Onkológiai terápiák mellékhatásainak kezelése

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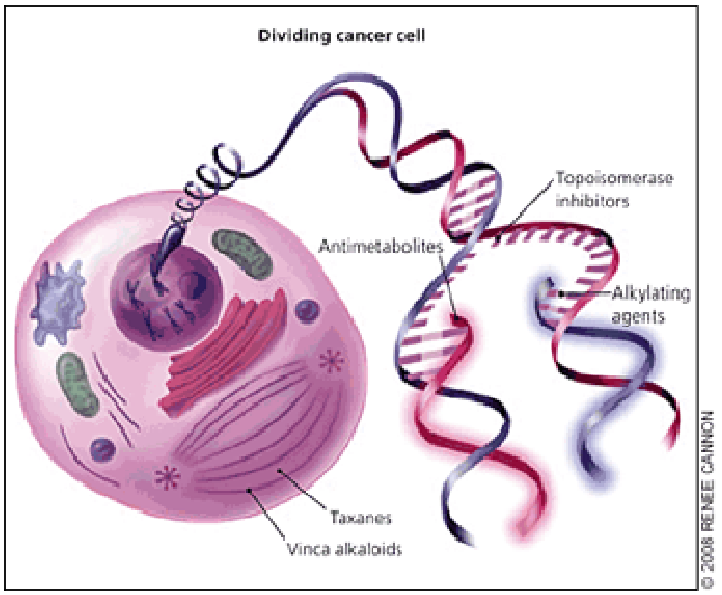
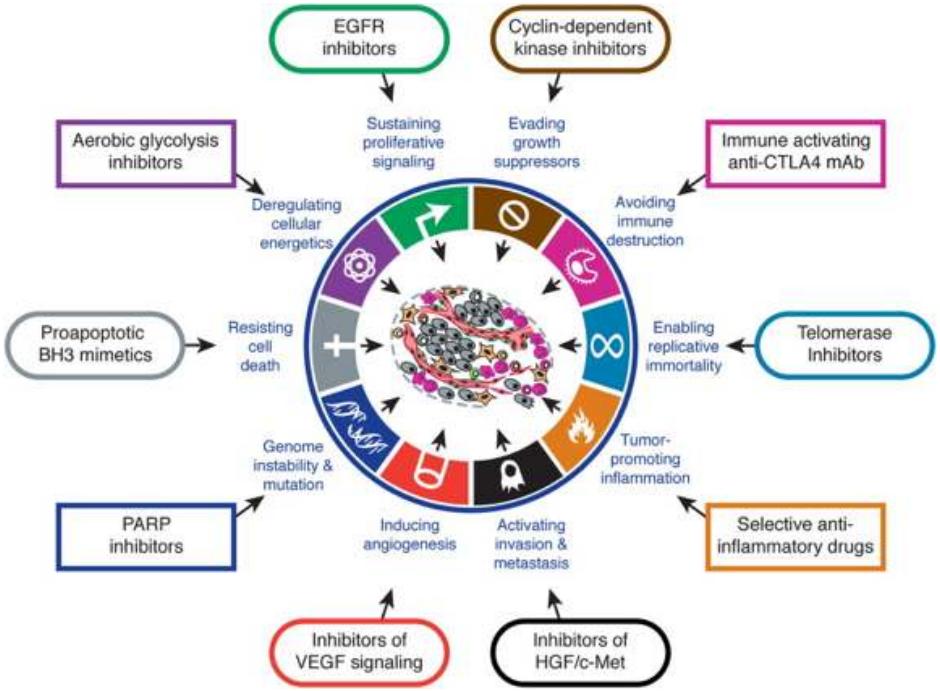
gondolkodás, hangulati változások
dehidráció
étkezési problémák
elesések
fáradékonyság
sexualis mellékhatások
láz
hajhullás
csuklás
infekció
lábgörcsök
vérképzőszervi mellékhatások
lymphedema
mucositis
hasmenés
hányinger, hányás
fájdalom
perifériás neuropathia
művégtag
dyspnoea
bőrtünetek
alvászavarok
izzadás
edema
gyengeség

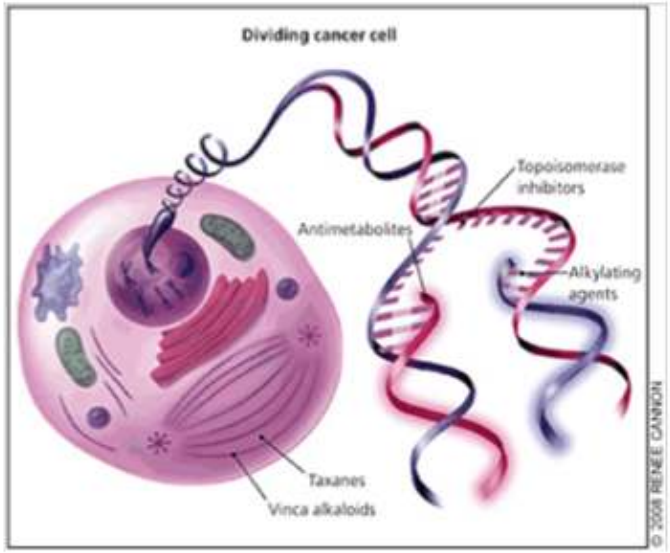
Daganatterápiás szerek

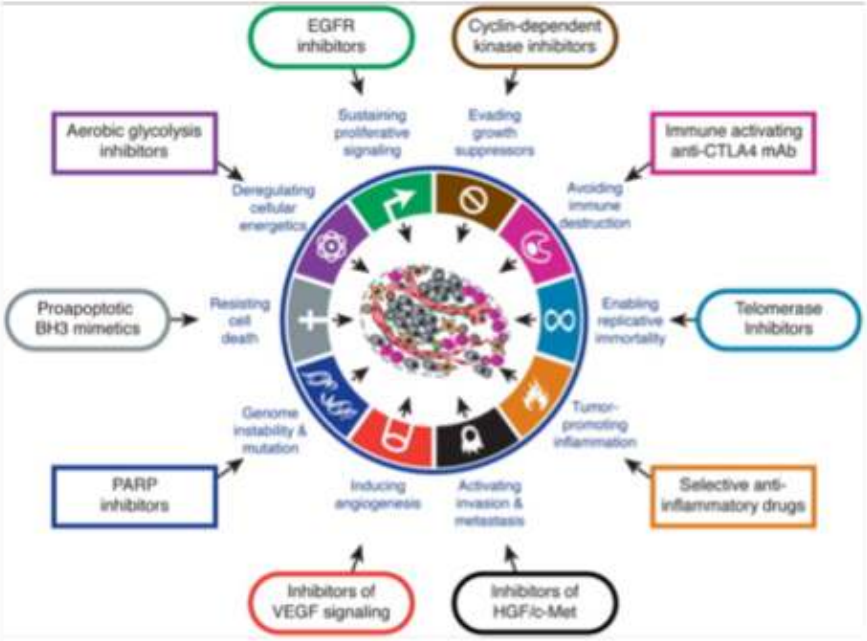
antimetabolitok
alkiláló szerek
anti-mikrotubulus szerek
tumorellenes antibiotikumok
topizomeráz gátlól
monoklonális antitestek
kis molekulasúlyú TKI
hormonok
csontra ható szerek
egyéb szerek





Cytotoxics	Hormone-Therapy	Targeted Agents		Immunotherapy	
Alkylating agents	Antiestrogens	Monoclonal Antibodies		Cytokines	IL-2, IFN-gamma
Antifolates	Aromatase inhibitors	Antibody Drug Conjugates		Monoclonal Antibodies	
Antimetabolites	GH-RH Agonist	Small molecules			Anti-CTLA4
Antimicrotubule drugs	GH-RH Antagonist		Kinase inhibitors		Anti-PD1 / Anti-PDL1
Antitumour antibiotics	Antiandrogens		Enzime inhibitors	Vaccines	
Cytidine analogues			Protein inhibitors	Cell therapy	
Fluoropyrimidines			Agonist/antagonist	Small Molecules	
Platinum analogues		Other			
Topo-isomerase inhibitors			Peptides		
			Oligonucleotides		

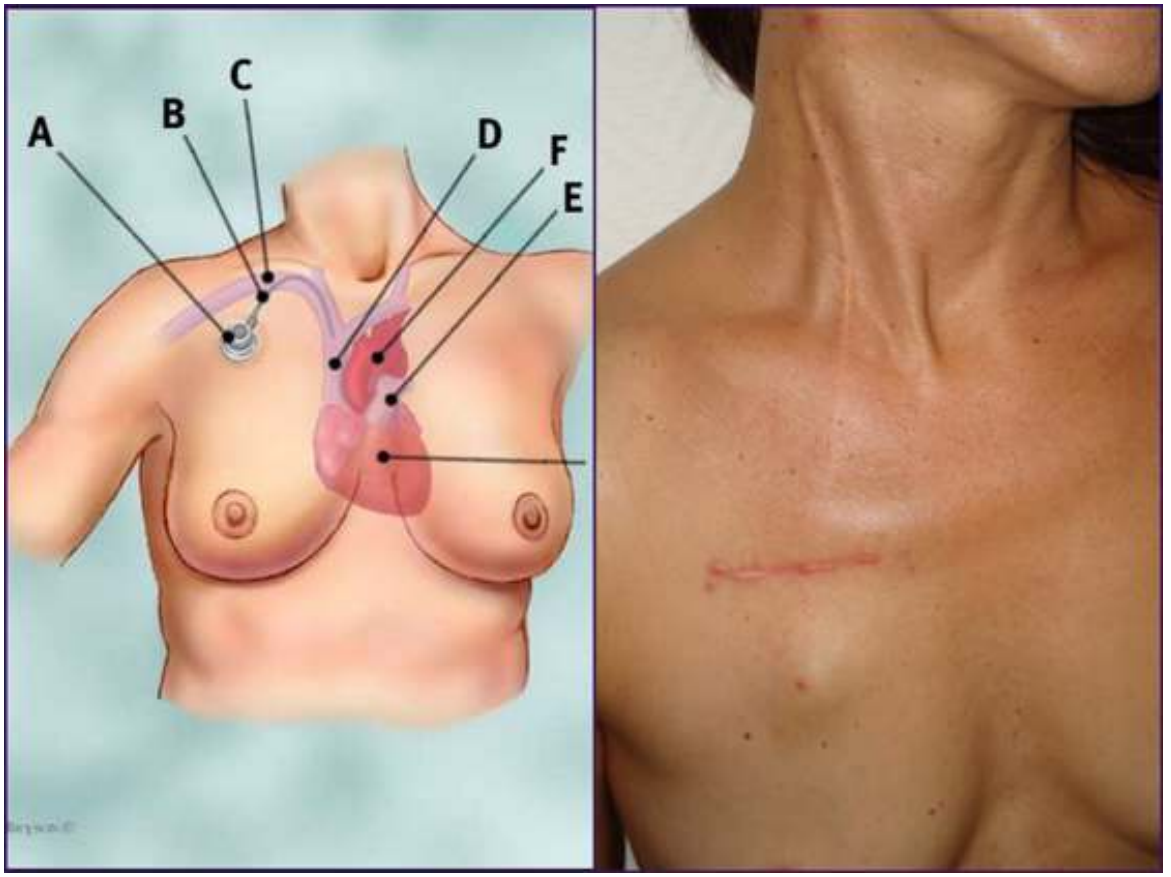




kemoterápia

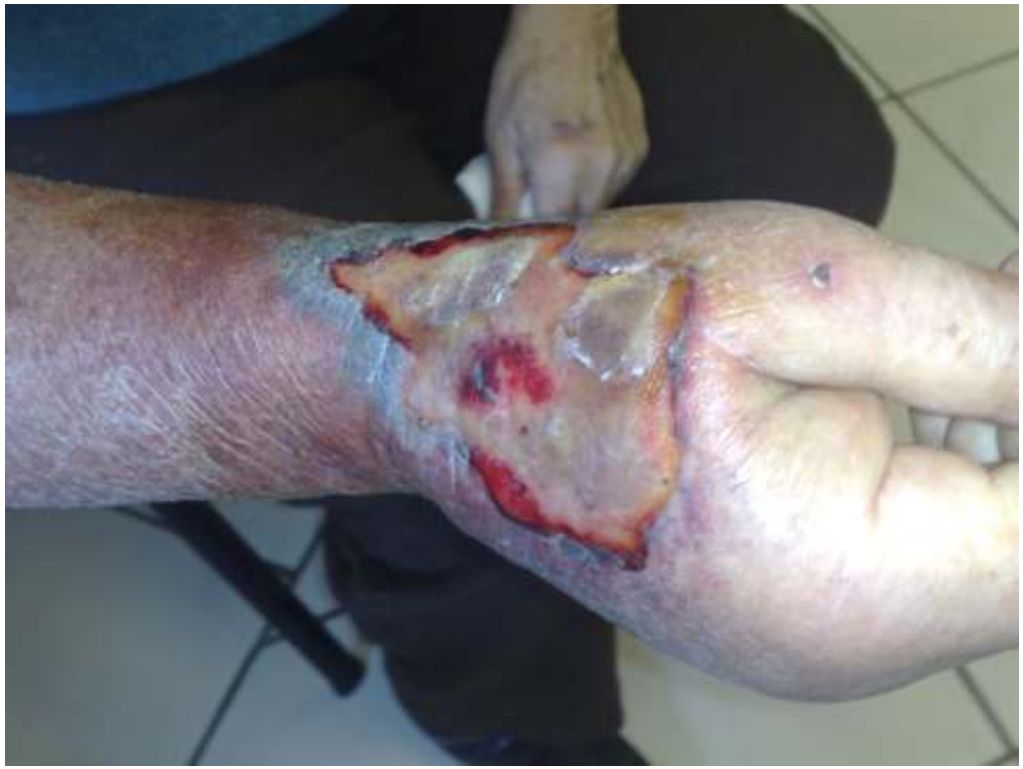
- A szisztémás kezelés a disszeminált folyamat terápiája
- A kemoterápia fejlődésével számos tumor esetén kuratív hatás érhető el (pl hererák)
- A kezelés ciklusokból áll- számos ciklus megadása szükséges
- A terápia hatása a kezelés alatt
- Alkalmazás:
  - Neoadjuváns, vagy primer szisztémás, vagy indukciós terápia
  - Adjuváns kezelés
  - Palliatív terápia
  - Transarteriális kemoembolizáció
  - Peritonealis kemoterápia
  - Intraoperative adott kezelés- hőterápiával kombinálva

Kemoterápia beadása port a cath -on keresztül



SE Radiológiai és Onkoterápiás Klinika saját képanyag archivumából

Paravasatio



Anaemia

aganat és kemoterápia okozta anaemia gyakori, daganatos betegek 30-90%-ban fordul elő

Tünete: sápadtság, fáradékonyság, légszomj
Kezelés:
OK? (csökkent képződés, fokozott pusztulás, vérzés)
(társbetegségek, kemoterápia hatása)

erthyrocyta adása (azonnali korrekció)
erythropoetin adása (korrekció kb 2 hét)

Grade	Hgb (g/dl
1 (enyhe)	10 - 12 (norm alsó határa)
2 (közepes)	8-10
3 (súlyos)	6.5-8
4 (életevszély)	

diagnosztika

kemoterápia direkt hatása a hematopoesisre
kemoterápiás nefrotoxicitás
antok kezelésénél gyakori az anaemia, platina alapú kemoterápiáknál a kombinált myelo-

Figyelni kell: Hgb 11 g/dl alatt, és/vagy kiindulási hgb csökkenése 2g/dl-nél többel

morfológia: - microcyter (vashiány)
macrocyter (gyógyszer, alkoholizmus, B12, folsav hiány
normocyter (vérzés, hemolizis, krónikus gyulladás, veseelégtelenség)

kinetika - reticulocytaszám

nutricionális hiány - vas, B12 - vérből mérni
vérzés - széklet vér, endoscopia
hemolizis - LDH, DIC panel,, inderekt Bi emelkedése
öröklött anarmia - anamnézis, család

Terápia

Transzfúzió - azonnali hatás

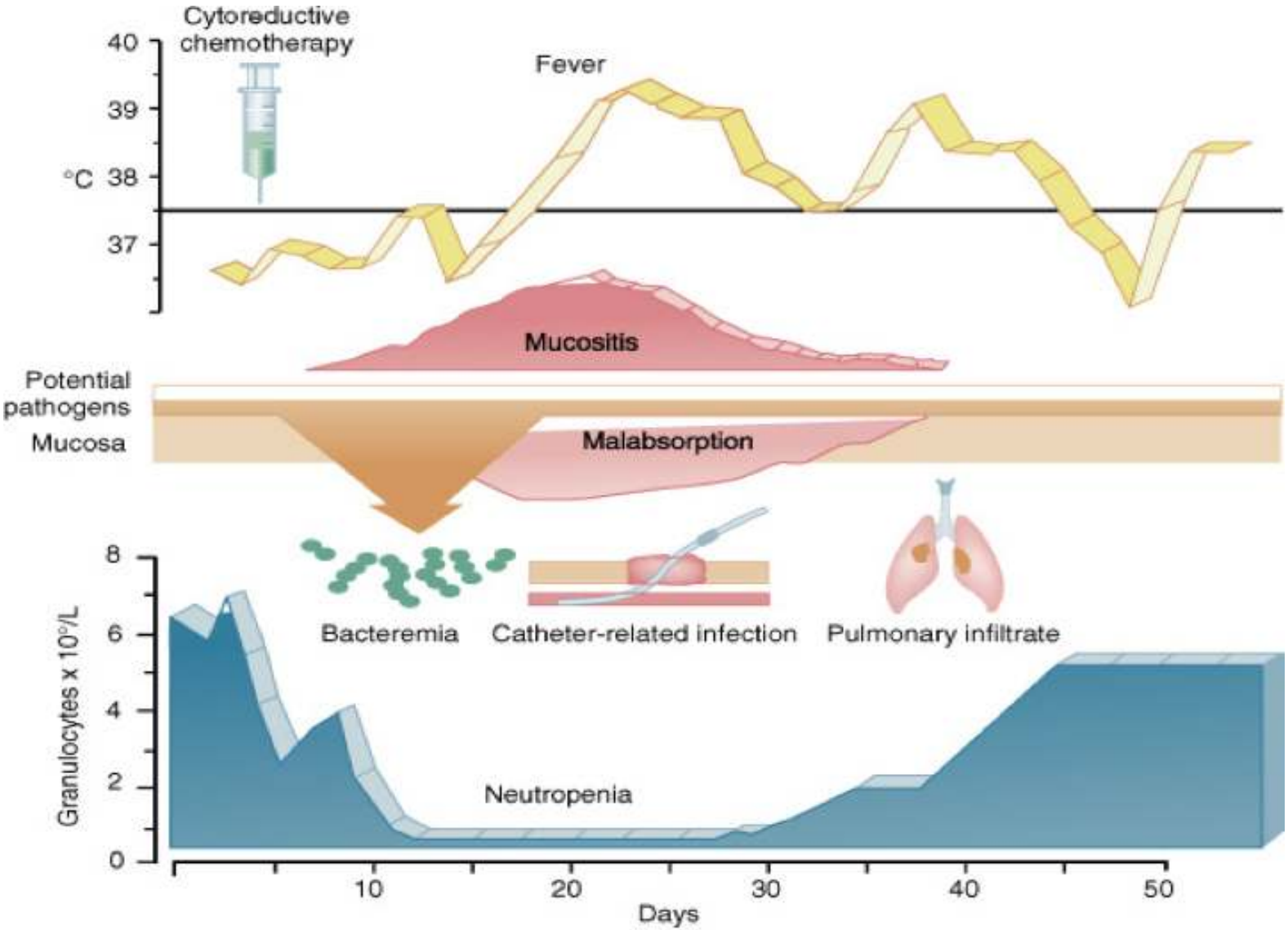
Erythropoetin (epoetin alfa 40000 U/hét) darbepoetin alfa) célérték elérése hetekig tarthat

mellékhatások

- **tumornövekedés ↑ - nem javasolt használatuk kuratív célú kezelések esetén (adjuváns kemoteráoia korai emlőrák, NSCLC, lymphoma, hererák)**
- **thromboembolia (10 G/dl értékig várva, ez ritkább)**
- **OS↓- ez vitatott**
- **hypertonia,**
- **vörösvértest aplasia - ritka, erythropetin neutralizáló antitestek okozzák, főleg krónikus veseelégtelenségben sznevedő daganatos betegeknél alakulhat ki**

Vas szint rendezése szükséges !! , iv. vaspótlás effektívebb

Lázas neutropenia (FN)



Lázas neutropenia - oralis hőmérséklet > 38.3 C, vagy 2 óra különbséggel mért 38 C láz, és A

Daganatterápiák leggyakoribb, és legsúlyosabb szövődménye.

- 8 eset /1000 páciens
- 10%-os kórházi mortalitás

neutropeniat okozó kezelések: 20% < high risk, 10-20% intermedier, 10%> low risk

FN rizikót emelő egyéb tényezők:

- idős kor
- előrehaladott betegség
- korábbi FN
- nem kapott antibiotikus vagy GCSF profilaxist
- mucositis
- gyenge PFS
- kardiovaszkularis betegség

FN prognosztikai index
MASCC - Multinational Association of Supportive Care in Cancer

Table 1. MASCC febrile neutropaenia risk index

Characteristics	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Patients with scores ≥21 are at low risk of complications. Points attributed to the variable 'burden of illness' are not cumulative. The maximum theoretical score is therefore 26 [2]. Reprinted with permission.

BP, blood pressure.

FN profilaxis

Kémiai profilaxis:
1990 óta fluorokinolonok - ára van: rezisztens bakterium törzsek ….
ESMO, EORTC, ASCO: csak azon pácoenseknél ahol FN rizikó magas.

Profilaktikus GnCSF indikációi:
Ciklus 1 KT után adott G-CSF 50%-kal csökkenti a FN kockázatát (tumor választ, OS-t nme befolyásolja)
20% feletti rizikónál javasolt (ld algoritmus)

Adagolás:
filfastrim - 5ug/kg/nap sc. 24-72 órával a KT utolsó napját követően, addig míg stabil postnadir ANC kialakul.

pegfilgastrim 100 ug/kg vagy 6 mg sc. KT után egy nappal . (2w és 3w ciklusoknál adható, 1w ciklusoknál nem)

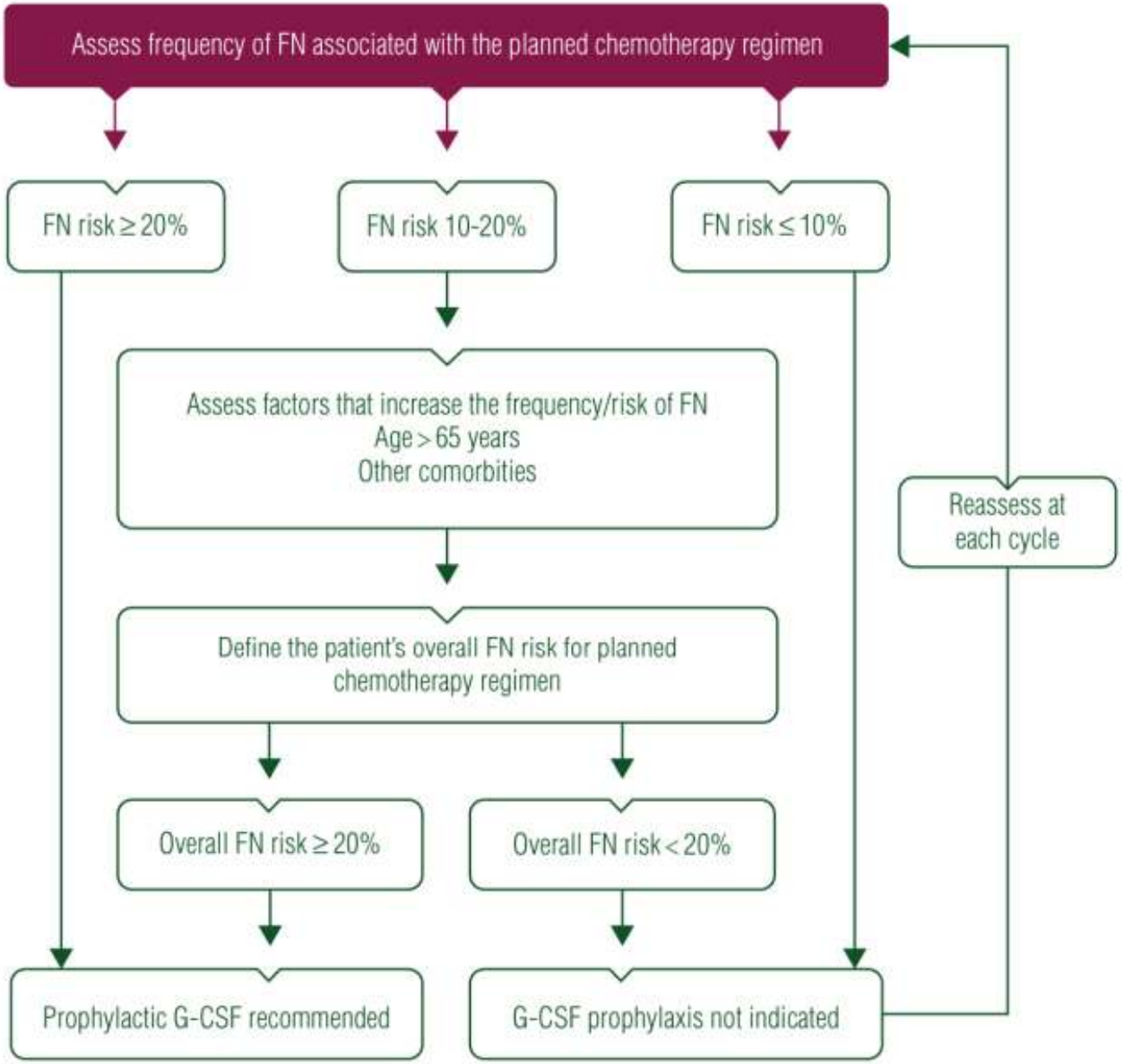


Figure 1. Algorithm to decide primary prophylactic granulocyte colony-stimulating factor usage, adapted from European Organisation for Research and Treatment of Cancer guidelines. FN, febrile neutropaenia; G-CSF, granulocyte colony-stimulating factor. Reprinted from [8], with permission from Elsevier.

20% feletti FN rizikót jelentő KT-k (néhány pl)

emlőrák: AC-docetaxel, doxorubicin/docetaxel, doxorubicin/paclitaxel,
petefészekrák: docetaxel, paclitaxel
hererák : BEP, VEIP
gyomorrák: LVFU, LVFU-cisplatin, LVFU-irinotecan

FN kezelése

Észlelés:

1. **van-e vénás katéter?**
2. **tünetek - légzőrendszer, GI rendszer, bőr, perinealis régió/genitalis húgyuti váladék, orr-torok, CNS**
3. **korábbi pozitív mikrobiológiai vizsgálat?**
4. **rutin vizsgálatok: vérkép, kémia (vese, máj?) alvadási paraméterek, CRP, hemokultúra, vizelet üledék/tenyésztés, széklettensésztés, bőrlesiok, mellkas rtg**
5. **súlyos elhúzódó FN: HR-CT mellkasról (ha 72 órán túli pyrexia), nronchoalveolaris lavage**

FN esetén kórházba kerülve 1 órán belül el kell kezdeni a kezelést.

low risk páciens: (hemodinamikailag stabil, nincsen penumonia, egyéb "organ-failure") oralis antibiotikum adható - pl. moxifloxacin

high-risk: széles spektrumú iv. antibiotikum - ceftazidim, imipenem, meropenem…stb.

katéter related infection: eltávolítás, vancomycin.

FN kezdeti kezelése

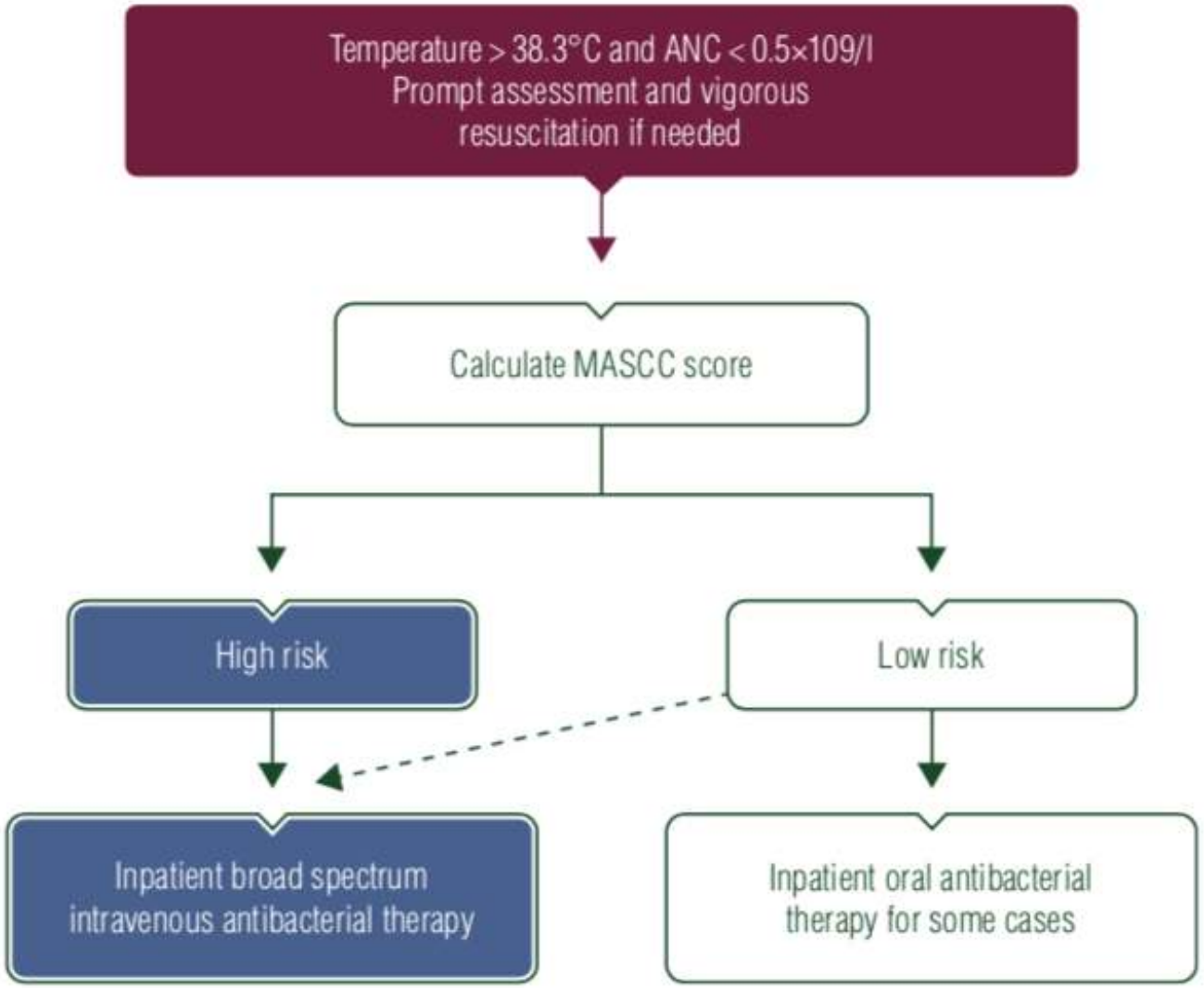


Figure 2. Initial management of febrile neutropaenia. ANC, absolute neutrophil count; MASCC, Multinational Association of Supportive Care in Cancer.

48 h kezelés után….

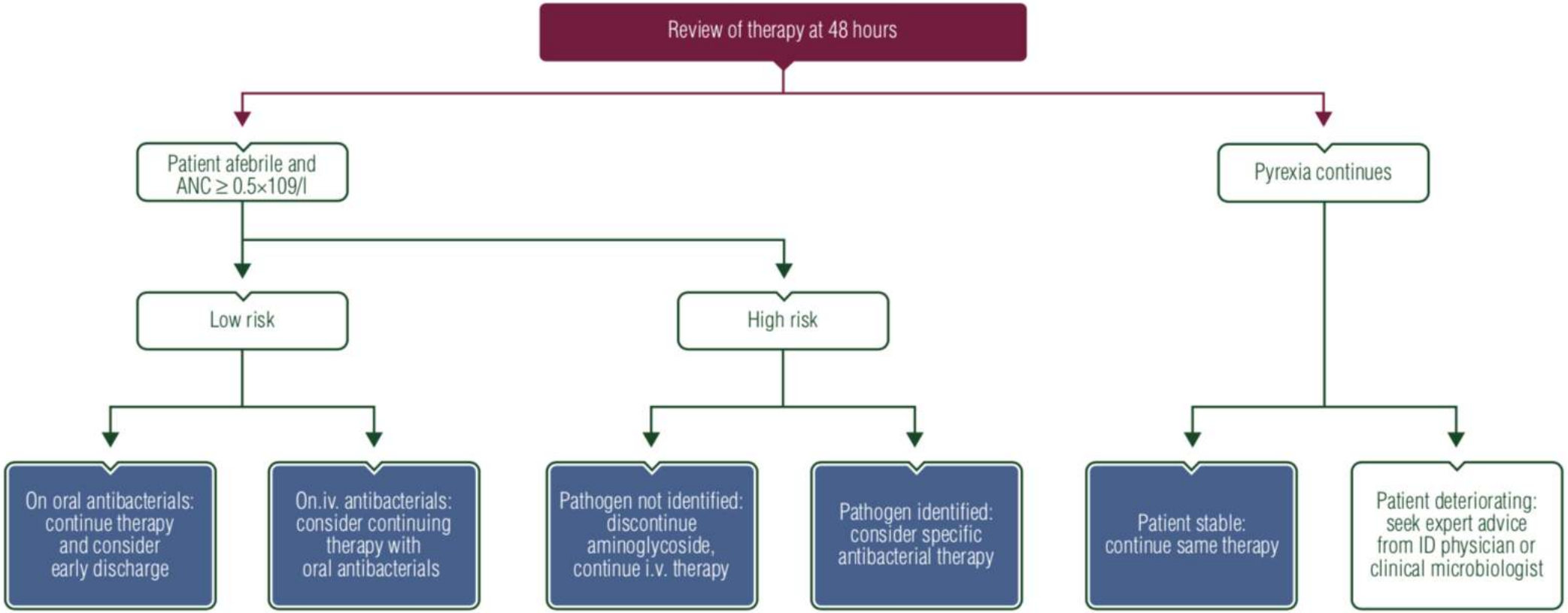


Figure 3. Assessment of response and subsequent management. ANC, absolute neutrophil count; i.v., intravenous; ID, infectious disease.

FN javaslatok ESMO

- **FN kemoterápiát kapó páciensek +/-1%-nál jelentkezik, morbiditás 20-30%, mortalitás 10%**
- **GCSF adásával megelőzhető. Primer prevenció javasolt 20% feletti rizikót jelentő KT-k esetében.**
- **FN fellépte esetén MASCC score használata szükséges súlyosság felmérésére**
- **low risk FN esetében ambulanter per os antibiotikum elegendő lehet, szoros követéssel**
- **high risk FN azonnali hospitalizáció és széles spketrumú antibiotikus kezelés indítása, szoros monitorozással.**

Hányinger, hányás

1979 randomizát vizsg.: KT okozta hányinger/hányás: 83%
2014-ben ASCO: elmúlt 50 éve “top 5” eredménye a hányáscsillapítás

Patofiziológia - KT szerek neurotranszmitter receptorokat aktiválva okoznak hányinger/hányást.
centralis (kési fázis) - area postrema (substabce P - neurokinin receptorok)
perifériás (kora 24 h-án belüli) - vagalis affarensek terminálján neurotransmitter receptorok , gyomor chromaffin sejtjei mellett. (serotnin - HT3 receptor)

1970 - dopamin receptor antagonisták (metoclopramid, haloperidol)

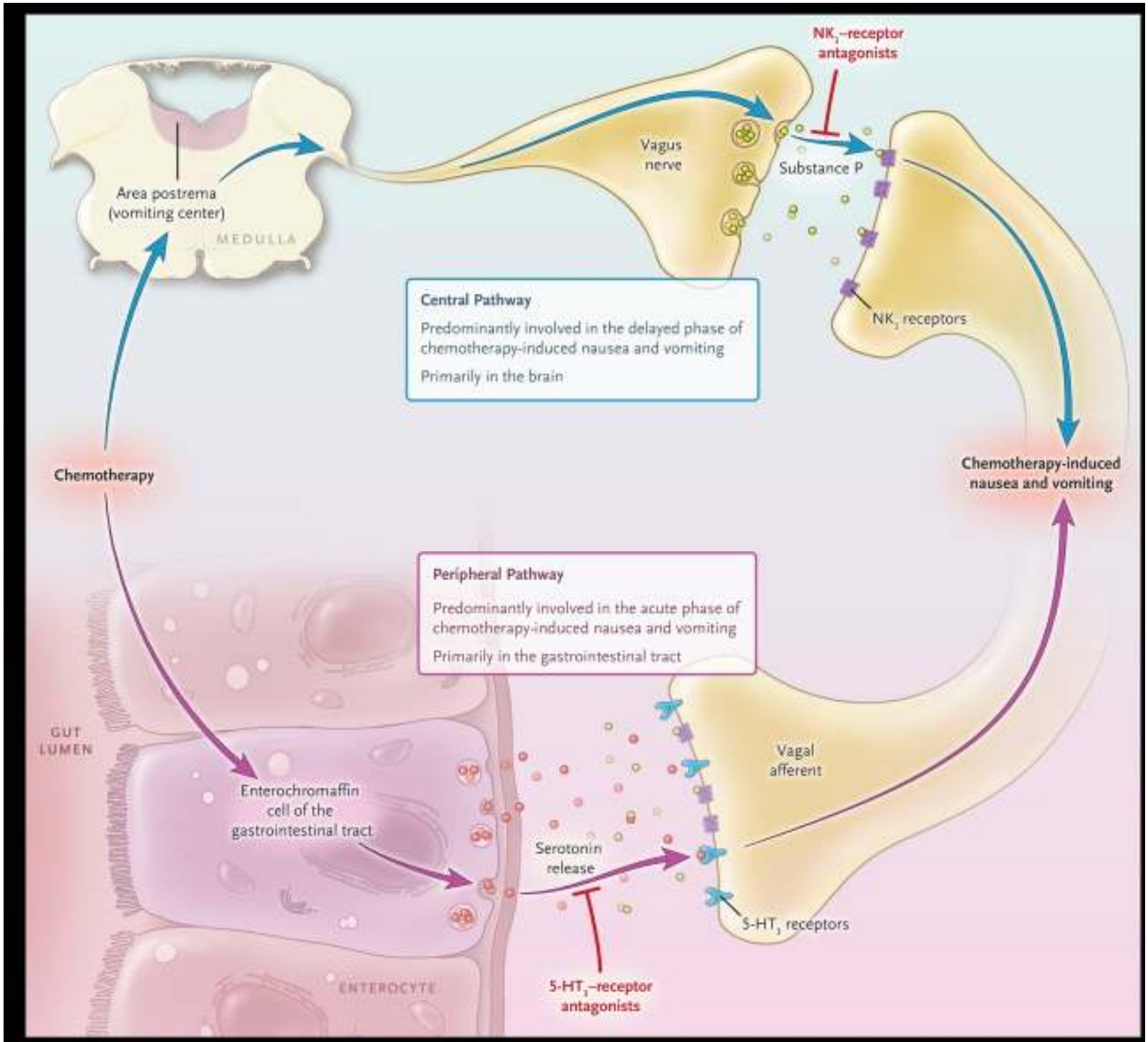
1978 cisplatin - erős emetogén

1981 - nagy dózisú metoclopramid + dexamethason

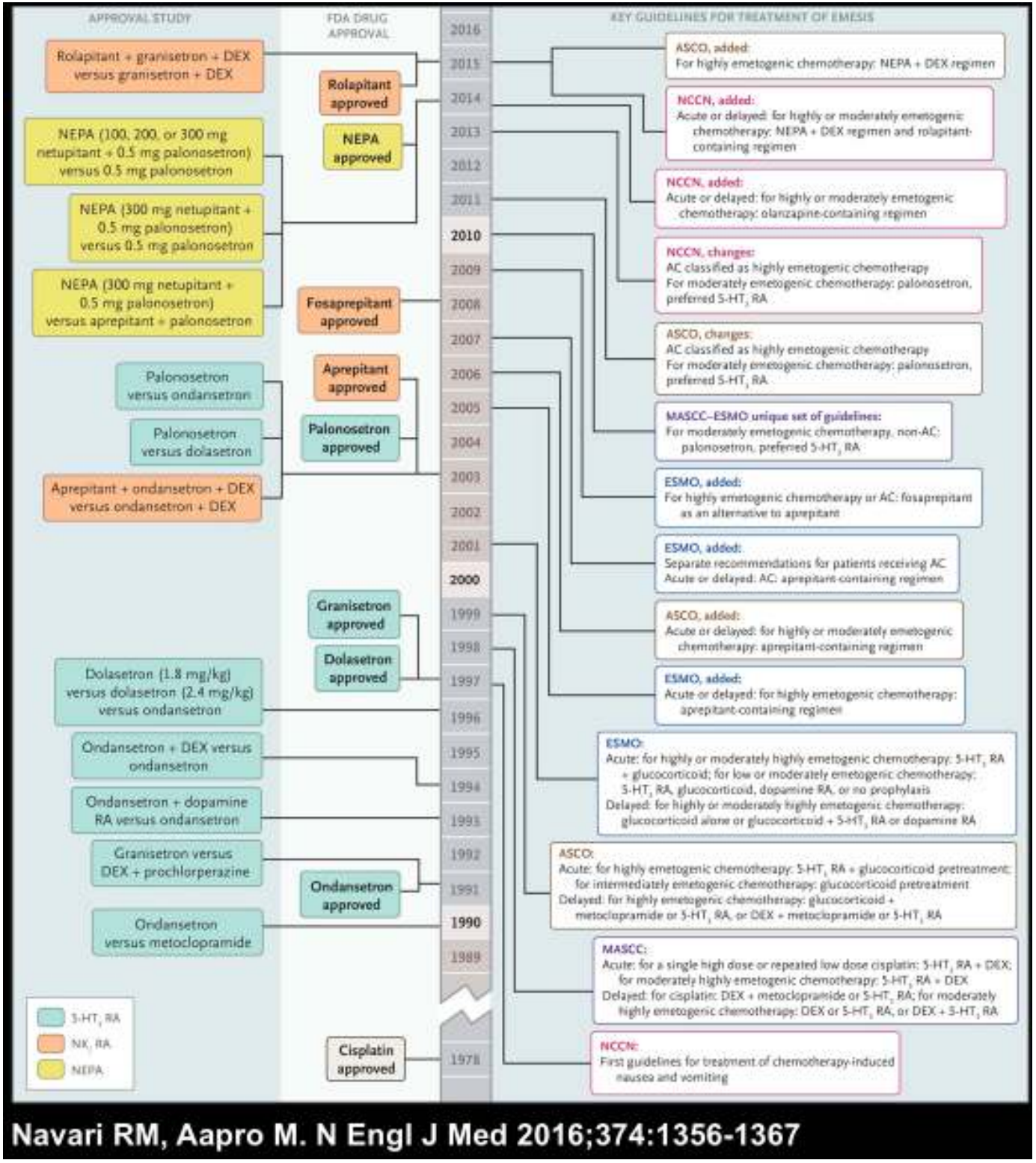
1990 - serotoinin (HT3 receptor) antagonisták (1991 ondanstron) hasonló: granisteron, dolasetron. (mh: obstipáció, QT megnyúlás)

2003 2nd generációs serontonin antagonisták: palonosteron (hosszabb T50, magasabb receptor affinitás, triggereli a HT3 receptor internalizációt, és gátolja a HT3-NK crosstalk-ot.

2003 első NK1 inhibitor a piacon: aprepitant,
2013-2015 : netupitan, rolatipant



Navari RM, Aapro M. N Engl J Med 2016;374:1356-1367



Navari RM, Aapro M. N Engl J Med 2016;374:1356-1367

Kemoterápia indukált hányás típusai

Table 1. Classes of Chemotherapy-Induced Nausea and Vomiting.

Classification	Definition
Acute	Occurring within the first 24 hours after initiation of chemotherapy[10]; generally peaks after 5 to 6 hours[11]
Delayed	Occurring from 24 hours to several days (days 2 to 5) after chemotherapy[12]
Breakthrough	Occurring despite appropriate prophylactic treatment[13]
Anticipatory	Occurring before a treatment as a conditioned response to the occurrence of chemotherapy-induced nausea and vomiting in previous cycles[14]
Refractory	Recurring in subsequent cycles of therapy, excluding anticipatory chemotherapy-induced nausea and vomiting[13]

Table 2. Levels of Emetogenic Potential of Chemotherapeutic Agents.

Level	Emetogenic Potential (% of Patients with Emesis)
1	Minimal (0 to <10%)
2	Low (10 to 30%)
3	Moderate (>30 to 90%)
4	High (>90%)

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Table 3. Antiemetic Treatment Recommendations for Emetogenic Intravenous Chemotherapy.*

Emetogenic Risk Level	Antiemetic Therapy	
	Acute Phase	Delayed Phase
MASCC–ESMO guidelines[17]		
High	5-HT_3–receptor antagonist, dexamethasone, and either aprepitant or fosaprepitant	Dexamethasone and aprepitant†
AC	5-HT_3–receptor antagonist, dexamethasone, and either aprepitant or fosaprepitant	Aprepitant‡
Moderate (associated with agents other than AC)	Palonosetron and dexamethasone	Dexamethasone
Low	Dexamethasone, 5-HT_3–receptor antagonist, or dopamine-receptor antagonist	—
ASCO guidelines[6]		
High (including AC)	5-HT_3–receptor antagonist, dexamethasone, and aprepitant	Dexamethasone and aprepitant
	NEPA and dexamethasone	Dexamethasone
Moderate	Either palonosetron and dexamethasone or 5-HT_3–receptor antagonist, dexamethasone, and aprepitant	5-HT_3–receptor antagonist, dexamethasone, or aprepitant
Low	Dexamethasone	—
NCCN guidelines[11]		
High (including AC)	5-HT_3–receptor antagonist and dexamethasone, plus one of the following agents: aprepitant, fosaprepitant, or rolapitant§	Aprepitant plus dexamethasone¶
	NEPA and dexamethasone§	Dexamethasone
	Olanzapine, palonosetron, and dexamethasone§	Olanzapine
Moderate	5-HT_3–receptor antagonist and dexamethasone, with or without aprepitant, fosaprepitant, or rolapitant§	5-HT_3–receptor antagonist,‖ dexamethasone, or aprepitant with or without dexamethasone**
	NEPA and dexamethasone§	Dexamethasone may be used
	Olanzapine, palonosetron, and dexamethasone§	Olanzapine
Low	Dexamethasone§, metoclopramide§, prochlorperazine§, or 5-HT_3–receptor antagonist§ (ondansetron, granisetron, or dolasetron)	—

* AC denotes anthracycline plus cyclophosphamide, ASCO American Society of Clinical Oncology, ESMO European Society for Medical Oncology, 5-HT_3 5-hydroxytryptamine type 3, MASCC Multinational Association of Supportive Care in Cancer, NCCN National Comprehensive Cancer Network, and NEPA netupitant plus palonosetron.
† Use dexamethasone alone, if fosaprepitant was used on day 1.
‡ Do not use any drug if fosaprepitant was used on day 1.
§ This regimen can be administered with or without lorazepam and with or without an H_2 blocker or proton pump inhibitor.
¶ If aprepitant was used on day 1, continue treatment with aprepitant on days 2 and 3; if fosaprepitant was used on day 1, no additional aprepitant is needed.
‖ No additional therapy is required if a palonosetron or granisetron patch is given on day 1.
** Use this regimen if aprepitant was given on day 1.

Navari RM, Aapro M. N Engl J Med 2016;374:1356-1367

ESMO 2016 - emetogén KT szerek

Table 1. Emetogenic potential of single intravenous antineoplastic agents

	IV chemotherapy		Oral chemotherapy[a]
High	Anthracycline/cyclophosphamide combination[b]		Hexamethylmelamine
	Carmustine		Procarbazine
	Cisplatin		
	Cyclophosphamide ≥1500 mg/m^2		
	Dacarbazine		
	Mechlorethamine		
	Streptozocin		
Moderate	Alemtuzumab	Epirubicin	Bosutinib
	Azacitidine	Idarubicin	Ceritinib
	Bendamustine	Ifosfamide	Crizotinib
	Carboplatin	Irinotecan	Cyclophosphamide
	Clofarabine	Oxaliplatin	Imatinib
	Cyclophosphamide <1500 mg/m^2	Romidepsin	Temozolomide
	Cytarabine >1000 mg/m^2	Temozolomide[c]	Vinorelbine
	Daunorubicin	Thiotepa[d]	
	Doxorubicin	Trabectedin	

ESMO 2016 - antiemetogén dózisok

Table 2. Recommended doses of serotonin $(5\text{-HT})_3$ receptor antagonists

Agent	Route	Antiemetics
Ondansetron	IV	8 mg or 0.15 mg/kg
	Oral	16 mg[a]
Granisetron	IV	1 mg or 0.01 mg/kg
	Oral	2 mg (or 1 mg[b])
Dolasetron	Oral	100 mg
Tropisetron	IV	5 mg
	Oral	5 mg
Palonosetron	IV	0.25 mg
	Oral	0.5 mg

[a]Randomised studies have tested the 8 mg twice daily schedule.
[b]The 1 mg dose is preferred by some panellists.

Table 3. Recommended doses of corticosteroids[a] (dexamethasone)

Dexamethasone	Dose and schedule
High risk	
Acute emesis	20 mg once [12 mg when used with (fos) aprepitant or netupitant][b]
Delayed emesis	8 mg bid for 3–4 days [8 mg once daily when used with (fos)aprepitant or netupitant]
Moderate risk	
Acute emesis	8 mg once
Delayed emesis	8 mg daily for 2–3 days (many panellists give the dose as 4 mg bid)
Low risk	
Acute Emesis	4–8 mg once

[a]While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.
[b]The 12 mg dose of dexamethasone is the only one tested with (fos) aprepitant/netupitant in large, randomised trials.

Table 4. Recommended doses of neurokinin $(NK)_1$ receptor antagonists

NK1 receptor antagonist	Dose and schedule
Aprepitant[a] and fosaprepitant: acute emesis	Aprepitant: 125 mg once on the day or chemotherapy[a] Or Fosaprepitant: 150 mg i.v., once on the day of chemotherapy
Aprepitant[a] and fosaprepitant: delayed emesis	Aprepitant: 80 mg orally, once daily for the 2 days after chemotherapy; or none if fosaprepitant is used
Rolapitant	180 mg orally once on the day of chemotherapy
Netupitant	300 mg netupitant/0.5 mg palonosetron orally once on the day of chemotherapy

[a]Aprepitant 165 mg as a single dose before chemotherapy (and none days 2–3) is registered by EMA and other authorities, but no randomised clinical trials have tested this dose schedule.

ESMO 2016 - sugárterápia okozta emesis

Table 5. Radiotherapy emetic risk levels and MASCC/ESMO antiemetic guidelines update

Emetic risk level	Area of treatment	Antiemetic guideline	MASCC level of scientific confidence/level of consensus	ESMO level of evidence/grade of recommendation
High	Total body irradiation	Prophylaxis with a 5-HT_3-RA + DEX	High/high (for the addition of DEX: moderate/high)	II/B (for the addition of DEX: III/C)
Moderate	Upper abdomen, craniospinal	Prophylaxis with a 5-HT_3-RA + optional DEX	High/high (for the addition of DEX: moderate/high)	II/A (for the addition of DEX: II/B)
Low	Cranium	Prophylaxis or rescue with DEX	Low/high	IV/D
	Head and neck, thorax region, pelvis	Prophylaxis or rescue with DEX, a dopamine RA or a 5-HT_3-RA	Low/high	IV/D
Minimal	Extremities, breast	Rescue with DEX, a dopamine receptor antagonist or a 5-HT_3-RA	Low/high	IV/D
Concomitant CRT	In patients undergoing concomitant CRT, the antiemetic prophylaxis should be according to the guidelines for CINV for the used chemotherapy. However, in case the emetic risk of RT is higher than that of the concomitant CT, then the risk level of RT has to be chosen to tailor the antiemetic treatment		Low/high	IV/D

5-HT_3-RA, 5-HT_3-receptor antagonist; CINV, chemotherapy-induced nausea and vomiting; CT, chemotherapy; CRT, chemoradiotherapy; DEX, dexamethasone; RT, radiotherapy.

Mucositis (ESMO 2015)

mucositis - gyulladásos és/vagy ulceratív léziók a szájüregben, a GI traktusban bárhol. Fő okok: kemoterápia, fej-nyaki besugárzás. Egyéb okok: infekció, immunhiány.

oral mucositis - kemoterápiás szerek, sugárterápia okozza. Típusos manifesztáció: erythema, ulceratio. Lokalis faktorok felerősíthetik: infekció, trauma
"alimentary tract mucositis" - szájüregtől az anusig
(pl. *cyclophosphamid, doxorubicin, vincristin, etoposide, ifosfamide, methotrexate, docetaxel, paclitaxel, cisplatin, carboplatin, oxaliplatin, irinotecan, 5-FU, leucovorin, vinorelbine)*

stomatitis - szájüregi szövetek gyulladásos állapota. **NEM** kemoterápiás szerek, vagy ionizáló sugárzás okozzák !!! Jellemző a szájüregi funkciók zavara: izérzés változása, megszűnése, szájüregi érzékenység, fájdalom (erre utaló lézió nélkül), xerostomia. célzott terápiás szerkere jellemző, pl: bevacizumab, erlotinib, sorafenib, sunitinib, gefitinib, lapatinib.

mIAS - mTOR inhibitor-associated stomatitis -

oral mucositis, dirrhoae grading

WHO scale for oral mucositis

Grade 0 = no oral mucositis
Grade 1 = erythema and soreness
Grade 2 = ulcers, able to eat solids
Grade 3 = ulcers, requires liquid diet (due to mucositis)
Grade 4 = ulcers, alimentation not possible (due to mucositis)

National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [26]

The definition used for this grading is 'A disorder characterised by inflammation of the oral mucosal [sic: "mucosa"]'.

Grade 1 = asymptomatic or mild symptoms; intervention not indicated
Grade 2 = moderate pain; not interfering with oral intake; modified diet indicated
Grade 3 = severe pain; interfering with oral intake
Grade 4 = life-threatening consequences; urgent intervention indicated
Grade 5 = death

diarrhoea

Definition: A disorder characterised by frequent and watery bowel movements

NCI-CTCAE version 4.03 [26].

Grade 1 = increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline
Grade 2 = increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline
Grade 3 = increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared with baseline; limiting self-care activities of daily living (ADL)
Grade 4 = life-threatening consequences; urgent intervention indicated
Grade 5 = death

Szájápolás

Table 1. Example of a Basic Oral Care Protocol (expert opinion)

Two key strategies for mitigation of oral mucosal injury before and during treatment are

- Maintenance of optimal nutritional support throughout the entire period of cancer therapy.
- Developing a daily oral hygiene routine, including brushing teeth and the gums four times a day with a soft brush and using mouth rinses. This approach can contribute to the reduction and, ideally, prevention of oral tissue injury and associated pain, nutritional compromise, and related adverse outcomes.

The following information is presented as a portfolio of patient-based instructions for which health professional guidance is recommended

General measures	• Inspect your oral mucosa daily. • Have your dental team eliminate sources of trauma (e.g. ill-fitting prostheses; fractured teeth). • Lubricate lips with (sterile) vaseline/white paraffin (petrolatum), lip balm, or lip cream. Be aware that vaseline/white paraffin (petrolatum) should not be used chronically on the lips, as this promotes mucosal cell dehydration and is occlusive leading to risk of secondary infection. • Drink ample amount of fluids to keep the mouth moist.
Brushing teeth and gums	• Use a soft toothbrush or swab (as tolerated) after meals and before sleep. Brushing with a soft toothbrush reduces risk of bleeding. Each month you should utilise a new soft toothbrush. • Clean the dentition and gingiva with a mild fluoride-containing, non-foaming toothpaste. • Brush teeth twice a day (after meals and at bedtime) according to the Bass or modified Bass method. If using an electric toothbrush, utilise the techniques cited in the product description instead. • Rinse the brush thoroughly after use with water and store the toothbrush in a cup with the brush head facing upward. • If you are used to do so, clean the area between the teeth once a day. Consult a dental hygienist/dentist about the most appropriate interdental cleaner (floss, toothpick, brushes). In case you are not used to use interdental cleaners on a regular base, do not start with it while on cancer therapy, since it can break the epithelial barrier, visible through gingival bleeding.
Rinse mouth	• Rinse mouth with an alcohol-free mouthwash upon awakening and at least four times a day after brushing, for ~1 min with 15 ml mouthwash; gargle; and then spit out. During the first half hour after rinsing, avoid eating and drinking.
Denture care	• Remove dentures before performing oral care. Brush dentures with toothpaste and rinse with water; clean the gums. • Defer wearing dental prostheses as much as possible until the lining tissues of your mouth are healed. If in the hospital, soak the denture for 10 min in an antimicrobial solution (e.g. chlorhexidine 0.2% if available) before inserting in your mouth.
Avoid painful stimuli	• Smoking • Alcohol • Certain foods such as tomatoes, citrus fruits, hot drinks and spicy, hot, raw, or crusty foods.

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Table 2. MASCC/ISOO Clinical Practice Guidelines for Oral and Gastrointestinal Mucositis [3] [(level of evidence for each recommendation is in brackets following the recommendation statement)]

Oral mucositis

RECOMMENDATIONS **IN FAVOR** OF AN INTERVENTION (i.e. strong evidence supports effectiveness in the treatment setting listed)

1) The panel *recommends* that 30 min of oral cryotherapy be used to *prevent* oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy (II).
2) The panel *recommends* that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to *prevent* oral mucositis (at a dose of 60 μg/kg per day for 3 days before conditioning treatment and for 3 days after transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy (II).
3) The panel *recommends* that low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2), be used to *prevent* oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy, with or without total body irradiation (II).
4) The panel *recommends* that patient-controlled analgesia with morphine be used to *treat* pain due to oral mucositis in patients undergoing HSCT (II).
5) The panel *recommends* that benzydamine mouthwash be used to *prevent* oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).

SUGGESTIONS **IN FAVOR** OF AN INTERVENTION (i.e. weaker evidence supports effectiveness in the treatment setting listed)

1) The panel *suggests* that oral care protocols be used to *prevent* oral mucositis in all age groups and across all cancer treatment modalities (III).
2) The panel *suggests* that oral cryotherapy be used to *prevent* oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT (III).
3) The panel *suggests* that low-level laser therapy (wavelength ~632.8 nm) be used to *prevent* oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer (III).
4) The panel *suggests* that transdermal fentanyl may be effective to *treat* pain due to oral mucositis in patients receiving conventional or high-dose chemotherapy, with or without total body irradiation (III).
5) The panel *suggests* that 0.2% morphine mouthwash may be effective to *treat* pain due to oral mucositis in patients receiving chemoradiation therapy for head and neck cancer (III).
6) The panel *suggests* that 0.5% doxepin mouthwash may be effective to *treat* pain due to oral mucositis (IV).
7) The panel *suggests* that systemic zinc supplements administered orally may be of benefit to *prevent* oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (III).

RECOMMENDATIONS **AGAINST** AN INTERVENTION (i.e. strong evidence indicates lack of effectiveness in the treatment setting listed)

1) The panel *recommends* that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (II).
2) The panel *recommends* that iseganan antimicrobial mouthwash *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II), or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer (II).
3) The panel *recommends* that sucralfate mouthwash *not* be used to *prevent* oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for head and neck cancer.
4) The panel *recommends* that sucralfate mouthwash *not* be used to *treat* oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (II) for head and neck cancer.
5) The panel *recommends* that intravenous glutamine *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).

SUGGESTIONS **AGAINST** AN INTERVENTION (i.e. weaker evidence indicates lack of effectiveness in the treatment setting listed)

1) The panel *suggests* that chlorhexidine mouthwash *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (III).
2) The panel *suggests* that granulocyte–macrophage colony-stimulating factor (GM-CSF) mouthwash *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (II).
3) The panel *suggests* that misoprostol mouthwash *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (III).
4) The panel *suggests* that systemic pentoxifylline, administered orally, *not* be used to *prevent* oral mucositis in patients undergoing bone marrow transplantation (III).
5) The panel *suggests* that systemic pilocarpine, administered orally, *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (III), or in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).

Gastrointestinal Mucositis (not including the oral cavity)

RECOMMENDATIONS **IN FAVOR** OF AN INTERVENTION (i.e. strong evidence supports effectiveness in the treatment setting listed)

1) The panel *recommends* that i.v. amifostine be used, at a dose of ≥340 mg/m^2, to *prevent* radiation proctitis in patients receiving radiation therapy (II).
2) The panel *recommends* that octreotide, at a dose of ≥100 μg s.c. twice daily, be used to *treat* diarrhea induced by standard- or high-dose chemotherapy associated with HSCT, if loperamide is ineffective (II).

SUGGESTIONS **IN FAVOR** OF AN INTERVENTION (i.e. weaker evidence supports effectiveness in the treatment setting listed)

1) The panel *suggests* that i.v. amifostine be used to *prevent* esophagitis induced by concomitant chemotherapy and radiation therapy in patients with non-small-cell lung carcinoma (III).
2) The panel *suggests* that sucralfate enemas be used to *treat* chronic radiation-induced proctitis in patients with rectal bleeding (III).
3) The panel *suggests* that systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to *prevent* radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (II).
4) The panel *suggests* that probiotics containing *Lactobacillus* species be used to *prevent* diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (III).
5) The panel *suggests* that hyperbaric oxygen be used to *treat* radiation-induced proctitis in patients receiving radiation therapy for a solid tumor (IV).

RECOMMENDATIONS **AGAINST** AN INTERVENTION (i.e. strong evidence indicates lack of effectiveness in the treatment setting listed)

1) The panel *recommends* that systemic sucralfate, administered orally, *not* be used to *treat* gastrointestinal mucositis in patients receiving radiation therapy for a solid tumor (I).
2) The panel *recommends* that 5-acetyl salicylic acid (ASA), and the related compounds mesalazine and olsalazine, administered orally, *not* be used to *prevent* acute radiation-induced diarrhea in patients receiving radiation therapy for a pelvic malignancy (I).
3) The panel *recommends* that misoprostol suppositories *not* be used to *prevent* acute radiation-induced proctitis in patients receiving radiation therapy for prostate cancer (I).

SUGGESTIONS **AGAINST** AN INTERVENTION (i.e. weaker evidence indicates lack of effectiveness in the treatment setting listed)

None.

Gy, grays; HSCT, hematopoietic stem cell transplantation; MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology.

HFS hand foot syndrome - palmar-plantar erythrodysesthesia (PPE)

PPE - dermatológiai toxicitás - tenyerek talpak (néha egyéb testfelszínek) erythemája és fájdalma. (más nevei: HFS, kemoterápia indukálta akralis erythema)

kéz és láb reakció: erythemával körülvett elszarusodás főleg nyomásnak kitett helyeken a tenyereken és talpakon.

Okok:

- mikrovaszkularis toxicitást okozó kemoterápia - capecitabine, pegilalt liposomalis doxorubicin, 5-FU, sorafenib, sunitinib, lapatinib, docetaxel, paclitaxel, etoposide

- társbetegségek - veseelégtelenség, beszűkült májfunkció, korábbi bőrbetegség (seborrhoeas dermatitis, actinic keratosis)

- egyéb: idős kor, melegebb testhőmérséklet (forró fürdő, láz, klíma), nyomásnak kitett testfelületek, fizikai munka, erős edzésmunka

HFS grade

- **Grade 1 -** minimalis erythema, oedema, keratosis - fájdalom nélkül
- **Grade 2** - hámlás, hólyagok, oedema, hyperkeraosis, fájdalom, mindennapi aktivitást limitálja (pl. bevásárlás)
- **Grade 3 -** mint Gr2 de súlyosabb, otthoni aktivitást is befolyásolja (mosakodás, öltözködés, táplálkozás, wc használat, gyógyszerek bevétele)

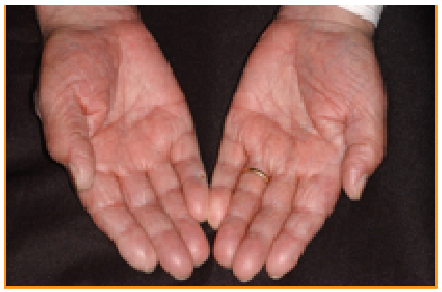
Grade 1 - nem sürgető ellátás - bőr higiénia, lágyító krémek, mechanikai stress kerülése, hő kerülése

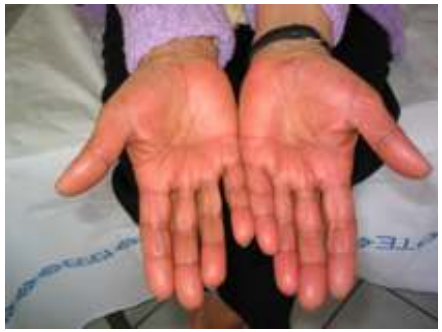
Grdae 2 - sürgős ellátás 24h-án belül - fájdalom: lokális szteroid, fájdalomcsillapító, jegelés. Sz.sz. antibiotikum. bőrinteritás sérülése esetén kötözés, hydrocolloid kötözés.

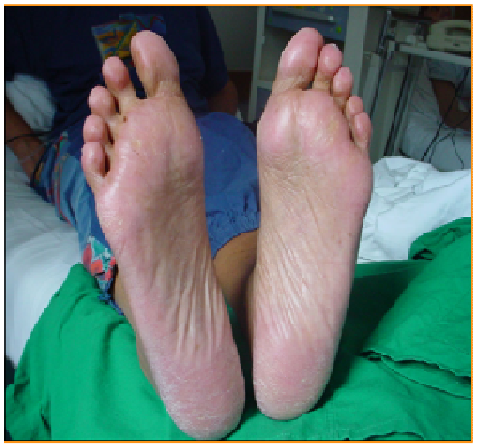
Grade 3 - sürgős, azonnali ellátás - hospitalizáció. fájdalomcsillapítás, lokális és iv. anti-infektív kezelés (antibiotikum, antifungalis, antiviralis kezelés). Perzisztáló vérzés esetén thrombocyta is szükséges lehet. Vitalis jelek monitorozása.

SE Radiológiai és Onkoterápiás Klinika saját képanyag archívumából

Grade 1







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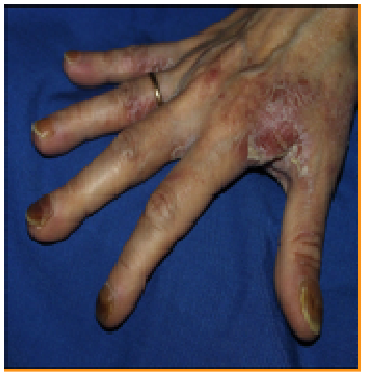

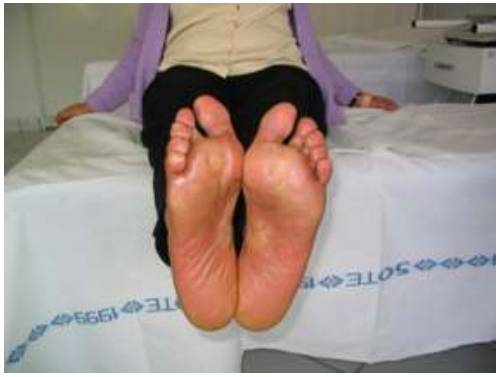

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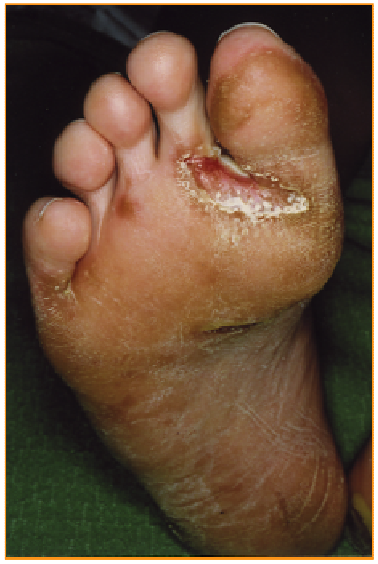
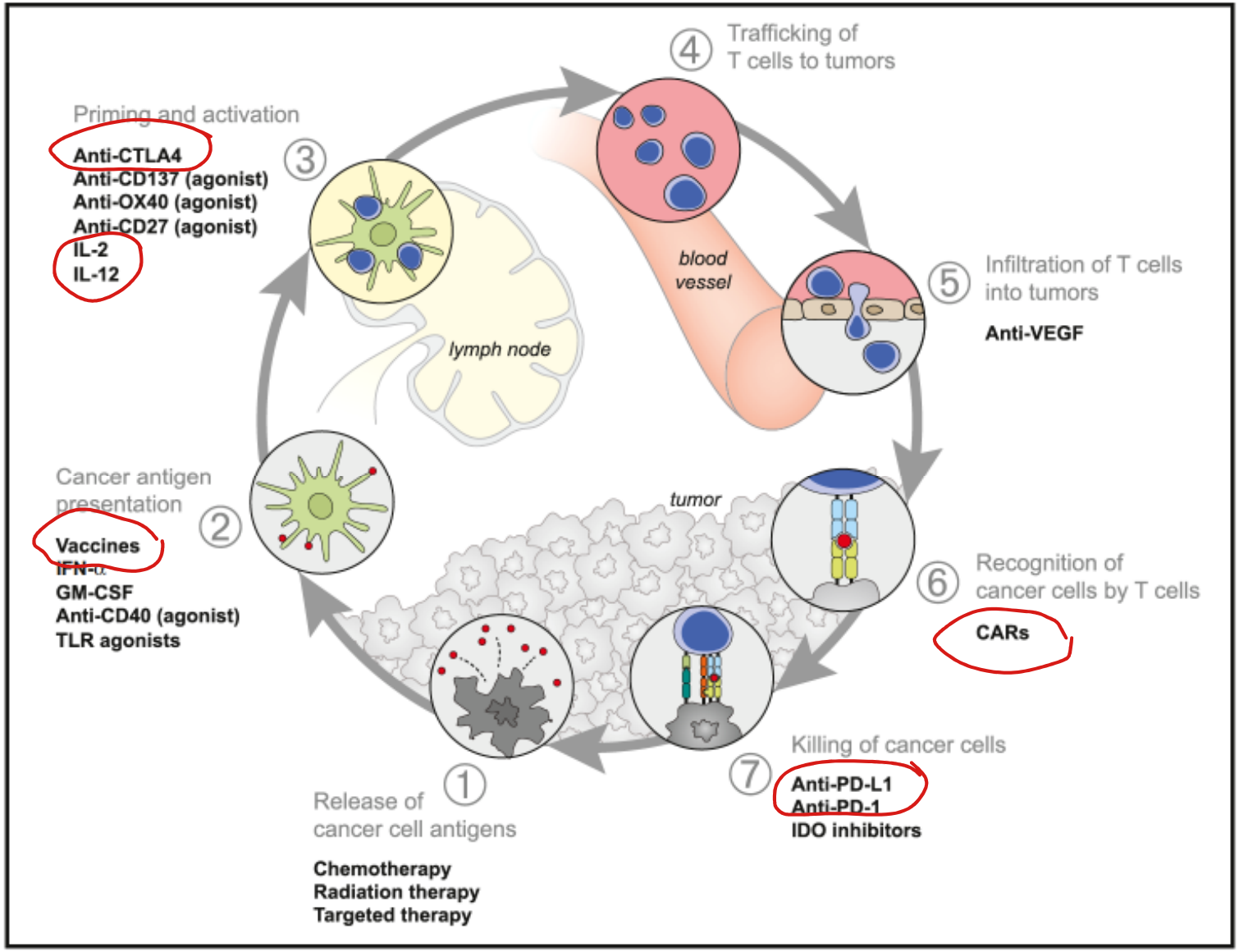


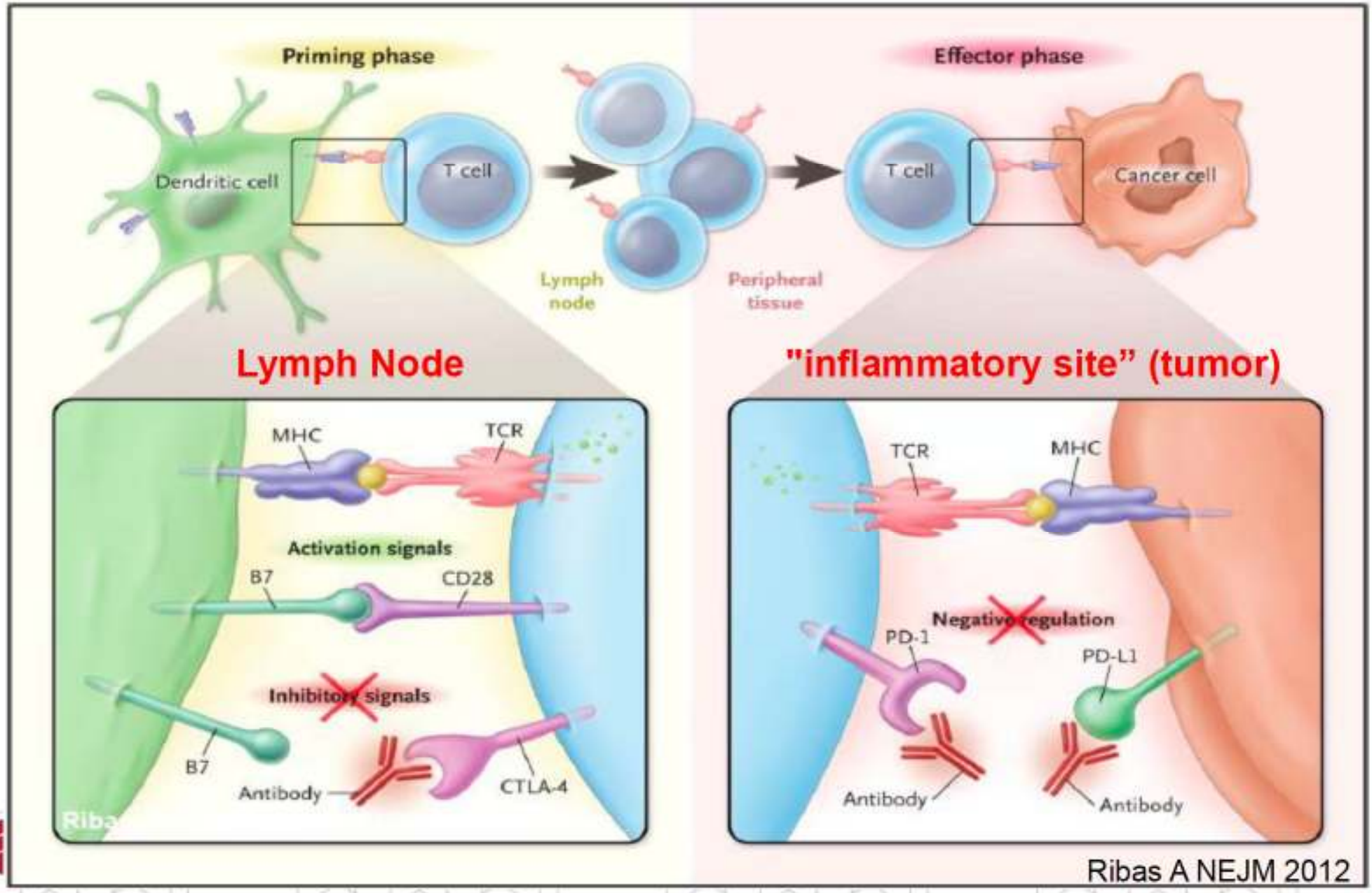
Immunterápiás lehetőségek

- Cytokine
- Vakcinák
- T sejt manipuláció
- Checkpoint inhibitors



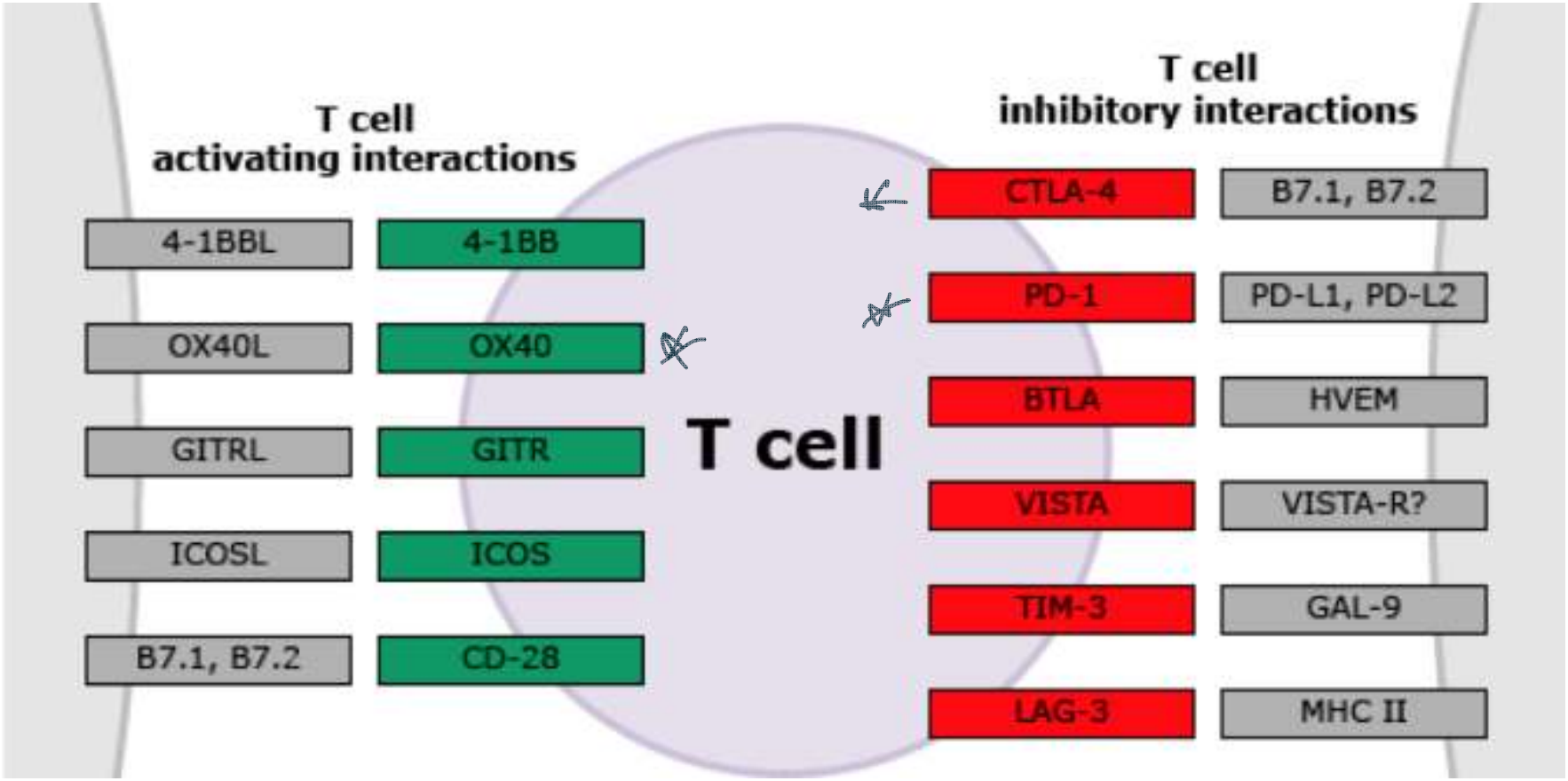
Immunity 2013, 39(1):1-10

Targeting CTLA-4 and PD-1 to release the brakes on T cells



Ribas A NEJM 2012

Costimuláció



2. TÁBLÁZAT. Európában és az USA-ban engedélyezett immunellenőrzőpont-gátlók

Gyógyszer	Hatásmechanizmus	FDA-engedély	FDA-indikáció	EMA-engedély	EMA-indikáció
Ipilimumab	anti-CTLA-4	2011	melanóma	2011	melanóma
Nivolumab	anti-PD-1	2014	melanóma, NSCLC, RCC, cHL, HNSCC, UCC	2015	melanóma, NSCLC, RCC, cHL, HNSCC
Pembrolizumab	anti-PD-1	2014	melanóma, NSCLC, HNSCC, cHL	2015	melanóma, NSCLC
Atezolizumab	anti-PD-L1	2016	UCC, NSCLC	-	-
Avelumab	anti-PD-L1	2017	MCC	-	-
Durvalumab	anti-PD-L1	2017	UCC	-	-

PD-1: programozott sejthalál fehérje 1; PD-L1: programozott sejthalál ligandum 1; CTLA-4: citotoxikus T-limfocita antigén 4; FDA: Food and Drug Administration; EMA: European Medicines Agency; RCC: vesesejtes rák; HNSCC: fej-nyaki laphámsejtes rák; NSCLC: nem kissejtes tüdőrák; cHL: klasszikus Hodgkin-limfóma; UCC: urotelsejtes rák; MCC: Merkel-sejtes karcinóma

ESMO 2017

Table 1. Approved indications for ICPis

Drug	Indications	EMA/FDA approval
Ipilimumab	Metastatic melanoma	EMA + FDA
	Adjuvant therapy stage III melanoma	FDA
Nivolumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC	EMA + FDA
	2nd line metastatic RCC	EMA + FDA
	Classical Hodgkin's disease[a]	EMA + FDA
	Recurrent or metastatic SCCHN[b]	EMA + FDA
	Locally advanced or metastatic UCC[c]	EMA + FDA
Pembrolizumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC (PD-L1 $\geq$ 1%)	EMA + FDA
	1st line metastatic NSCLC (PD-L1 $\geq$ 50%)	EMA + FDA
	1st line metastatic NSCLC in combination with pemetrexed + carboplatin	FDA
	Classical Hodgkin's disease	EMA[a] + FDA[d]
	Locally advanced or metastatic UCC[c]	FDA
	MSI-H or MMR deficient metastatic malignancies[e]	FDA
Atezolizumab	Locally advanced or metastatic UCC[c]	FDA
	2nd line metastatic NSCLC	FDA
Avelumab	Locally advanced or metastatic UCC[c]	FDA
	Metastatic Merkel cell carcinoma	FDA
Durvalumab	Locally advanced or metastatic UCC[c]	FDA
Ipilimumab + nivolumab	Metastatic melanoma	EMA + FDA

[a]For the treatment of patients with cHL who have relapsed or progressed after auto-HSCT and post-transplantation brentuximab vedotin. [b]For the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy. [c]For patients with locally advanced or metastatic UCC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. [d]For the treatment of adult and pediatric patients with cHL who are refractory or have relapsed after 3 or more lines of therapy. [e]For adult and paediatric patients with unresectable or metastatic, MSI-H or dMMR that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Auto-HSCT, autologous hematopoietic stem cell transplantation; cHL, classic Hodgkin's lymphoma; CRC, colorectal cancer; dMMR, deficient MMR; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICPi, immune checkpoint inhibitor; MMR, DNA mismatch repair; MSI-H, microsatellite instability-high; NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; UCC, urothelial carcinoma.

Immunterápia mellékhatásai

infúziós reakciók

immun related adverse effects (irAEs) - adverse effects of special interests (AEoSI)

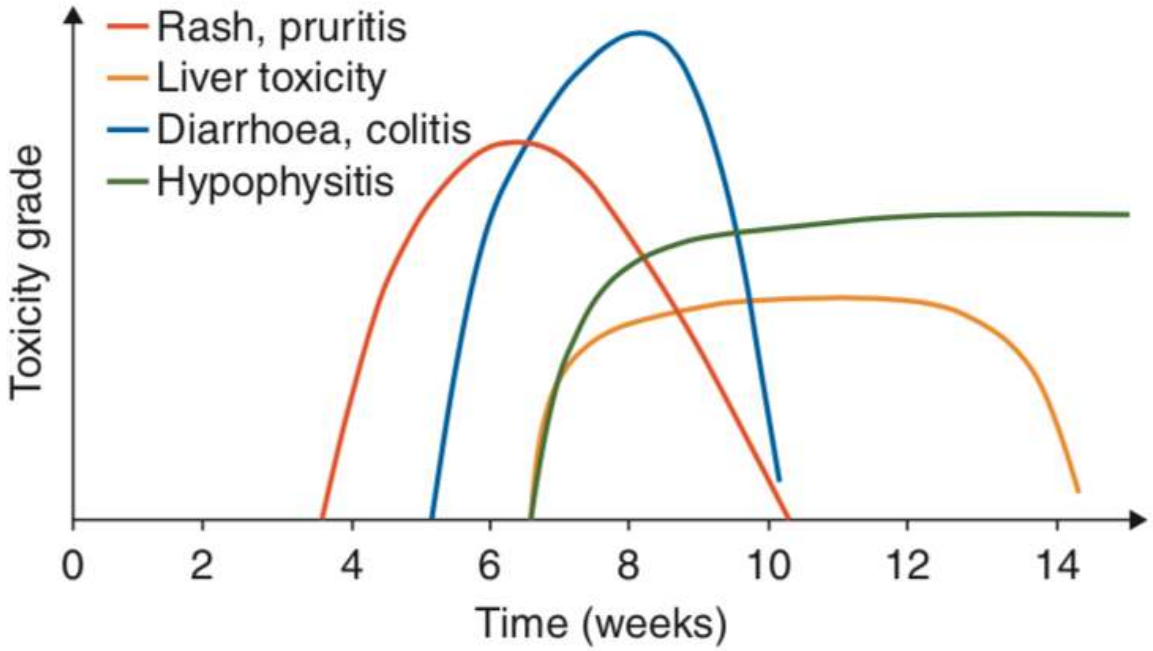


Figure 1. Timing of occurence of immune-related adverse events following ipilimumab treatment.

Immunellenőrző-pont-gátlók mellékhatásai

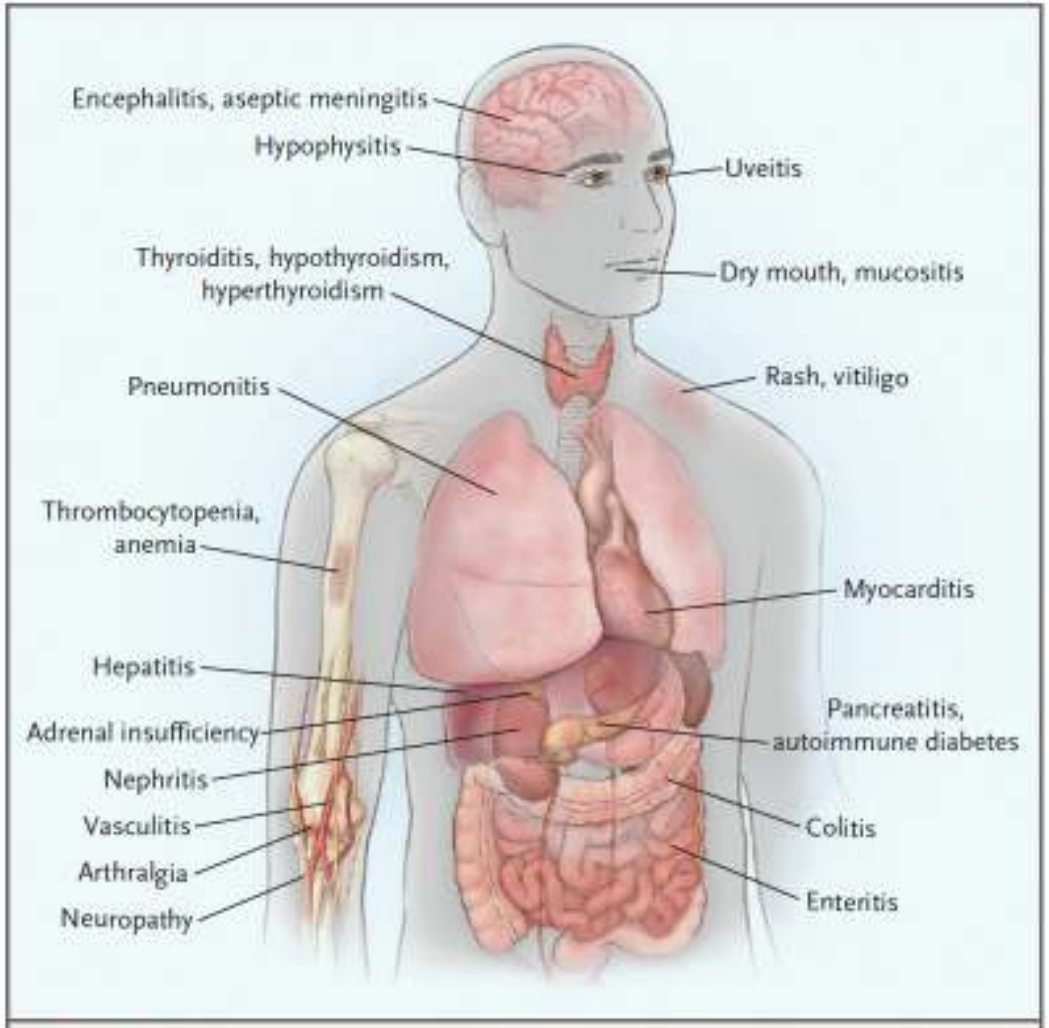


Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

Postow et al. 2018 NEJM 378,2

- pontos mechanismus nem ismert
- legjobb kezelés módja nem ismert. Immunszuppresszió.
- IRAE általában az első néhány hétben, hónapban jelentkeznek (de bármikor előfordulhatnak) a bőrtünetek jellenek meg elsőként
- ICI kezelés eredményessége nem függ a mellékhatások miatt alkalmazott immunszupressziótól
- Súlyos mellékhatások utan ICI kezelés újraindítható, rizikó a korábbi mellékhatással arányos
- Ha a kezdeti ICI-ra adopt terápiás válasz jó, de a kezelést mellékhatás miatt fel kell függeszteni, a terápiás válasz általában “perzisztál”.
- Mellékhatásra esélyes páciensek (pl. autoimmun betegségben szenvedők) esetében is várható terápiás eredméby ICI kezeléstől.

Chapman et al. MSKCC Letter to the Editor N Engl J Med 2015; 372:2073-2074

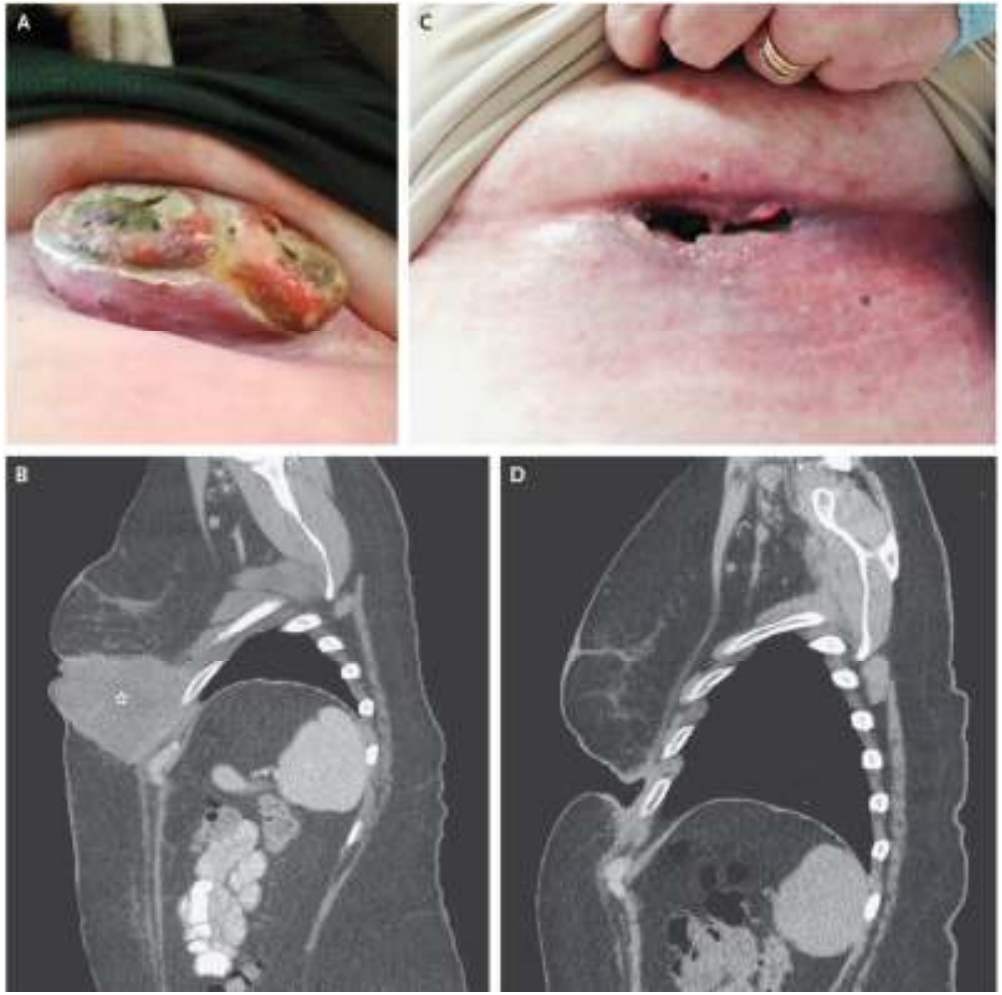
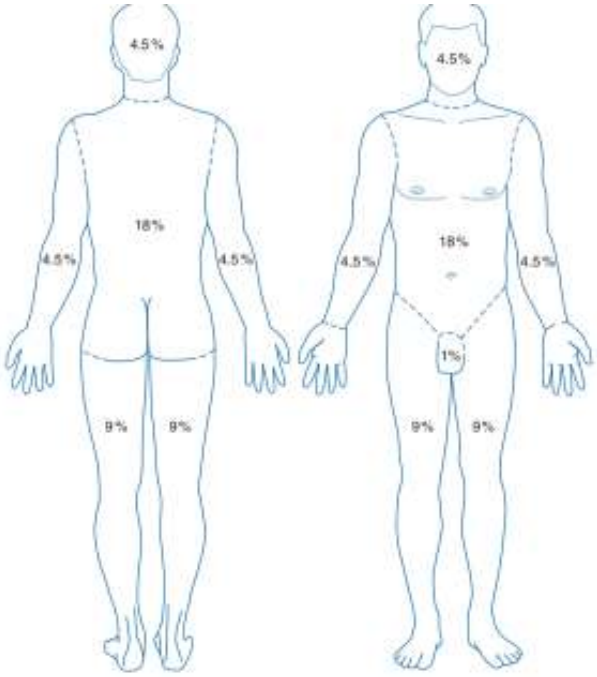


Figure 1. Response of a Large Chest-Wall Melanoma Metastasis to One Dose of Ipilimumab plus Nivolumab.

A pretreatment photograph (with the camera pointing upward from the patient's waist) (Panel A) and a pretreatment CT scan with soft-tissue windows (Panel B) show the chest-wall mass (asterisk). Three weeks after the first treatment, the tumor resolved, leaving a cavity (Panel C). Six weeks after the first treatment, a CT scan showed resolution of the chest-wall mass (Panel D).

gyakori mellékhatások

Immuntx okozta bőr mellékhatások - Ipi 43-45% PD-1 (nivo pembro) 34%
rash, pruritus, vitiligo (utóbbi melanomában, ott tx hatékonyságot is jelez)



- Grade 1 - macula/papula < 10% BSA , tünetmentes, tünetes (viszketés, égőérzés, feszülés)
- Grade 2 - " < 10-30 % BSA napi aktivítást némileg gátolja
- Grade 3 - " > 30% BSA tünetmentes/tünetes napi önellátást gátolja
- Grade 4 - papulopustular rash, életet veszélyeztető felülfertőződéssel (Steven-Johnson snydrome, toxikus epidermalis necrolysis, bullosus dermatitis) intezív osztályos kezelést igényel.

- gr 1-2 bőr AE esetében kezelés folytatható, lokalis ellátás: bőrpuhító krém, antihisztamin, lokalis szteroid.
- gr. 3 - kezelés felfüggesztése lokalis bőrlágyító, antihsiztamin, erős szteroidos krém
- gr.4 - kezelés leállítása, bőrgyógyász konzilium, azonnal iv. metilőrednizolon 1-2 mg/kg

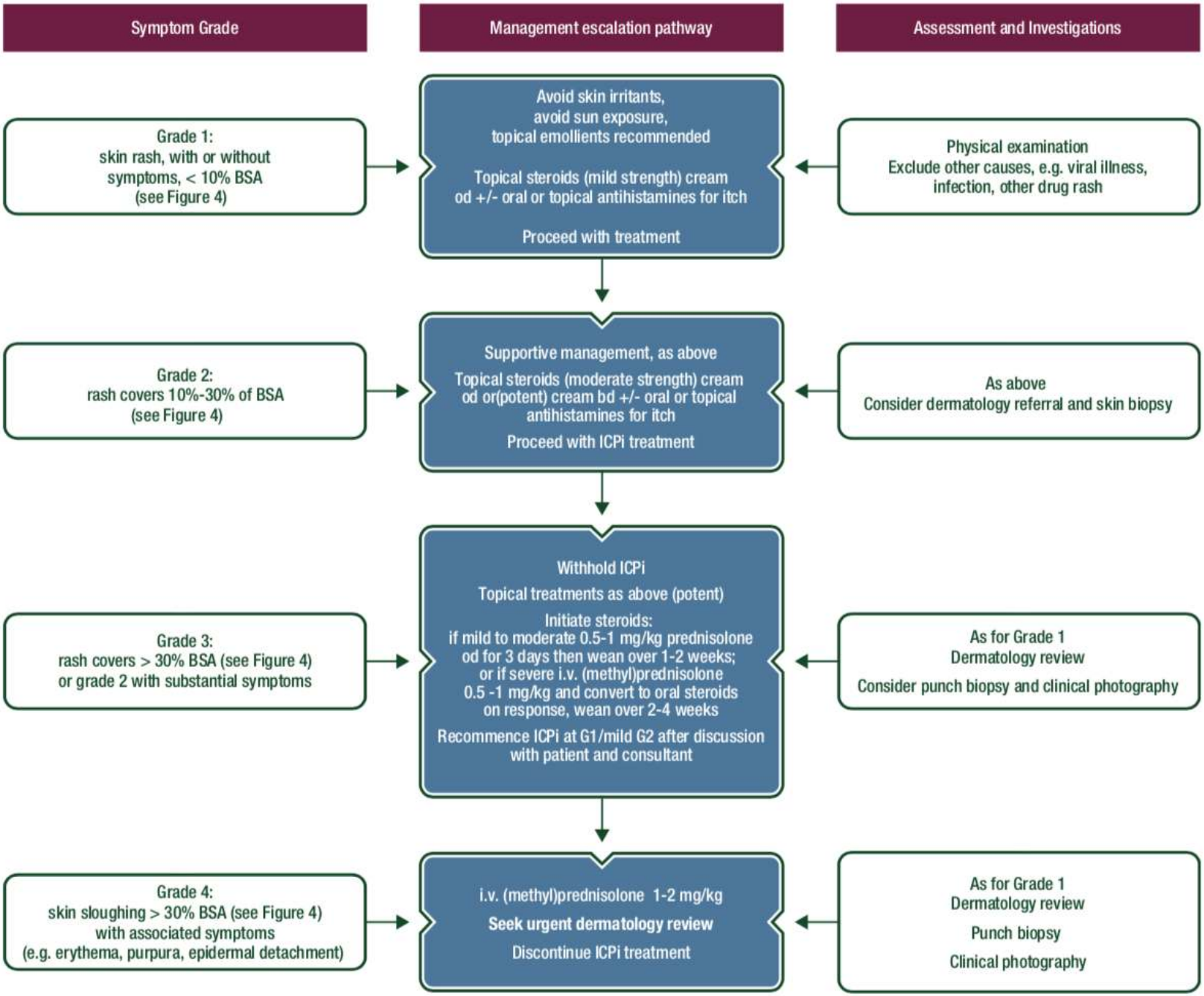


Figure 3. ICPi-related toxicity: management of skin rash/toxicity.

Recognised skin AEs include: (i) most common: erythema, maculopapular and pustulopapular rash; (ii) rare: toxic epidermal necrolysis, Steven-Johnson syndrome and DRESS; (iii) vasculitis may also be present with purpuric rash.

AE, adverse event; bd, twice daily; BSA, body surface area; DRESS, drug rash with eosinophilia and systemic symptoms; ICPi, immune checkpoint inhibitor; i.v., intravenous; od, once daily.

endocrinopathia

- Hyperthyreosis - ICPi kezelés megszakítása, beta-blokkoló, majd restart ICPi
- hypothyreosis HRT (L-thyroxin) indítása szükséges
- hypophysitis - fejfájás, diplopia, neurológiai tünetek - MR - metilprednizolon 1mg/kg per os, 2-4 hét alatt csökkentve vissza a dózist. Ha szükséges HRT (LT4, hydrocortisone, testosterone)
- I. DM - hospitalizáció.

hepatotoxicitás

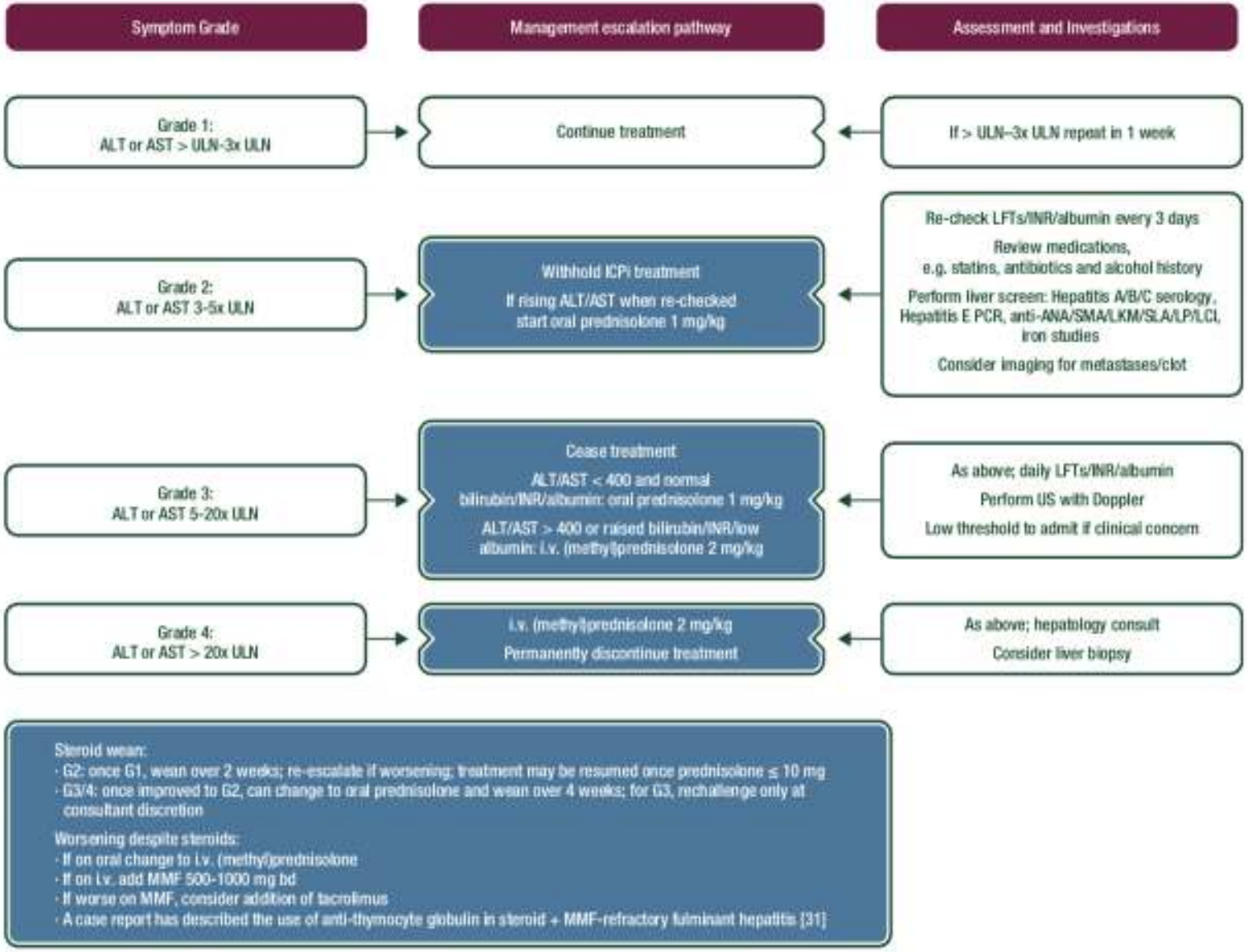


Figure 7. ICPi-related toxicity: management of hepatitis.

ALT, alanine transaminase; ANA, antinuclear antibodies; AST, aspartate transaminase; bd, twice daily; ICPi, immune checkpoint inhibitor; INR, international normalised ratio of prothrombin time; i.v. intravenous; LCI, lung clearance index; LFTs, liver function tests; LKM, liver kidney microsomal; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; SLA/LP, soluble liver antigen/liver-pancreas antibody; SMA, smooth muscle autoantibody; ULN, upper limit of normal; US, ultrasound.

Diarrhoae, colitis

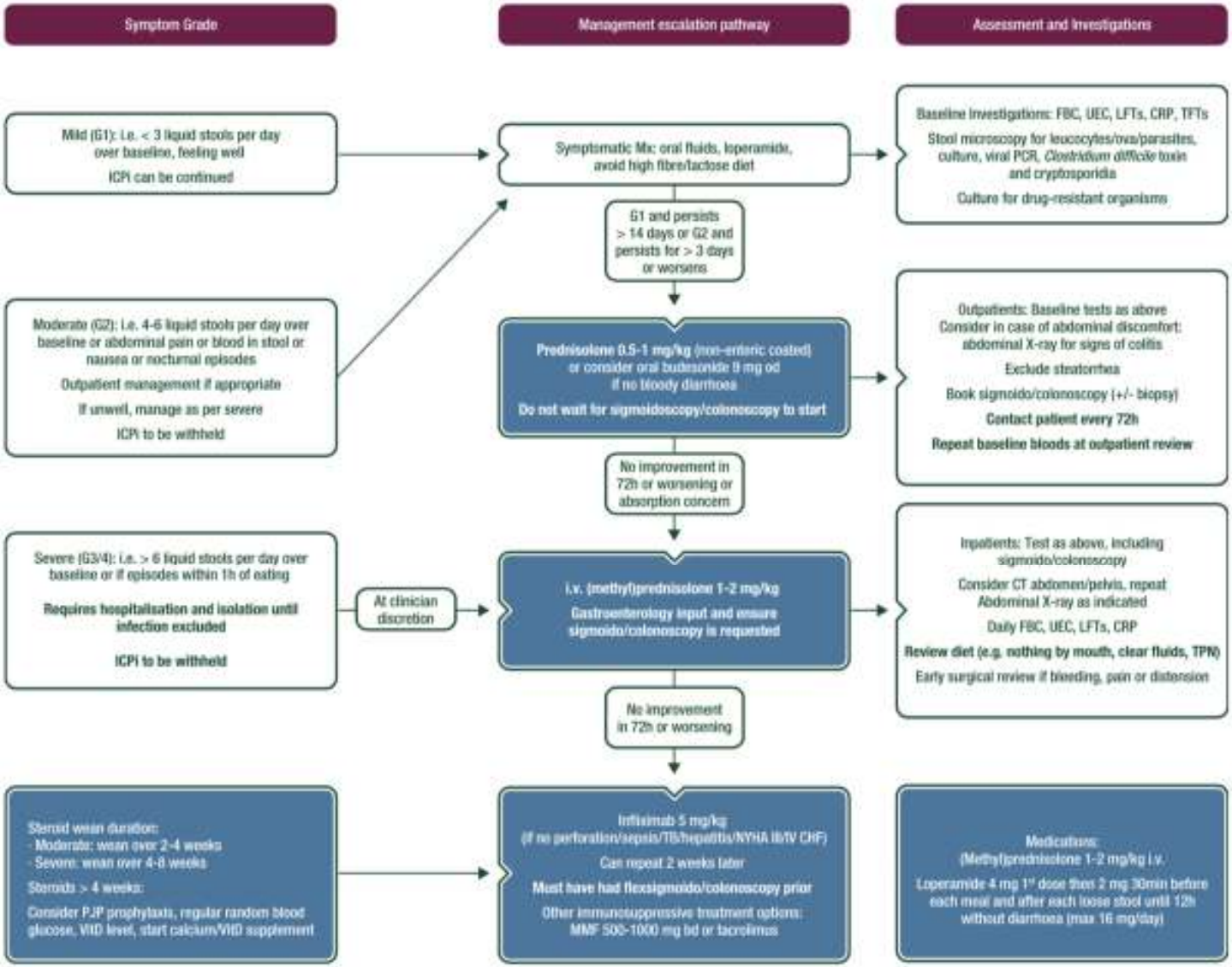


Figure 8. ICPi-related toxicity: management of diarrhoea and colitis.
bd, twice daily; CHF, congestive heart failure; CRP, C-reactive protein; CT, computed tomography; FBC, full blood count; ICPi, immune checkpoint inhibitor; i.v. intravenous; LFTs, liver function tests; MMF, mycophenolate mofetil; Mx, management; NYHA, New York Heart Association; od, once daily; PCR, polymerase chain reaction; PJP, Pneumocystis jiroveci pneumonia; TB, tuberculosis; TFTs, thyroid function tests; TPN, total parenteral nutrition; UEC, urea, electrolytes, creatinine; VitD, vitamin D.

pneumonitis

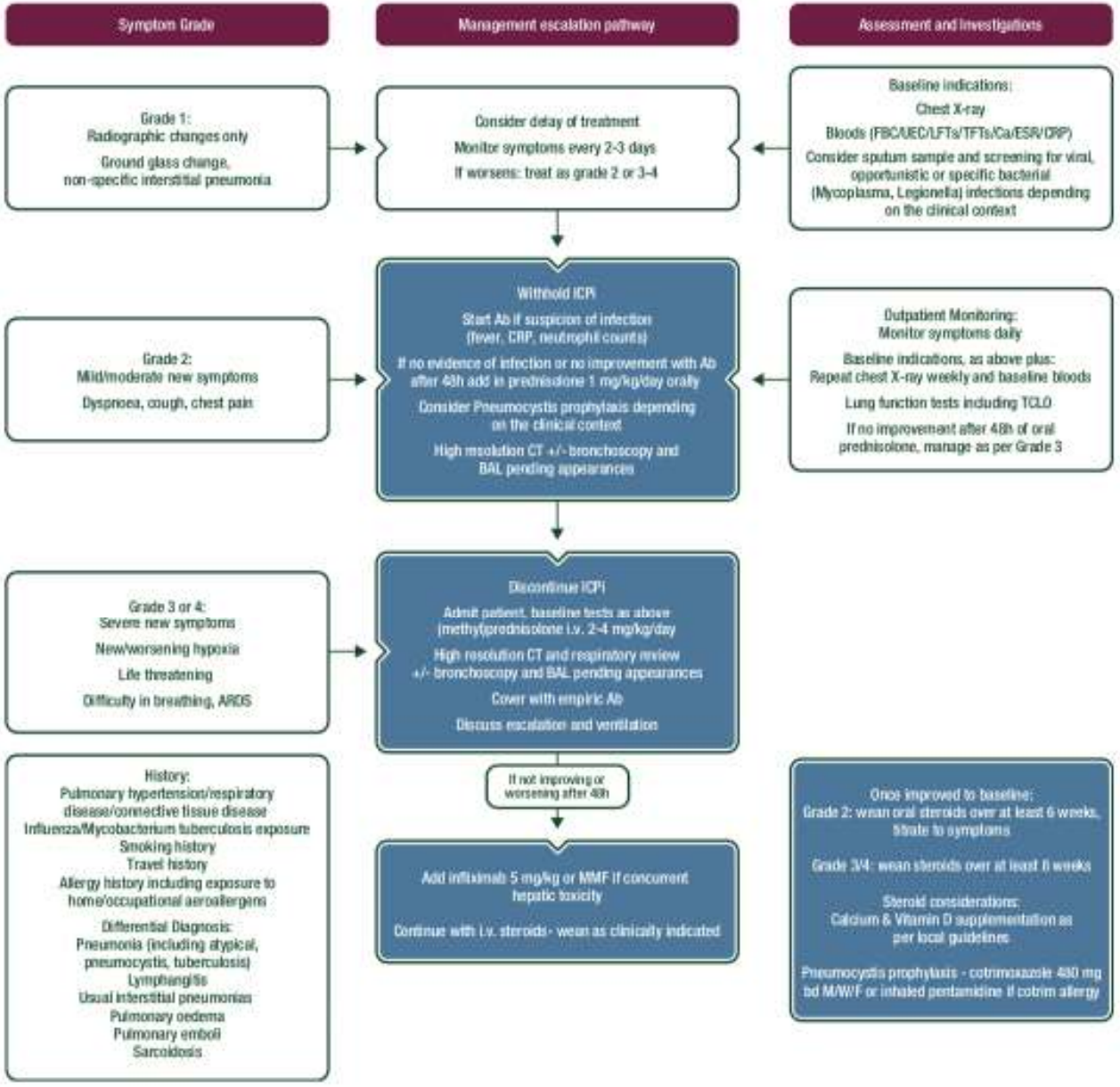


Figure 9. ICPi-related toxicity: management of pneumonitis.
Ab, antibody; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; bd M/W/F, twice daily Monday/Wednesday/Friday; Ca, calcium; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FBC, full blood count; ICPi, immune checkpoint inhibitor; i.v., intravenous; LFT, liver function tests; MMF, mycophenolate mofetil; TCLO, transfer factor for carbon monoxide; TFT, thyroid function tests; UEC, urea, electrolytes, creatinine.

Ritkább mellékhatások (1-2%)

- **Neurológiai toxicitás** - enyhe esetben kezelést szüneteltetni kell, diagnosztika: MR, liquor vizsgálat. Súlyosbodás esetén metilprednisolon 1-2 mg/tskg per os. v. iv. Guillan-Barre vagy myasthenia szerű tünetek esetében plasmapheresis megfontolandó.

- **Cardiotoxicitás -** myocarditis gyanúja esetében 1-2mg/tskg metilprednizolon, ha nem elegendő, akkor immunszuppresszív kezelés.

- **reumatológiai toxicitás -** enyhe arthralgia: NSAID, low dose steroid. Súlyos polyarthritis esetében perdnisone 1mg/tskg, szükség esetén infliximab vagy más TNF alfa gátló.

- **nephrotoxicitás -** nefritis esetén előbb egyéb okú veseelégtelenséget kell kizárni. Kezelést fel kell függeszteni. 1 mg/tskg metilprednizolon. Vesebiopsia is megfontolandó