Aktuelle Therapieempfehlungen -Antiemese-

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Fragen von gestern

Dosierung Dexamethason

		Akute Phase	Verzögerte Phase
hoch	mit Apr	12 mg	8 mg
	ohne Apr	20 mg	8 mg
moderat		8 mg	8 mg
niedrig		8 mg	8 mg

Brauchen wir einen 5 HT_3 RA in der verzögerten Phase?

Moderat 30% - 90%	1. 5-HT_3-RA + Dex+ Aprepitant (125) 2. 5-HT_3-RA + Dex	$\Rightarrow$	1. Aprepitant (80) (Tag 2-3) 2. Dex oder **5-HT_3-RA**

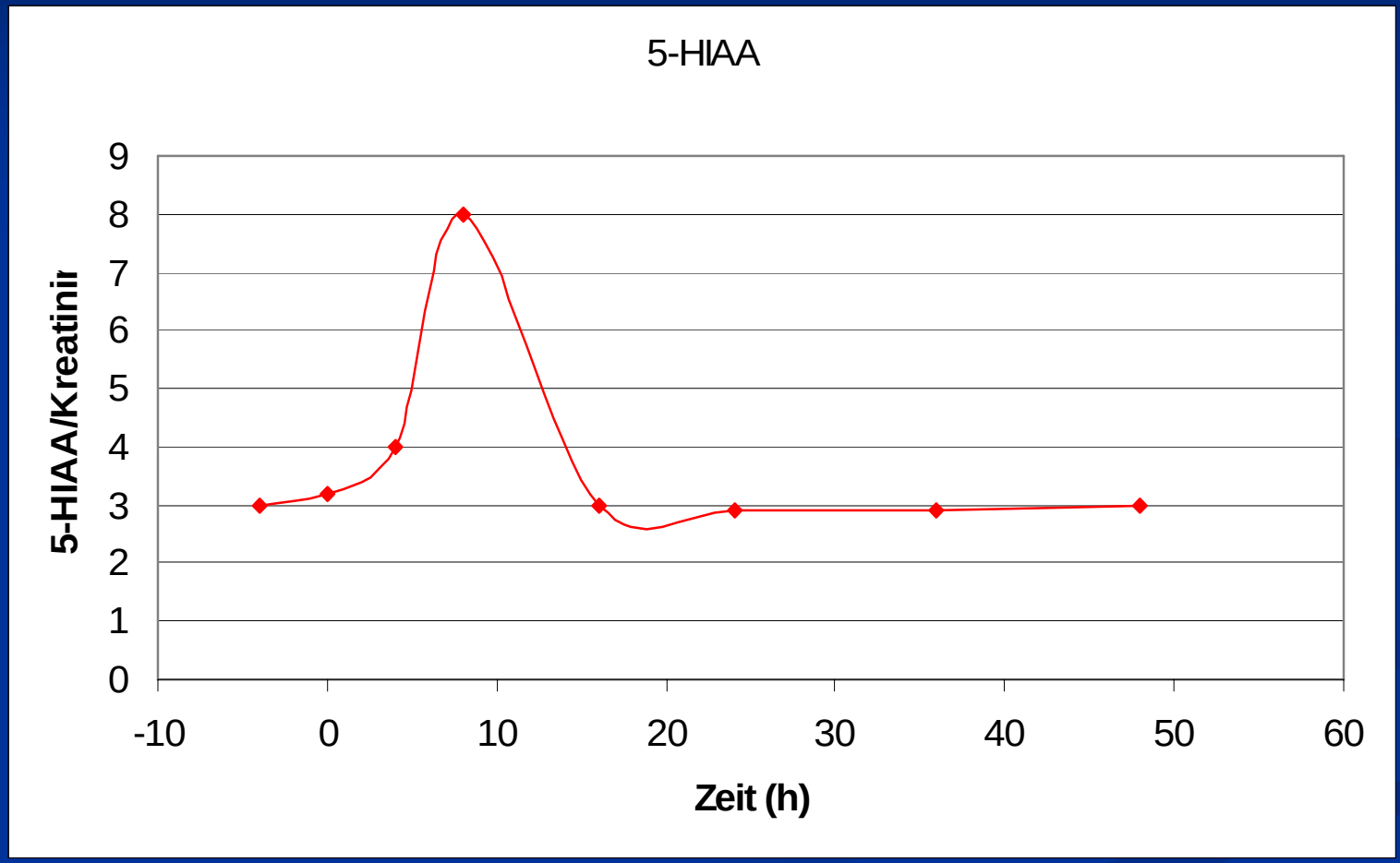
Metaanalyse: 5-HT_3 Antagonisten in der verzögerten Phase

- 5 Studien (1.716 Patienten)

„Neither clinical evidence nor considerations of cost effectiveness justify using 5-HT_3 antagonists beyond 24 hours after chemotherapy for prevention of delayed emesis.“

Geling 2005, JCO

NEIN!!



Wilder-Smith; OH; Cancer 1993

Palonosetron

CTX	Study	Pts.	Dose (mg/day)			Acute complete response (%)		P value
						Delayed complete response (%)		
			Palo	Ond	Dola	Palo	Comparator	
Cisplatin	Aapro 2006	667	0.25 0.75	32		59.2 65.5	57.0	NS
Non-cisplatin based	Gralla 2003	563	0.25 0.75	32		81.0 73.5	68.8	0.0085
						74	**51**	
* 5% der Pat. Zusätzlich Steroid	Eisenberg 2003*	569	0.25 0.75		100	63.0 57.1	52.9	0.049
						54	**38,7**	

Pharmacokinetic parameters of 5-HT_3-receptor-antagonists

	Ondansetron	Granisetron	Tropisetron	Dolasetron	Palonosetron
Half-life (h)	4.0	9.0	8.0	7.5	40
Receptor binding constant, pK_i	8.1	8.4	8.8	7.6	10.5

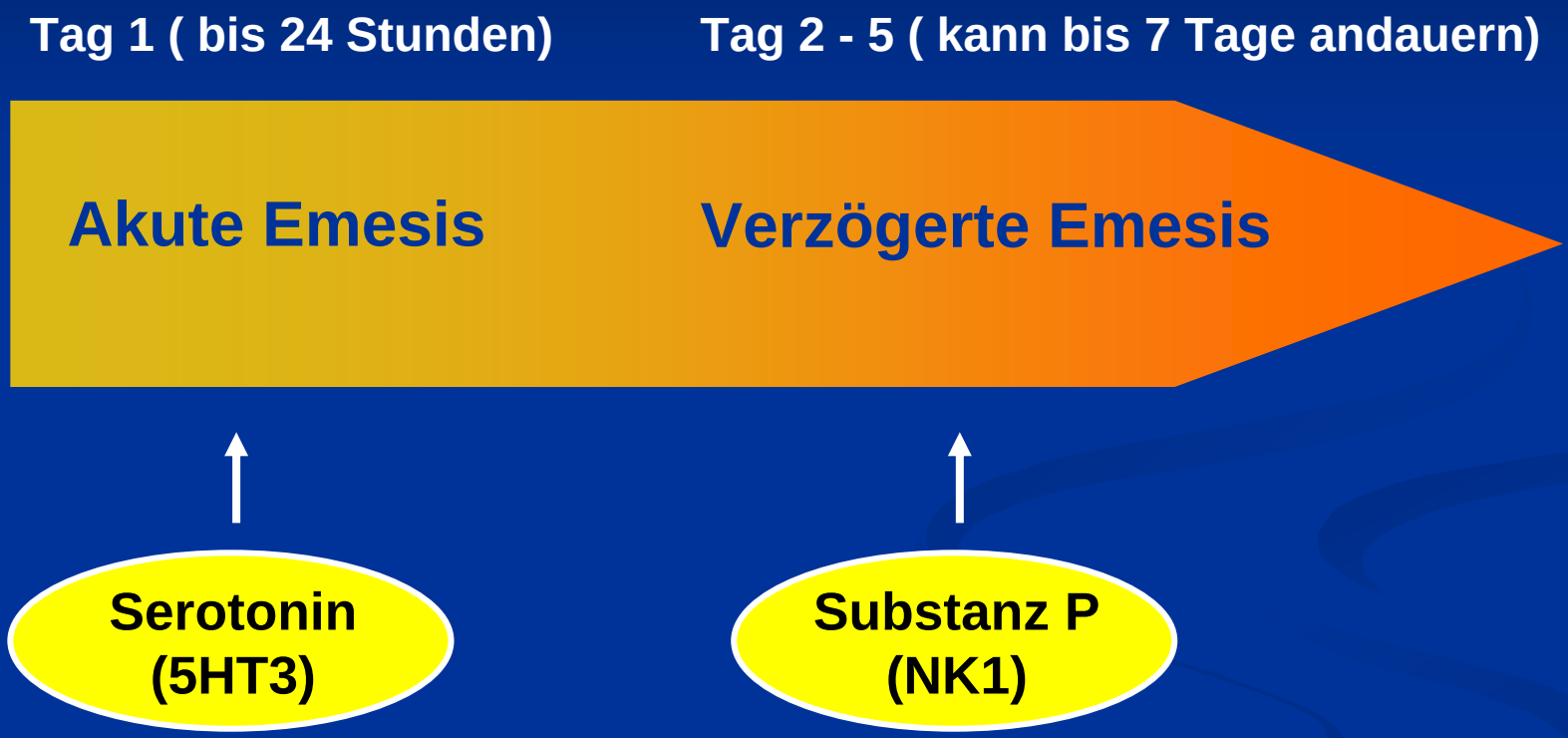
„Wo ist das Metoclopramid abgeblieben?“

Moderat 30% - 90%	1. 5-HT_3-RA + Dex+ Aprepitant 2. 5-HT_3-RA Dex+	⇒	1. Aprepitant (80) (Tag 2-3) 2. Dex oder 5-HT_3-RA **oder ……**

Olanzapin

- Bei „Breakthrough Emesis“ (MASCC und NCCN)
- Empfohlene Dosierung:
  2,5-5 mg Olanzapin

Zeitverlauf von Emesis und Nausea



Vier emetogene Risikogruppen

Chemo-therapie	Risiko, ohne Antiemese zu erbrechen	Beispielsubstanzen
Hoch	> 90 %	Cisplatin, Streptozotocin
Moderat	30-90%	Carboplatin, Cyclophosphamid, Doxorubicin, Oxaliplatin, Irinotecan
Gering	10-30%	Capecitabin, Gemcitabin, 5- FU, Docetaxel, Paclitaxel
Minimal	< 10%	Bleomycin, Rituximab, Vinca-Alkaloide

Roila, F Ann Oncol 2006, Kris, M JCO 2006

Emetogenes Potential

Orale Zytostatika

High (>90%)	Hexamethylmelamine, Procarbazine
Moderate (30–90%)	Cyclophosphamide, Etoposide, Temozolomide, Vinorelbine, Imatinib
Low (10–30%)	Capecitabine, Fludarabine
Minimal (<10%)	Chlorambucil, Hydroxyurea, L-Phenylalanine mustard, 6-Thioguanine, Methotrexate, Gefitinib

Roila, F; Ann Oncol 2006, Einhorn, L; JSC 2006

Wirkort	Klasse	Beispiel	Antiemetische Wirksamkeit	
			Akute Emesis	Verzög. Emesis
5-HT_3-Rezeptor	5-HT_3-Antagonisten	Ondansetron Granisetron	++	(+)
multipel	Steroide	Dexa-methason	+(+)	+(+)
Neurokinin-1-Rezeptor	Neurokinin-1-Antagonisten	Aprepitant	+	++
Dopamin-D2-Rezeptor	Benzamide	Meto-clopramid	(+)	+
GABA-Chlorid-Kanal	Benzodiazepine	Lorazepam, Diazepam	(+)	(+)
Dopamin-D_2-Rezeptor	Neuroleptika	Haloperidol Olanzapin	(+)	(+)
Nicht bekannt	Cannabinoide	Dronabinol	(+)	(+)
Muscarin-Cholin-Rez.	Antihistamine	Diphenhy-dramin	-	-

Guidelines Gemeinsamkeiten und Unterschiede

- MASCC Jan. 2006, Roila F. (Ann Oncol)
- ASCO Juni 2006, Kris M. (JCO)
- NCCN, Januar 2008, www.nccn.org

Table 5. Antiemetic prevention based on emesis risk category (MASCC, ASCO, NCCN) [4–6]

	Recommendation							
	High		Moderate		Low		Minimal	
Group	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV
MASCC	5-HT_3RA + dexamethasone + aprepitant	Dexamethasone + aprepitant	1. Anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone + aprepitant	Aprepitant or dexamethasone	Dexamethasone	[a]	[a]	[a]
			2. Other than anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone	Dexamethasone, 5-HT_3RA may be used as an alternative				
ASCO	5-HT_3RA + dexamethasone + aprepitant	Dexamethasone + aprepitant	1. Anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone + aprepitant	Aprepitant	Dexamethasone	[a]	[a]	[a]
			2. Other than anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone	Dexamethasone or a 5-HT_3RA				
NCCN	5-HT_3RA + dexamethasone + aprepitant ± lorazepam	Dexamethasone + aprepitant ± lorazepam	1. Anthracycline/ cyclophosphamide or in selected patients 5-HT_3RA + dexamethasone + aprepitant ± lorazepam	Aprepitant ± dexamethasone ± lorazepam	Dexamethasone ± Lorazepam or Prochlorperazine ± lorazepam or metoclopramide ± lorazepam or	[a]	[a]	[a]
			2. Other than anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone ± lorazepam	Dexamethasone or 5-HT_3RA, both ± lorazepam				

[a]No routine prophylaxis.
Abbreviations: 5-HT_3RA, 5-HT_3-receptor antagonist; ASCO, American Society of Clinical Oncology; CINV, chemotherapy-induced nausea and vomiting; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network.

Jordan K., The Oncologist, 9, 2007

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ASCO			1. Anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone + aprepitant	Aprepitant	Dexamethasone	[a]	[a]	[a]
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NCCN	5-HT_3RA + dexamethasone + aprepitant ± lorazepam	Dexamethasone + aprepitant ± lorazepam	1. Anthracycline/ cyclophosphamide or in selected patients 5-HT_3RA + dexamethasone + aprepitant ± lorazepam	Aprepitant ± dexamethasone ± lorazepam	Dexamethasone ± Lorazepam or Prochlorperazine ± lorazepam or metoclopramide ± lorazepam or	[a]	[a]	[a]
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Dosierung
- Antiemetika-

Optimale Dosierung – Setrone
1 x täglich, oral= i.v.

Ondansetron (Zofran®)	8 mg	16-24 mg
Granisetron (Kevatril®)	1 mg	2 mg
Tropisetron (Navoban®)	5 mg	5 mg
Dolasetron (Anemet®)	100 mg	100-200mg
Palonosetron (Aloxi®)	0,25 mg	-

NK_1 Antagonist, Aprepitant

- Tag 1: 125 mg Aprepitant
- Tag 2-3: 80 mg Aprepitant
- Unklar, ob bereits gebundene Substanz P durch Aprepitant aus der Bindungsstelle gelöst wird
- Aprepitant ist ein moderater CYP3A4 Inhibitor: Reduktion der Dexamethason Dosis erforderlich!

Hochdosischemotherapie/ Mehrtageschemotherapie

An den Tagen der Chemotherapie Gabe von einem 5 HT_3 - RA in Kombination mit einem Steroid

Die zusätzliche Gabe von Aprepitant kann erwogen werden

Zusammenfassung

- Klar formulierte antiemetische Leitlinien
- Sie müssen „nur noch“ gekannt werden und „nur noch“ umgesetzt werden