

SUPPORTIVE CARE IN ONCOLOGY

Jiří Šedo, Radka Obermannová, Ondřej Sláma
Medical Oncology, Masaryk Memorial Cancer Institute

Understanding....

□ Anti-cancer Therapy

- Radiotherapy
- Chemotherapy, Targeted treatment
- Surgery
-

□ Supportive Therapy

- Management of cancer-related symptoms and complications
- Management of the anti-cancer therapy side effects

Case report

- Young man, student, born 1995
- Without comorbidities
- Diagnosed with Superior Vena Cava Syndrom
- autumn 2016

Superior Vena Cava Syndrom symptoms

- Oedema (swelling due to excess fluid) of the face and arms,
- Development of swollen collateral veins on the front of the chest wall,
- Shortness of breath,
- Difficulty of swallowing,
- Headache, stridor, epiglottitis, edema of the brain reported.

Diagnosis

- Metastatic high grade lung adenocarcinoma
- Molecular analysis- ALK positive tumor
- 3-5%, usually younger patients

Supportive treatment

- Superior Vena Cava Syndrom- LMWH, corticosteroids, fluids, radiotherapy
- antidepressants
- Jewett spinal brace
- Hypercalcaemia- bisphosphonates
- Pain - analgetics (fentanyl, NSAID)

Treatment trajectory

Traditional palliative care



Early palliative care



Side-effects of the Anti-cancer Therapy

- **Common side-effects**
 - Haematologic toxicity
 - Gastrointestinal toxicity
- **Specific side-effects**
 - Nephrotoxicity
 - Urotoxicity
 - Cardiotoxicity
 - Neurotoxicity
 - Pneumotoxicity
 - Skin toxicity

Adverse events of chemotherapy (Toxicity)

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Grading

Grade	0	1	2	3	4
		mild	moderate	severe	Very severe/ Life-threatening
Neutropenia	Granulocytes >2.0 x 10 ³	1.5 – 1.9	1.0 – 1.4	0.5 - 0.9	<0.5
Thrombocytopenia	WN Plt x 10 ³	75.0 - normal	50.0 – 74.9	25.0 – 49.5	<25
Anemia	WNL Hgb	10.0 - normal	8,0 – 10,0	6,5 – 7,9	<6.5
Vommiting	none	1 episode in 24 hours	2-5 episodes in 24 hours	2-5 episodes in 24 hours	>10 episodes in 24 hrs or parenteral support
Diarrhoea	none	increase of 2-3 stools/day	4-6 stools or nocturnal stools or moderate cramping	7 – 9 stools or incontinence or severe cramping	> 10 stools / day or grossly bloody diarrhea, or need of parenteral support
Sensoric Neuropathy	No or no change	Mild parethesias, loss of deep tendon reflexes	Mild or moderate objective sensory loss, moderate paresthesias	Severe objecitve sensory loss or paresthesias that interfere with function	

Case report

- V. M.
- 50 year old man treated for carcinoma of the urine bladder
- Underwent radical cystectomy, 8 out of 14 lymph nodes positive
- Undergoing adjuvant chemotherapy
- Coming to our office 10 days after second cycle of chemotherapy cisplatin/gemcitabine

V.M.

- Fatigue, weakness
- Temperatures of about 39°C with shivering yesterday
- Black stool
- Total loss of appetite, nausea, no vomiting

V.M.

- ▣ CBC:
 - Granulocytes: $0,3 \times 10^9/l$
 - Thrombocytes: $24,000 \times 10^6/l$
 - Hb: 8.2g/dl
- ▣ CRP: 130 mg/l
- ▣ Creatinine: 145 $\mu\text{mol/l}$
- ▣ Quick – INR: 1,35
- ▣ Summary:
 - ▣ Febrile neutropenia
 - ▣ Thrombocytopenia with internal bleeding
 - ▣ Impaired kidney function(nephrotoxicity, dehydration)

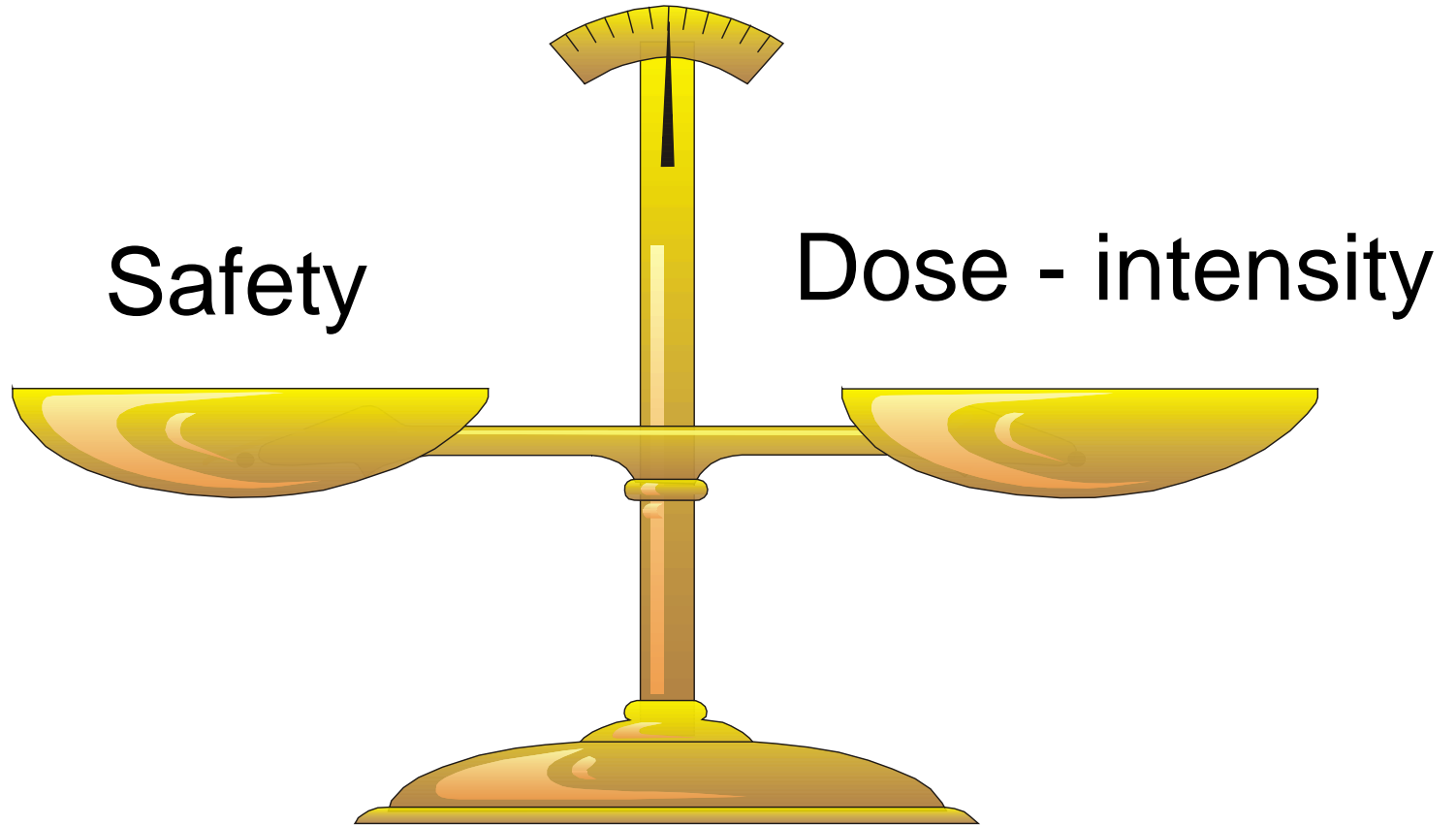
Grading

Grade	0	1	2	3	4
		mild	moderate	severe	Very severe/ Life-threatening
Neutropenia	Granulocytes >2.0 x 10 ³	1.5 – 1.9	1.0 – 1.4	0.5 - 0.9	<0.5
Thrombocytopenia	WN Plt x 10 ³	75.0 - normal	50.0 – 74.9	25.0 – 49.5	<25
Anemia	WNL Hgb	10.0 - normal	8,0 – 10,0	6,5 – 7,9	<6.5
Vommiting	none	1 episode in 24 hours	2-5 episodes in 24 hours	2-5 episodes in 24 hours	>10 episodes in 24 hrs or parenteral support
Diarrhoea	none	increase of 2-3 stools/day	4-6 stools or nocturnal stools or moderate cramping	7 – 9 stools or incontinence or severe cramping	> 10 stools / day or grossly bloody diarrhea, or need of parenteral support
Sensoric Neuropathy	No or no change	Mild parethesias, loss of deep tendon reflexes	Mild or moderate objective sensory loss, moderate paresthesias	Severe objecitve sensory loss or paresthesias that interfere with function	

Leukopenia/Neutropenia

- Most-significant and frequently limiting side effect of CHT
- Nearly always dose-dependent
- Nearly all conventional cytostatics can cause neutropenia – level depends on dose
- Maximal drop-off expect 7-10 days after initiation of the new cycle

Scales



Febrile neutropenia

- Definition:
 - ▣ 1x axillary temperature 38,3°C or 38°C lasting more than 1 hour
 - ▣ Neutropenia $< 0.5 \times 10^9/l$
or $< 1.0 \times 10^9/l$ and predicted decline
- Always serious condition
- High mortality especially among high-risk patients (14 - 36%)
 - ▣ **can be substantially decreased by appropriate management!**

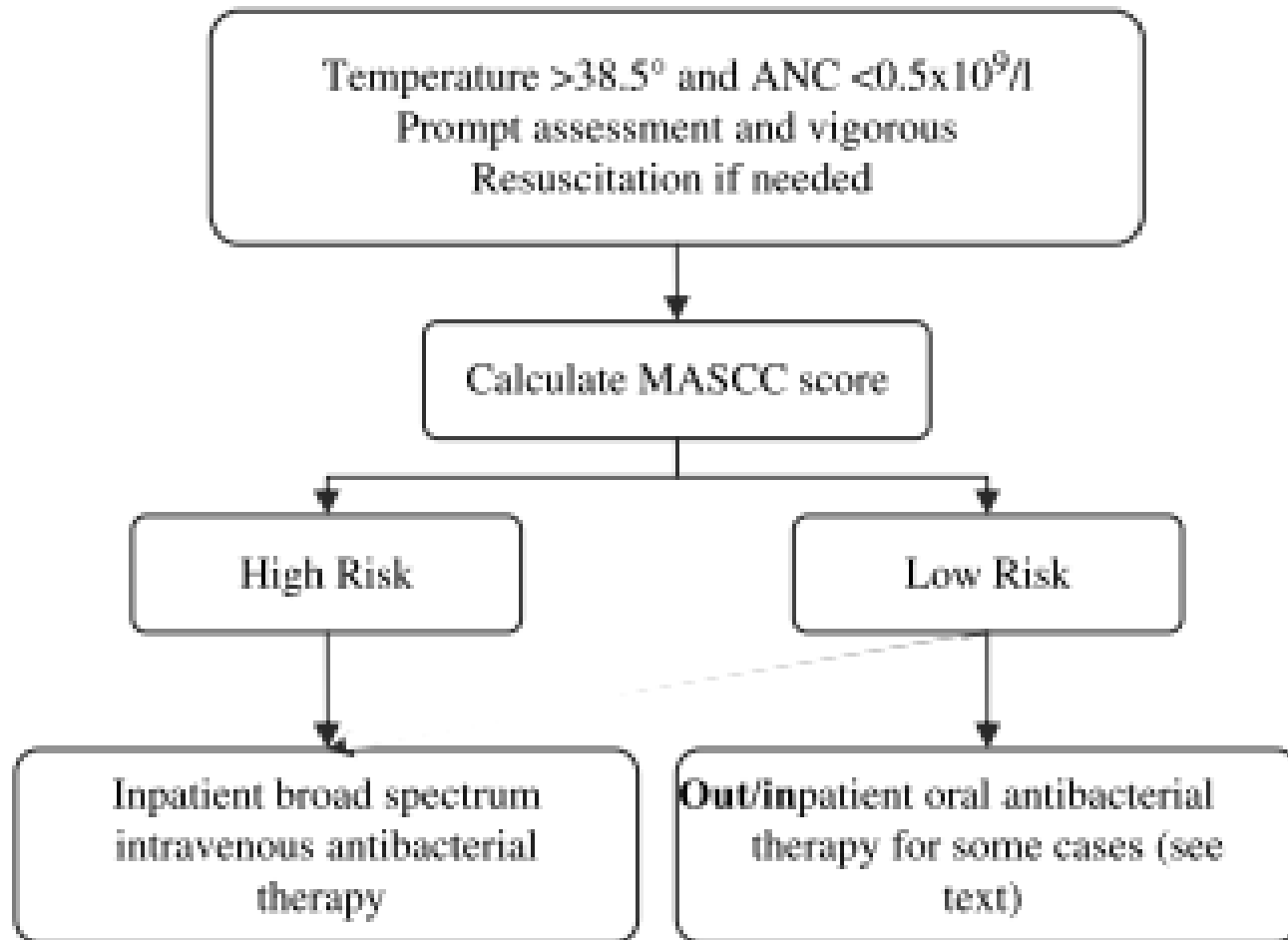
CAVE: corticosteroids can mitigate symptoms of infection

Febrile Neutropenia: Initial Examination

- PE
- CBC, basic chemistry, CRP, coagulation, urinalysis
 - ▣ Elective: Ig quantity, flow-cytometry
- Imaging:
 - ▣ Chest X-ray etc.
- Microbiology
 - ▣ Blood cultures 2x2
 - ▣ Urine
 - ▣ Elective: Catheters, stool, throat culture

Febrile Neutropenia

Stratification and ATB therapy



Febrile Neutropenia: Therapy

- ATB
 - ▣ Do not wait!
 - ▣ Use combinations of ATB!
- Isolation
- Vital functions monitoring
- If case of sepsis/SIRS
 - ▣ ICU monitoring
 - ▣ Consider G-CSF therapy
 - ▣ Specific recommendations for ATB therapy

G-CSF

- granulocyte colony-stimulating factor
- ***Filgrastim, ...***
 - ▣ Also available in PEGylated form
- ***Indications:***
 - ▣ *Prophylaxis of febrile neutropenia*
 - ▣ *Treatment of FN*

Thrombocytopenia

- One subgroup of myelotoxicity
- Risk of bleeding
- Which organs can be affected?
 - ▣ CAVE: brain meta, tumors in GI or GU tract!
- What is the only way of management?
 - ▣ **Thrombopoietic Growth Factors** – not effective, not available
 - ▣ Thrombocyte substitution – indications varies (donors + \$\$)
 - In case of bleeding and platelets bellow $20 \times 10^9/l$??
 - Platelets below $10 \times 10^9/l$ in asymptomatic patient?

Anaemia

- Usually not as a toxicity of chemotherapy
- Cancer patients:
 - Anaemia of chronic disease – redistribution of Fe accompanying malignancy itself
 - Post-hemorrhagic anaemia
 - bleeding tumors of GI and GU tract, ...
 - CAVE: thrombocytopenia
 - Other: deficiencies of B12, iron, folic acid, malnutrition, renal failure, chemotherapy

Management of anaemia

- Substitution of deficiencies if identified: folate, B12, Fe (not in case of redistribution!)
- **Blood transfusion**
 - + fast correction (1 item - increase approx. Hb 10 g/l)
 - general transfusion risks
- **Erythropoetin (EPO)**
 - Controversies persist
 - Slow increase in Hb per 10 g/l in 4 weeks

GASTRO-INTESTINAL TOXICITY

- Nausea and vomiting
- Diarrhea
- Mucosal toxicity (mucositis, malabsorption)

Nausea / vomiting . . .

□ Definition

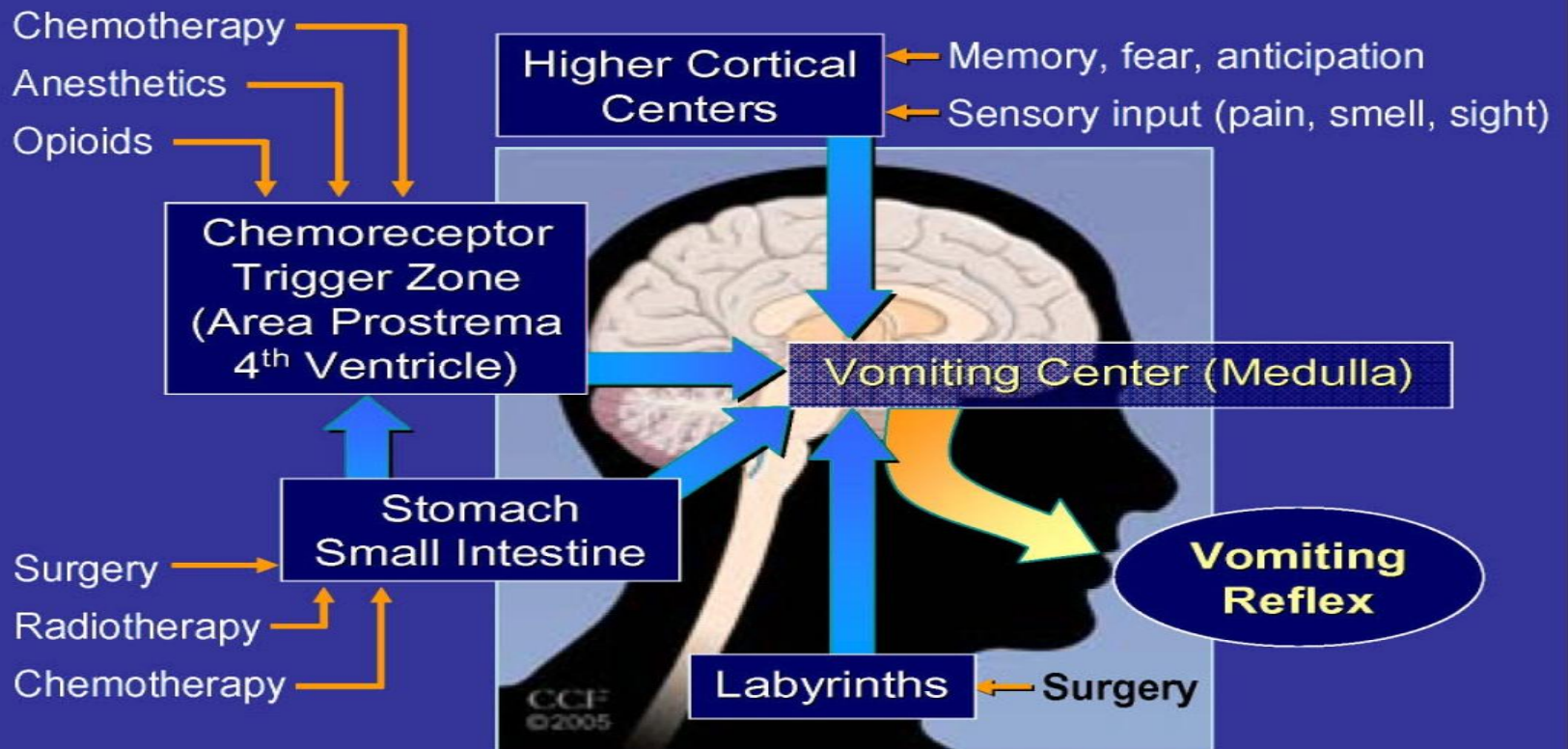
- Nausea is an unpleasant subjective sensation of being about to vomit.
- Vomiting is the reflex expulsion of gastric contents through the mouth

. . . Nausea / vomiting

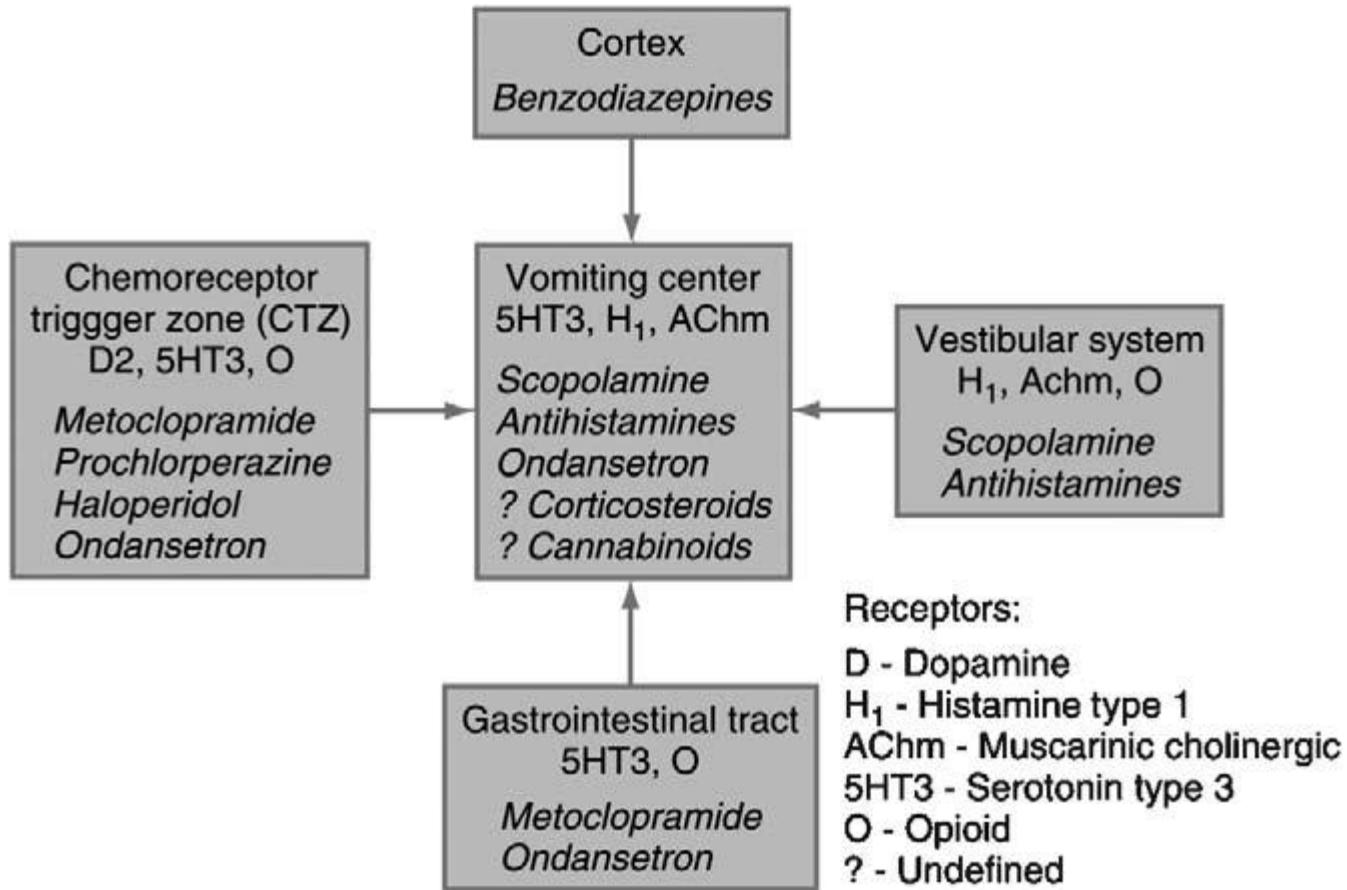
- Impact very distressing:
 - Awareness of nausea
 - Inability to keep food or fluids down ⇒ malnutrition, dehydration
 - Acid and bitter tastes
 - Unpleasant smells of vomitus

Pathophysiology

Pathways of Nausea & Vomiting



Pathophysiology



Case – D. J.

- 48 years old woman with metastatic lung cancer
- METS in both lungs, liver, adrenal glands, bones
- Without any signs of disease!
- Treated by chemotherapy cisplatin/etoposide
- What will you ask the patient ??

Assessment

- When?
- Intermittent or constant?
- Associated with sights or smells?
- Eating patterns?
- Bowel patterns?
- Medications?

Level of emetogenicity

Minimal (<10%)	Bleomycin Vinblastine Vincristine Methotrexate
Low (10-30%)	Capecitabine(Xeloda) Docetaxel Etoposide Gemcitabine Paclitaxel
Mild (30-60%)	Irinotecan Ifosfamide
Moderate (80-90%)	Carboplatin Doxorubicinn
High (>90%)	Carmustine Cisplatin Cyclophosphamide Dacarbazine

Stimulation of CTZ

□ anti-D2:

metoclopramide 10mg q8h

triethylperazine 6,5mg q8h

↑EPS (especially combination with AD)

haloperidol 0.5mg-1mg q6-12h

prochlorperazin(Compazine): 10mg q6-8h

□ anti 5-HT3:

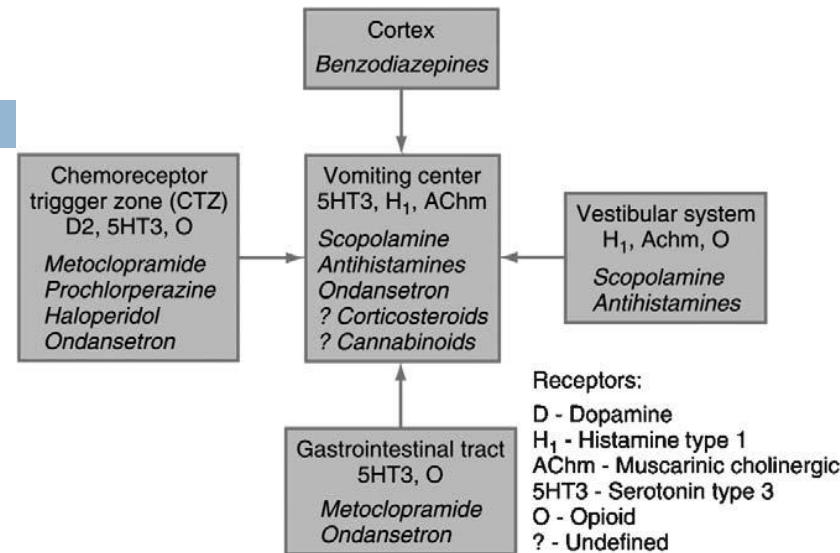
□ setrons:

■ *ondasetron* , *granisetron(Zofran)*: 8mg q8h

■ *palonosetron*,

□ next generation antipsychotics

■ *olanzapine* (Zyprexa)



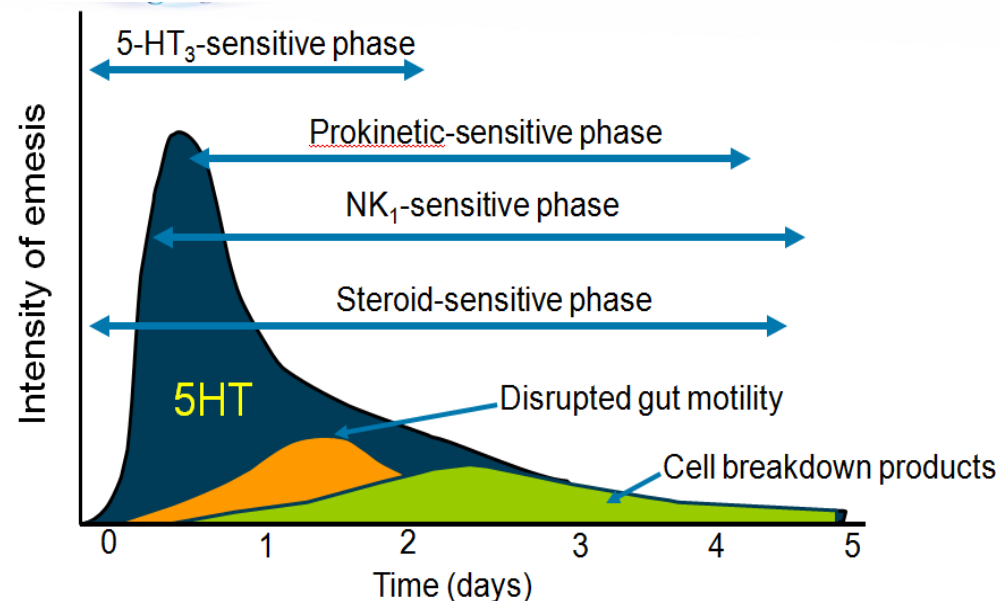
Chemotherapy induced nausea

- Neurokinin-1 antagonist
 - ▣ *Aprepitant , netupitant*
- Corticosteroids
 - ▣ *Dexamethasone 8mg i.v./p.o. daily*
- Anticipation nausea
 - ▣ Benzodiazepines:
 - alprazolam 0,25mg-0,5mg q8h*
 - bromazepam 1,5mg q8h*
- Other emetogenic drugs
 - Opioids, digoxin, antibiotics, iron supplementation

Chemotherapy-induced nausea

- Acute
 - <24 hours
 - Chemoreceptor trigger zone
 - Serotonin release in the gut

- Delayed
 - Unclear mechanism



D.J. management

□ Premedication:

- Dexamethasone 8mg i.v. 1-0-0 during CHT
- Netupitant/palonosetron 1x before CHT
- Olanzapine 5mg tbl. 1-0-0 during CHT

□ At home:

- Dexamethasone 4mg 1-0-0 for 3days
- Omeprazol 20mg 1-0-0
- PRN: Olanzapine 1x daily

If not working?

- Alprazolam 0,5mg tbl. before and during CT q8h – for anticipation nausea

A.S.

- 56 years old woman with breast cancer, multiple bone MTS
- Underwent 1st line chemotherapy last course 3weeks ago Effect: progression in bones
- 5 days ago started feeling nauseated, vomiting 3xD
- Headache
- Loss of consciousness – fall, injury
- **Comming to you**

A.S.

- She had a good appetite generally
- She used to throw up when she had finished her meal
- Now, she feels nauseated again - what medication should we use?

Dexamethasone 8mg /100ml saline i.v.
20minutes infusion q8h

+ ***Manitol*** 20% 200ml i.v. inf. Q8h

CT: multiple MTS in brain with collateral oedema

V.B.

- 60 years old man with carcinoma of the urether
- Resection of the right urether and nephrectomy
- Recurrence in retroperitoneal nodes and right pelvis
- Retroperitoneal lymph node dissection and resection of the tumor masses in right pelvis. - incidental transection of the right nervus obturatorius
- After surgery he suffered from pain deep in the right inguina which irradiated to his right limb.
- MRI 6/2010: mass 3x5cm in the right pelvis close to the the plexus sacroiliacus
- Already relatively high doses of opiates

V.B.

□ 8/2010

Patient coming to our office:

Total loss of appetite, losing weight,

Nausea not frequently

weak, sleeping whole day, constipation 4 days without stool,

What are the possible causes of nausea?

- Opioids
- Bowel obstruction, hypomotility, constipation

V.B.



Our medication:

haloperidol 1mg q8h

Mucosal toxicity and diarrhea

- **Oral mucositis**
- **Diarrhea**

Diarrhea

- ↑ frequency + ↓ consistency

Treatment:

- Rehydration, ion substitution
- Dietary changes, Management of intestinal dysmicrobia
- Total parenteral nutrition in severe cases
- ***Diosmecticum*** (Smecta)
- ***Loperamide*** and other derivatives active on opioid-receptors
- ***Octeotride*** (somatostatin analog)

Mucositis



Mucositis - management

- ↑ hygiene of oral cavity including oral antiseptics (*chlorhexidin*, local corticosteroids...)
- Diet changes
- Analgesics - orally preferred
- Realimentation (incl. parenteral nutrition)

Specific toxicity

- Nephrotoxicity
- Urotoxicity
- Cardiotoxicity
- Neurotoxicity
- Pneumotoxicity
- Skin toxicity

Nephrotoxicity

- Toxicity of cytostatics

Cisplatin most frequently (carboplatin or oxaliplatin **not**)

Prevention:

massive hydration + forced diuresis (Manitol)

- Hyperuricaemia as a part of ***tumor lysis syndrome***

Prevention:

- Hydratation
- Initial dose reduction
- **Rasburicase**
- Bicarbonate historically

Urotoxicity

- Hemorrhagic cystitis
 - ***Cyclophosphamide, Ifosfamide***
 - Prevention
 - adequate fluid intake
 - Mesna (assists to detoxify toxic metabolite *acrolein* by reaction of its sulfhydryl group)

Cardiotoxicity

- Cardiomyopathy

 - ***Anthracyclines***

 - Doxorubicin=adriamycin, Epirubicin*

 - use in breast cancer

 - CAVE: irreversible heart failure!!!

 - ***Targeted therapy***

 - Trastuzumab(Herceptin)* – in breast cancer

 - Usually reversible

- Dysrhythmias (anthracyclines, paclitaxel)

- Spasms of coronary arteries (5-fluorouracil)

Neurotoxicity

- Peripheral neuropathy
 - Paclitaxel, oxaliplatin,*
 - ▣ very frequent and often limiting toxicity
 - ▣ Symptoms:
 - Impaired sensitivity
 - Paresthesia
 - Neuropathic pain
 - ▣ Reversible/irreversible (cumulative dose principle)
 - ▣ Treatment – not very effective (antiepileptics)
- Bowel motility
 - Paralytic ileus

Pneumotoxicity

Bleomycin

- Character of
Pneumonitis/fibrosis/bronchospasms
- Prevention
 - ▣ Cumulative dose principle
 - ▣ Avoid in patients with pulmonary restriction or obstruction
 - ▣ Treatment very limited

Skin toxicity

- Alopecia
- Hand-and-foot syndrome by **5-fluorouracil**
- Specific skin changes after targeted therapy
 - ▣ Acne-like rash after **cetuximab** (colorectal, H&N)
 - ▣ Variable skin rash after **erlotinib** (NSCLC)
 - correlation between the severity of the skin reactions and increased survival
- Para-venous application of chemotherapeutics
 - ▣ necrosis after **doxorubicin**,
 - ▣ flebitis after **5-fluorouracil**

Hand-foot syndrom

sorafenib, sunitinib, capecitabin



EGFR antibodies, inhibitors



EGFR antibodies



EGFR antibodies

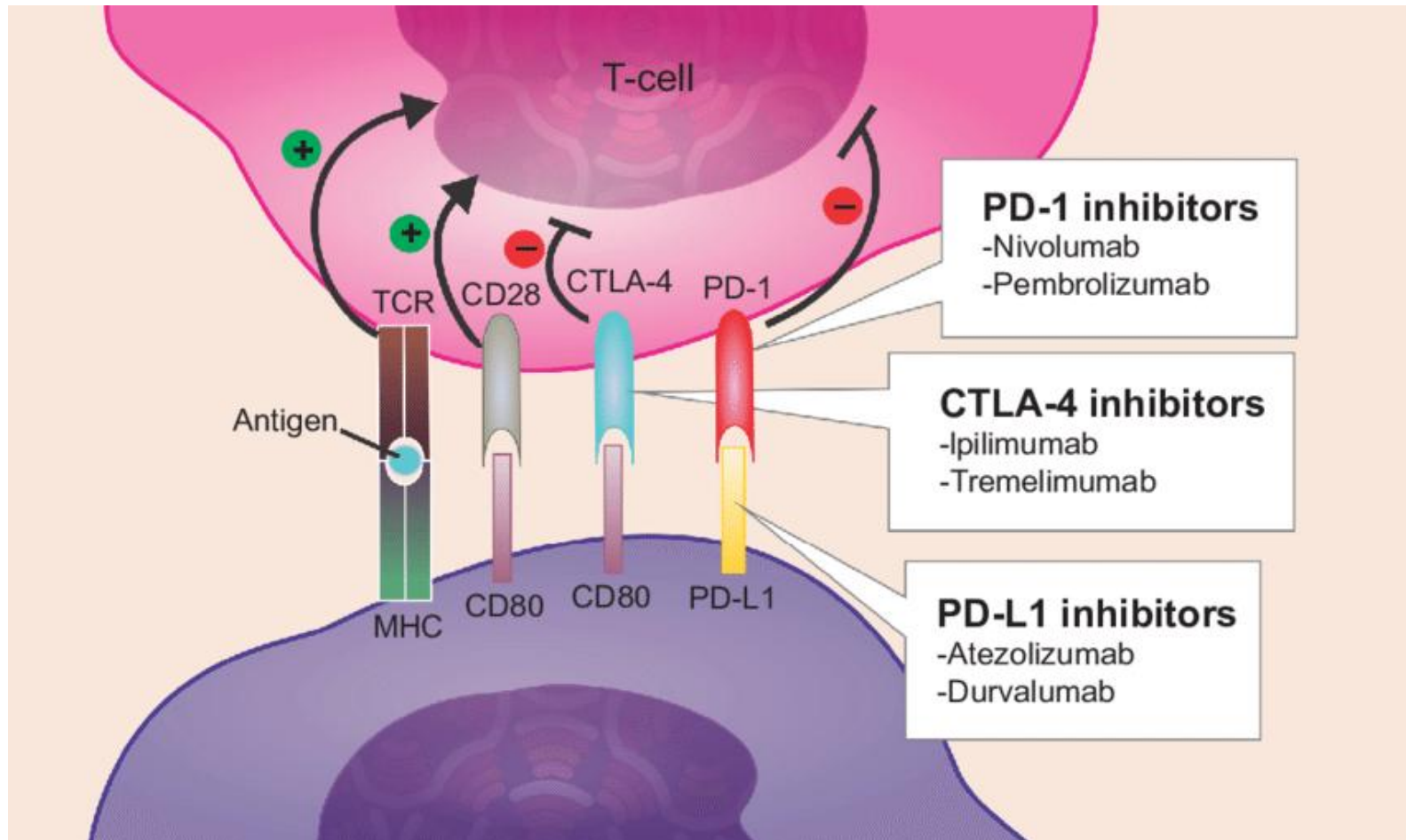


RTx and EGFR Ab



Side effects of Immunotherapy

Checkpoint inhibitors





Encephalopathy, aseptic meningitis, parasthesias, weakness

Hypophysitis



Sicca syndrome

Thyroiditis



Myocarditis

Pneumonitis



Diarrhea, colitis, perforation, megacolon



Lupus nephritis, acute interstitial nephritis



Hepatitis



Myositis



Vasculitis



Inflammatory arthritis

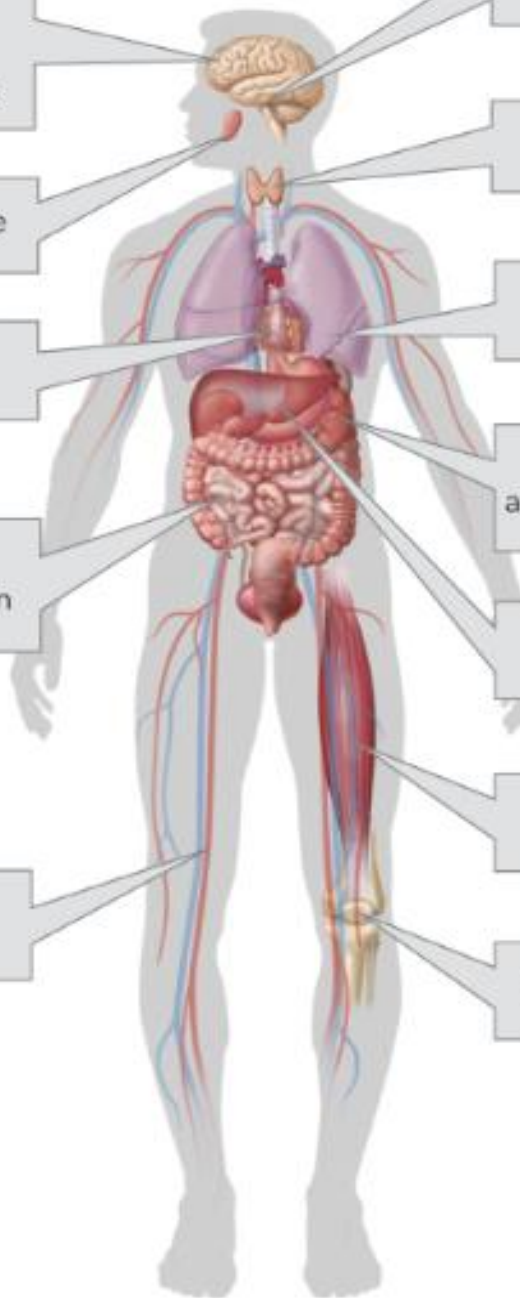


Table 2. Immune-Related Adverse Events Associated With Immune Checkpoint Blockade

Immune-Mediated Adverse Event	Symptoms	Management
Colitis	Diarrhea, abdominal pain, blood in stool	Antidiarrheal agents followed by systemic corticosteroids
Pneumonitis	Dyspnea, cough	Systemic corticosteroids
Hepatitis	ALT/AST, bilirubin elevation	Systemic corticosteroids; mycophenolate mofetil if refractory
Dermatitis	Pruritic/macular/papular rash, Stevens-Johnson syndrome (rare), toxic epidermal necrolysis (rare)	Topical betamethasone or oral antihistamines; systemic corticosteroids if refractory
Neuropathy	Sensory/motor neuropathy, Guillain-Barré syndrome (rare), myasthenia gravis	Systemic corticosteroids
Endocrinopathy	Hypo- or hyperthyroid, hypopituitarism, adrenal insufficiency, hypogonadism, Cushing syndrome (rare)	Systemic corticosteroids with appropriate hormone replacement (potentially long term)
Other irAEs	Arthritis, nephritis, meningitis, pericarditis, uveitis, anemia, neutropenia	Organ system specific

ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAEs, immune-related adverse events

Based on *Nat Rev Clin Oncol*. 2016;13(5):273-290.

Side effects of Immune Checkpoint inhibitors - management

Immune Checkpoint Inhibitors

clinicaloptions.com/oncology



CLINICAL CARE OPTIONS[®]
ONCOLOGY

Checkpoint Inhibition: Managing Grade 3/4 Treatment-Related AEs

Grade 3/4 pneumonitis, nephritis, enterocolitis, hepatitis, or infusion-related reaction

New or worsening neuropathy
Any life-threatening or grade 4 AE
Any severe or grade 3 recurrent AE

Initiate steroid therapy

If no improvement in colitis or pneumonitis, infliximab or mycophenolate[†]

Hepatitis associated with

- AST/ALT > 5 x ULN
- AST/ALT ≥ 50% ↑ from baseline lasting ≥ 1 wk*
- Total bilirubin > 3 x ULN

Permanently discontinue PD-1 tx

If no improvement in hepatitis, consider mycophenolate; infliximab contraindicated

Grade 4 elevation of pancreatic enzymes

Usually resolves with tx interruption[‡]

*In pts with liver metastasis who begin treatment with grade 2 elevation of AST/ALT.

[†]Pts receiving ipilimumab may tolerate treatment with PD-1/PD-L1 inhibitor alone.

[‡]Steroids do not appear to accelerate the rate of improvement.

Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide. Ipilimumab adverse reaction management guide.

Conclusions...

- Effective management of side effects of anti-cancer therapy is a key to success

Traditional palliative care



Early palliative care





- Thank you for your attention!