delayed), ACTH, TSH/FT4, LH, FSH, oestradiol if premenopausal, testosterone in men, IGF1, prolactin. Mineralocorticoid replacement is rarely necessary in hypopituitarism

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CLINICAL PRACTICE GUIDELINES

Immune related toxicities - endocrinopathies

Type 1 diabetes mellitus

Summary of recommendations
Blood glucose levels should be regularly monitored in patients treated with ICPi in order to detect the emergence of *de novo* DM
Patients with Type 2 DM may develop ketoacidosis, which should be treated according to standard local guidelines
The role of high-dose steroids in preventing total loss of pancreatic beta cells is unclear and is not recommended
C-peptide and antibodies against GAD and islet cells can distinguish between Type 1 and Type 2 DM
Restarting ICPi treatment can be considered once the patient has been regulated with insulin substitution

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CLINICAL PRACTICE GUIDELINES

Immune related hepatotoxicity

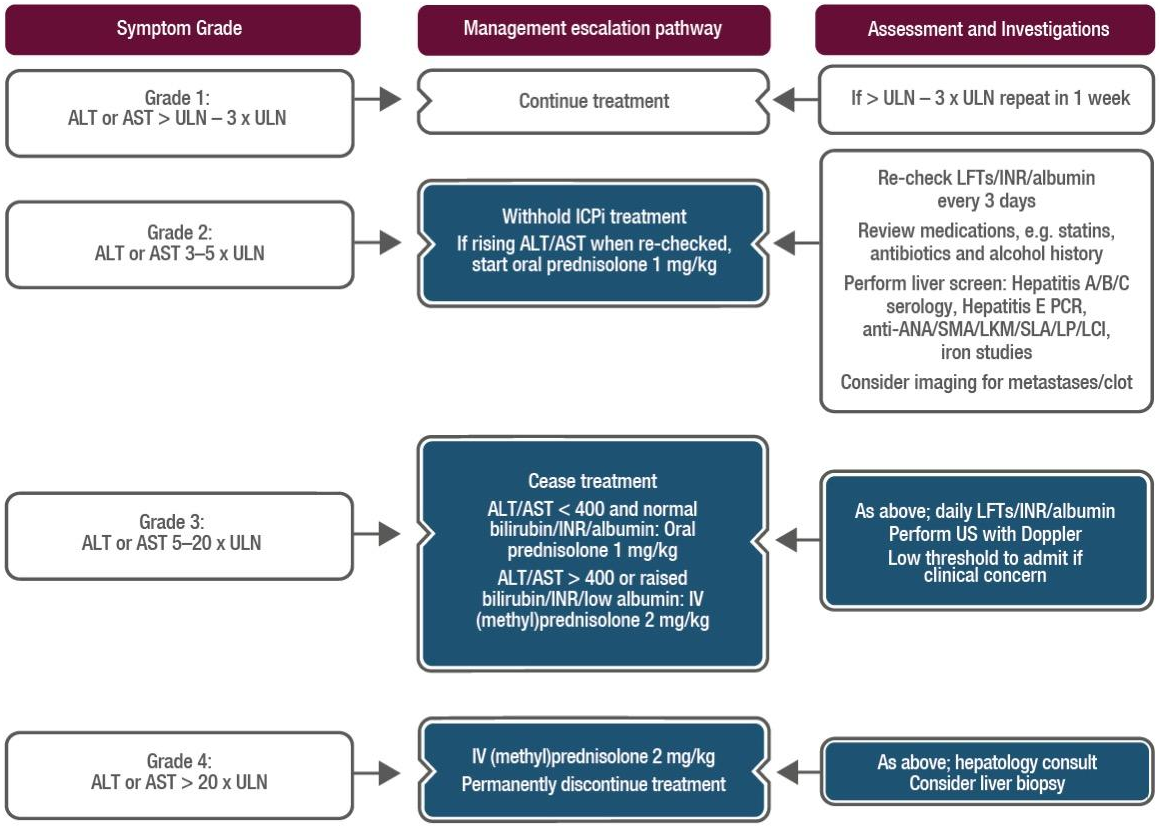
ICPi-related toxicity: Management of hepatitis

Steroid wean:

- Grade 2: Once grade 1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10 mg
- Grade 3/4: Once improved to grade 2, can change to oral prednisolone and wean over 4 weeks; for grade 3, re-challenge only at consultant discretion

Worsening despite steroids:

- If on oral change to IV (methyl)prednisolone
- If on IV add MMF 500–1000 mg bid
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis



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CLINICAL PRACTICE GUIDELINES

Immune related gastrointestinal toxicities

GI toxicity of ICPIs (most commonly observed with anti-CTLA-4 alone or anti-CTLA-4 + anti-PD-1/PD-L1)

Summary of recommendations	
Anti-PD-1	
Common symptoms	Diarrhoea, nausea/vomiting and abdominal pain, with a median time to symptom onset of 3 months
Endoscopic findings	Normal mucosa through mild erythema to severe inflammation and histological findings include lamina propria expansion, villus blunting, intra-epithelial neutrophils and increased crypt/gland apoptosis
Different patterns of GI irAEs	• Acute colitis • Microscopic colitis • Upper GI involvement • Pseudo-obstruction
Combined anti-CTLA-4 and anti-PD-1 antibodies	
With this combined treatment, pancreatitis and small bowel enteritis, which may be visible on CT scan, require ICPi treatment discontinuation and initiation of immunosuppression	

ESMO

CLINICAL PRACTICE GUIDELINES

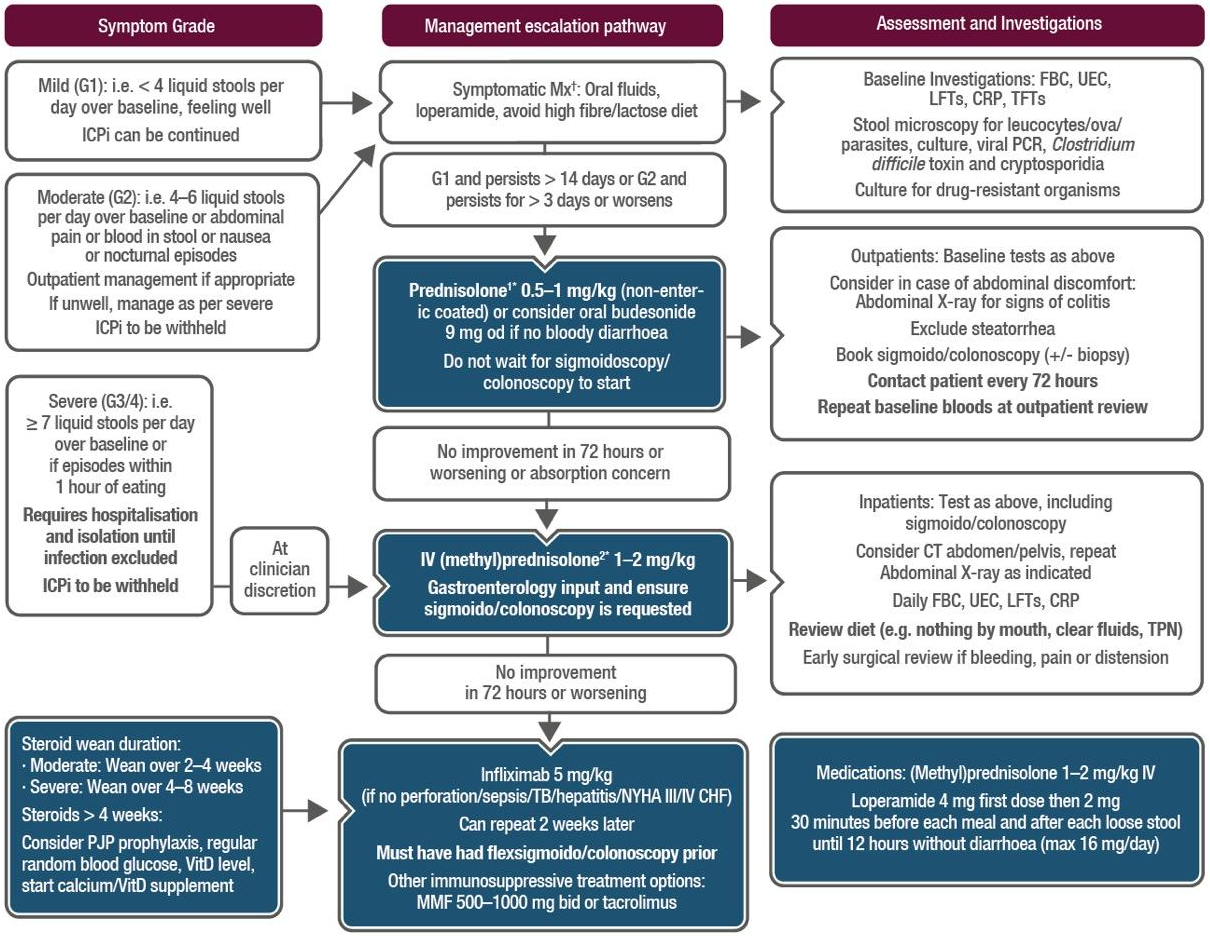
Immune related gastrointestinal toxicities

ICPi-related toxicity: Management of diarrhoea and colitis

†Loperamide 4 mg first dose then 2 mg 30 minutes before each meal and after each loose stool until 12 hours without diarrhoea (max 16 mg/day)

Steroid wean duration:
[1]Moderate: wean over 2–4 weeks
[2]Severe: wean over 4–8 weeks

*Steroids > 4 weeks: Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement



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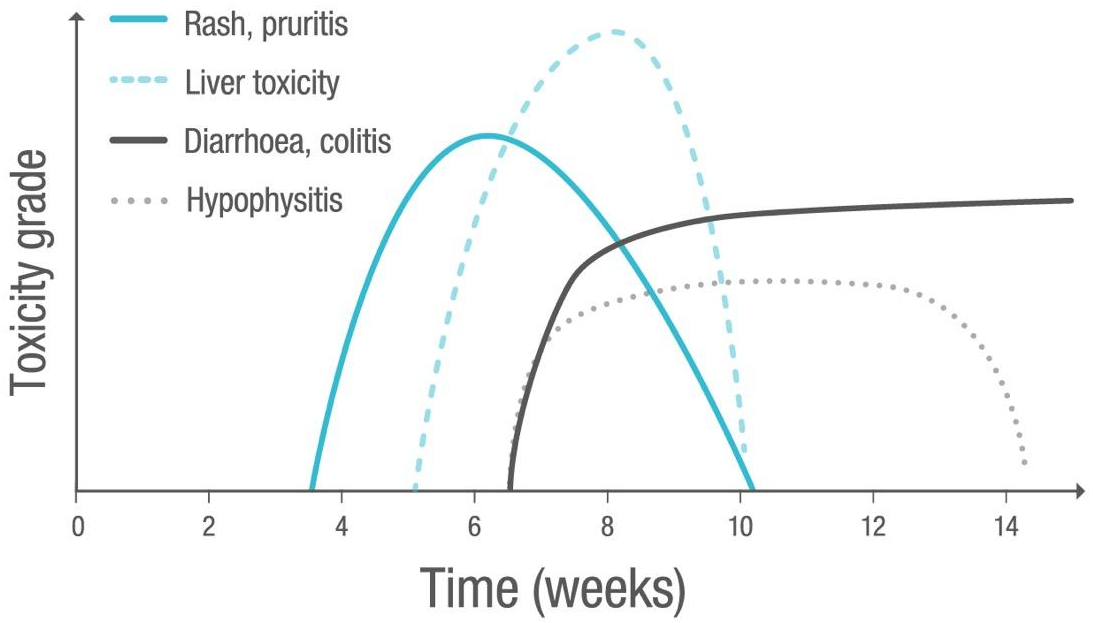

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CLINICAL PRACTICE GUIDELINES

Immune related pneumonitis toxicities

Management of pneumonitis

Summary of recommendations	
Immune-related pneumonitis is documented or suspected	Immunosuppressive treatment should be started immediately
When no possibility to rule out infection using bronchoscopy	Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment for grade ≥ 3 pneumonitis
Grade 1–2	Oral prednisone 1 mg/kg daily or equivalent with clinical assessment every 2–3 days initially is recommended, with additional radiological assessments for grade 2 pneumonitis, and possible ICPi treatment interruption. Following recovery, steroids should be tapered over 4–6 weeks and ICPi treatment reintroduction delayed until the daily steroid dose is ≤ 10 mg of oral prednisone
Grade 3–4 moderate-to-severe cases	Hospitalisation, treatment with high dose IV (methyl)prednisolone 2–4 mg/kg/day or equivalent and permanent discontinuation of ICPi treatment is recommended • If there is no improvement after 2 days, additional immunosuppressive strategies, such as infliximab, MMF or cyclophosphamide, are recommended • Steroids should be tapered slowly over at least 6 weeks to prevent recurrence

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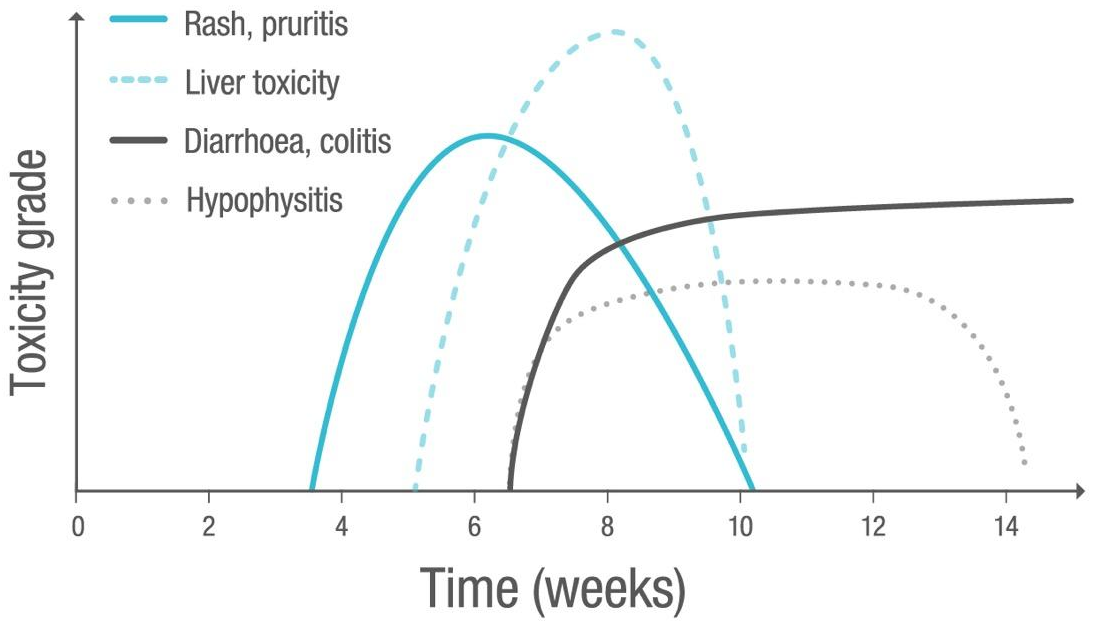
CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Time to onset and resolution of occurrence of immuno-related adverse events following Ipilimumab treatment



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CLINICAL PRACTICE GUIDELINES

Rare immune-related toxicities

ICPi-related toxicity: Management of nephritis: **grade 1-2**

Renal injury occurs in around 1–4% of patients treated with ICPis, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate

Attention needs to be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN

Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension

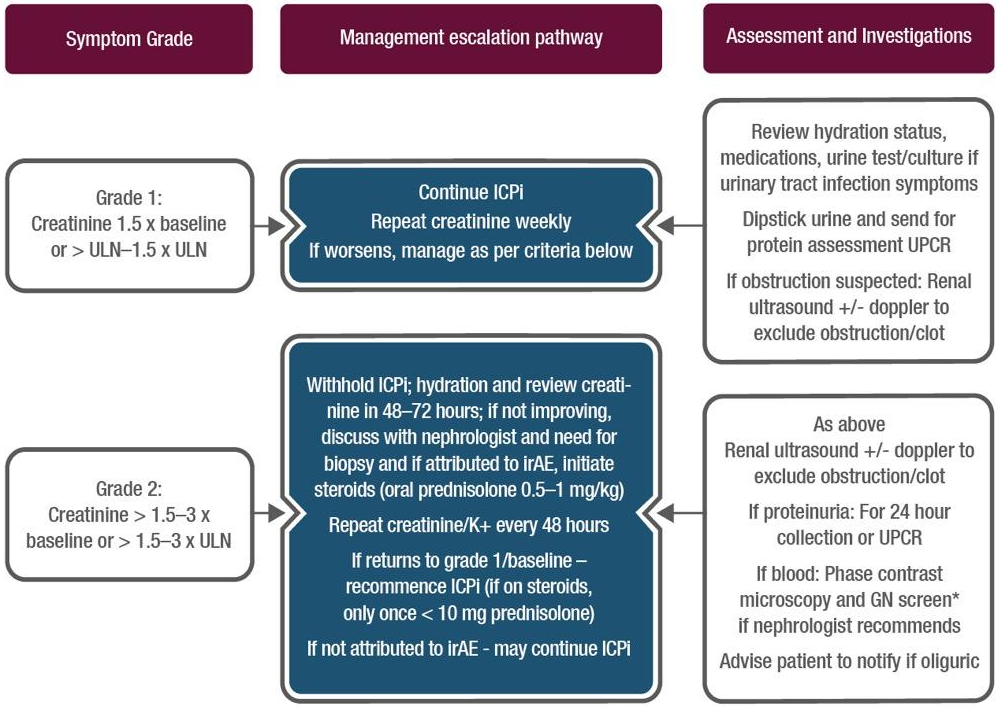
Early consideration for renal biopsy is helpful which may negate the need for steroids and determine if renal deterioration related to ICPis or other pathology

Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy

Steroid wean: Begin to wean once creatinine grade 1; grade 2 severity episode: wean steroids over 2–4 weeks; grade 3–4 episode: wean over ≥ 4 weeks

If on steroids for > 4 weeks–PJP prophylaxis, calcium/vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycaemia

*GN screen: ANA, complement C3, C4, ANCA, anti-GBM, hepatitis B and C, HIV, immunoglobulins and protein electrophoresis



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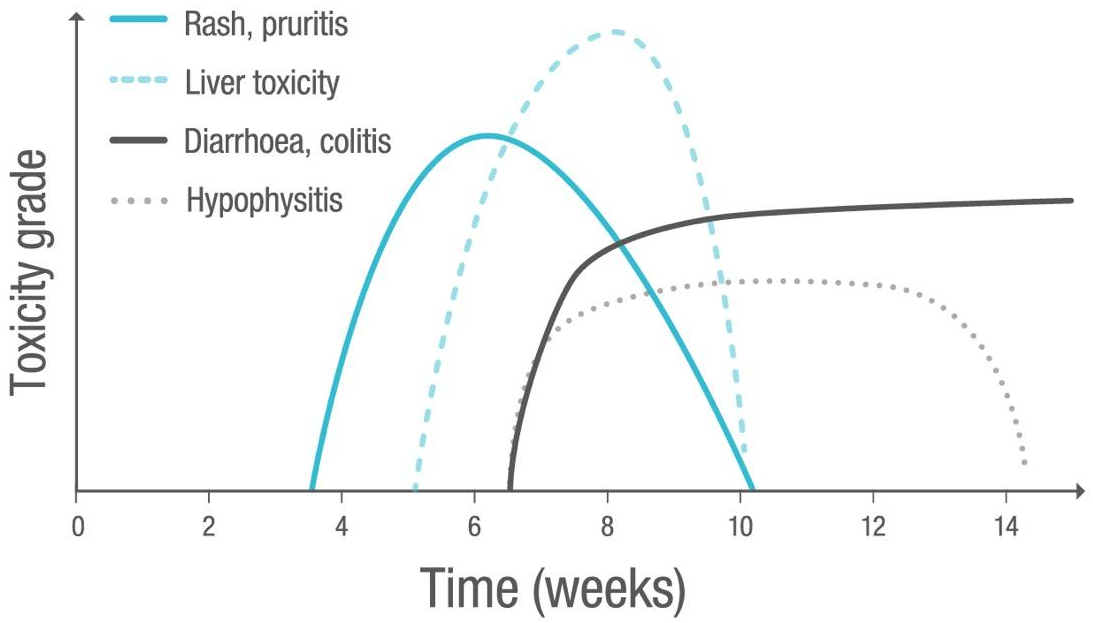

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CLINICAL PRACTICE GUIDELINES

Rare immune-related toxicities

Ocular toxicities
Haematological toxicities
Allograft rejection

Summary of recommendations
Ocular toxicities
Topical corticosteroids are recommended for episcleritis and anterior uveitis and systemic corticosteroids for severe ocular inflammation and orbital inflammation
Intravitreal anti-VEGF treatment is recommended for choroidal neovascularisation
Haematological toxicities
The optimal treatment for immune-related haematological AEs is unknown and initiation of high-dose corticosteroids and other immunosuppressive drugs should be performed in close collaboration with a haematologist
Allograft rejection
Use of ICPis may induce graft rejection. The risk of allograft rejection is probably lowest for anti-CTLA-4

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