

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

**Recherche und Synopse der Evidenz zur Bestimmung
der zweckmäßigen Vergleichstherapie nach § 35a
SGB V**

Vorgang: 2017-06-01-D-290 Rolapitant

Stand: März 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Rolapitant zur Prävention von verzögerter Übelkeit und Erbrechen, die mit moderater sowie hoch emetogener Chemotherapie assoziiert sind.				
Kriterien gemäß 5. Kapitel § 6 VerfO				
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Serotonin-5HT ₃ -Antagonisten: Ondansetron Granisetron Tropisetron Palonosetron	Prokinetika: Metoclopramid Domperidon Alizaprid	Neurokinin-1(NK1)-Rezeptor-Antagonisten: Aprepitant Fosaprepitant Netupitant/Palonosetron	Corticosteroide: Betamethason Dexamethason Methylprednisolon Prednisolon Prednison
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	<i>nicht angezeigt</i>			
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	<p>Festbetragsgruppen: Stufe:</p> <ul style="list-style-type: none"> ▪ Serotonin-5HT₃-Antagonisten (Ondansetron, Granisetron, Tropisetron) 2 ▪ Glucocorticoide, oral 2 ▪ Metoclopramid 1 ▪ Domperidon 1 ▪ Dexamethason 1 ▪ Prednisolon 1 ▪ Prednison 1 <p>Netupitant/Palonosetron Frühe Nutzenbewertung nach § 35a 04.02.2016</p>			
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	<i>Siehe Recherche und Synopse der Evidenz</i>			
Bei mehreren Alternativen ist die wirtschaftlichere Therapie zu wählen, vorzugsweise eine Therapie, für die ein Festbetrag gilt.	<i>entfällt</i>			
[...] vorzugsweise eine Therapie, [...] die sich in der praktischen Anwendung bewährt hat.	<i>nicht angezeigt</i>			

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Rolapitant A04AD14 Varuby®	Prävention von verzögerter Übelkeit und Erbrechen im Rahmen hoch oder moderat emetogener Chemotherapie zur Krebsbehandlung bei Erwachsenen. Varuby wird im Rahmen einer Kombinationstherapie verabreicht.
5-HT₃-A	
Ondansetron A04AA01 Zofran®	Übelkeit, Brechreiz und Erbrechen bei Therapie mit Zytostatika und Strahlentherapie.
Granisetron A04AA02 Generisch	Granisetron B. Braun wird zur Prophylaxe und Behandlung von <ul style="list-style-type: none"> • akuter Übelkeit und Erbrechen, hervorgerufen durch eine Chemotherapie und Strahlentherapie • post-operativer Übelkeit und Erbrechen angewendet. Granisetron B. Braun wird zur Prophylaxe von verzögertem Erbrechen und Übelkeit, hervorgerufen durch Chemotherapie oder Strahlentherapie angewendet. Granisetron B. Braun wird angewendet bei Kindern ab 2 Jahren und älter zur Prophylaxe von akuter Übelkeit und Erbrechen hervorgerufen durch Chemotherapie.
Tropisetron A04AA03 Navoban®	Übelkeit, Brechreiz und Erbrechen bei Therapie mit Zytostatika
Palonosetron A04AA05 Aloxi® Weichkapseln	Aloxi® wird angewendet bei Erwachsenen zur Prävention von Übelkeit und Erbrechen bei mäßig emetogener Chemotherapie aufgrund einer Krebserkrankung.
Palonosetron A04AA05 Aloxi® Injektionslösung	Aloxi ist indiziert zur <ul style="list-style-type: none"> • Prävention von akuter Übelkeit und Erbrechen bei stark emetogener Chemotherapie aufgrund einer Krebserkrankung bei Erwachsenen, • Prävention von Übelkeit und Erbrechen bei mäßig emetogener Chemotherapie aufgrund einer Krebserkrankung bei Erwachsenen.
NK-1-RA-	

Netupitant/Palonosetron A04AA55 Akynzeo®	Akynzeo wird angewendet bei Erwachsenen zur: – Prävention von akuter und verzögert auftretender Übelkeit und Erbrechen bei stark emetogener Chemotherapie auf Cisplatin-Basis aufgrund einer Krebserkrankung. – Prävention von akuter und verzögert auftretender Übelkeit und Erbrechen bei mäßig emetogener Chemotherapie aufgrund einer Krebserkrankung
Aprepitant A04AD12 Emend®	Zur Prävention von Übelkeit und Erbrechen bei hoch und moderat emetogener Chemotherapie bei Erwachsenen und Jugendlichen ab 12 Jahren. EMEND 125 mg/80 mg wird als Teil einer Kombinationstherapie angewendet (siehe Abschnitt 4.2).
Fosaprepitant A04AD12 Ivemend®	Zur Prävention akuter und verzögter Übelkeit und Erbrechen bei hoch emetogener, auf Cisplatin basierender Chemotherapie bei Erwachsenen. Zur Prävention von Übelkeit und Erbrechen bei moderat emetogener Chemotherapie bei Erwachsenen. IVEMEND 150 mg wird als Teil einer Kombinationstherapie gegeben (siehe Abschnitt 4.2).
Andere Antiemetika	
Nabilon A04AD11 Canemes®	Fachinformation Abschnitt 4.1: Canemes® 1 mg Kapseln sind für die Behandlung von chemotherapiebedingter Emesis und Nausea bei jenen Krebs-Patienten indiziert, die auf andere antiemetische Behandlungen nicht adäquat ansprechen.# 4.2: Dosierung Canemes® ist für die Verwendung beim Erwachsenen angezeigt, nicht für Kinder oder Jugendliche unter 18 Jahren, da die Sicherheit und Wirksamkeit nicht dokumentiert wurden.
Prokinetika	
Metoclopramid A03FA01 Generisch	MCP-ratiopharm® 10 mg wird angewendet bei Erwachsenen zur: – Vorbeugung von nach Chemotherapie verzögert auftretender Übelkeit und verzögert auftretendem Erbrechen (CINV) – Vorbeugung von Übelkeit und Erbrechen, die durch Strahlentherapie verursacht werden (RINV)
Domperidon A03FA03 Generisch	Domperidon-TEVA® wird angewendet zur Besserung der Symptome Übelkeit und Erbrechen..
Alizaprid A03FA05 Vergantán®	Zur Vorbeugung bzw. Behandlung von – Erbrechen, Übelkeit und Brechreiz im Zusammenhang mit der Zytostatikatherapie. – Strahlenkater nach Röntgen-, Telekobalt- oder Betatronbestrahlung.
Corticosteroide	
Betamethason H02AB01 Betamethason Acis Crinale®	Zur Vorbeugung bzw. Behandlung von – Erbrechen, Übelkeit und Brechreiz im Zusammenhang mit der Zytostatikatherapie. – Strahlenkater nach Röntgen-, Telekobalt oder Betatronbestrahlung
Dexamethason H02AB02 Generisch	Prophylaxe und Therapie von postoperativem oder Zytostatika-induziertem Erbrechen im Rahmen antiemetischer Schemata.

Methylprednisolon H02AB04 Generisch	Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen, Anwendung im Rahmen antiemetischer Schemata
Prednisolon H02AB06 Generisch	Prophylaxe und Therapie von Zytostatika- induziertem Erbrechen (DS: b – a), Anwendung im Rahmen antiemetischer Schemata.
Prednison H02AB07 Generisch	Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen (DS: b bis a), Anwendung im Rahmen antiemetischer Schemata.

Quellen: AMIS-Datenbank, Fachinformationen Stand März 2017

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

<u>Systematische Recherche:</u>	6
<u>Indikation:</u>	7
<u>IQWiG Berichte/G-BA Beschlüsse</u>	9
<u>Cochrane Reviews</u>	10
<u>Systematische Reviews</u>	11
<u>Leitlinien</u>	43
<u>Detaillierte Darstellung der Recherchestrategie</u>	59
<u>Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 16.01.2017</u>	59
<u>SR, HTAs in Medline (PubMed) am 17.01.2017</u>	59
<u>Leitlinien in Medline (PubMed) am 17.01.2017</u>	60
<u>Literatur:</u>	61
<u>Anhang:</u>	63

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *Übelkeit und Erbrechen bei hoch oder moderat emetogener Chemotherapie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 19.01.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 392 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 15 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Prävention von Übelkeit und Erbrechen im Rahmen hoch oder moderat emetogener Chemotherapie zur Krebsbehandlung bei Erwachsenen. Varuby wird im Rahmen einer Kombinationstherapie verabreicht.

Abkürzungen:

5 HT3 A	5-HT3-Antagonist
AGD	Aprepitant + Granisetron + Dexamethason
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AOD	Aprepitant + Ondansetron + Dexamethason
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CINV	Chemotherapy-induced nausea and vomiting
CCO	Cancer Care Ontario
CR	Complete Response
DAHTA	Deutsche Agentur für Health Technology Assessment
DN	Delayed nausea
DRKS	Deutsches Register Klinischer Studien
DV	Delayed vomiting
ESMO	European Society for Medical Oncology
FGD	Fosaprepitant + Granisetron + Dexamethason
G-BA	Gemeinsamer Bundesausschuss
GD	Granisetron + Dexamethason
GIN	Guidelines International Network
GRA	Granisetron
HEC	Highly emetogenic chemotherapy
ICTRP	International Clinical Trials Registry Platform
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MEC	Moderately emetogenic chemotherapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NEPA	Netupitant + palonosetron
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NK-1RA	Neurokinin-1 receptor antagonists
NN	No nausea
NV	No vomiting
OD	Ondansetron + Dexamethason
OND	Ondansetron
OR	Odds Ratio
PALO	Palonosetron
RGD	Rolapitant + Ondansetron + Dexamethason
SIGN	Scottish Intercollegiate Guidelines Network
TRAE	Treatment-related adverse events
TRIP	Turn Research into Practice Database

TRO	Tropisetron
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

<p>Gemeinsamer Bundesausschuss (G-BA), 2016 [3]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Netupitant/ Palonosetron vom 04. Februar 2016</p> <p>Siehe auch: IQWiG, 2015 [5]. Netupitant/ Palonosetron - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung); Auftrag A15-28</p>	<p>Fazit:</p> <p>Zweckmäßige Vergleistherapie</p> <p>a) Prävention von akuter und verzögert auftretender Übelkeit und Erbrechen bei mäßig emetogener Chemotherapie aufgrund einer Krebserkrankung Zweckmäßige Vergleichstherapie:</p> <ul style="list-style-type: none"> • Zweifachkombination aus Serotonin-Antagonist (Ondansetron oder Granisetron oder Tropisetron oder Palonosetron) + Dexamethason <p>Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Zweifachkombination aus Serotonin-Antagonist + Dexamethason:</p> <ul style="list-style-type: none"> • Ein Zusatznutzen ist nicht belegt. <p>b.) Prävention von akuter und verzögert auftretender Übelkeit und Erbrechen bei stark emetogener Chemotherapie auf Cisplatin-Basis aufgrund einer Krebserkrankung</p> <ul style="list-style-type: none"> • Dreifachkombination aus Serotonin-Antagonist (Ondansetron oder Granisetron oder Tropisetron oder Palonosetron) + Neurokinin-1-Rezeptorantagonist (Aprepitant oder Fosaprepitant) + Dexamethason <p>Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Dreifachkombination aus Serotonin-Antagonist + Neurokinin-1-Rezeptorantagonist + Dexamethason:</p> <ul style="list-style-type: none"> • Ein Zusatznutzen ist nicht belegt
--	---

Cochrane Reviews

Es sind keine Cochrane Reviews vorhanden.

Systematische Reviews

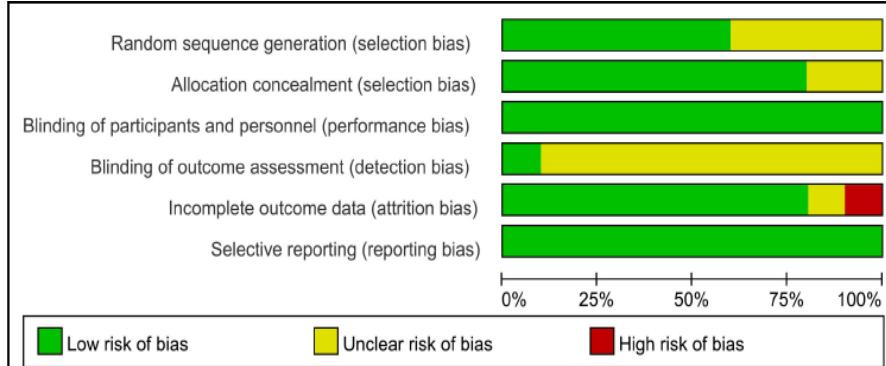
<p>Shi Q et al., 2015 [10].</p> <p>Prevention of cisplatin-based chemotherapy-induced delayed nausea and vomiting using triple antiemetic regimens: a mixed treatment comparison</p>	<p>1. Fragestellung A variety of triple antiemetic regimens are being used to prevent cisplatin-based chemotherapy induced delayed emesis and nausea in cancer patients. We performed a network meta-analysis to compare the efficacies of the different regimens.</p> <p>2. Methodik</p> <p>Population: patients receiving cisplatin-containing chemotherapy</p> <p>Intervention: Triple regimen of a NK-1 and 5-HT3 antagonist plus dexamethasone (DXM)</p> <p>Komparator: Vergleich miteinander bzw ohne NK1-Antagonisten</p> <p>Aufzählung verwendeter Regime: u.a.</p> <ul style="list-style-type: none"> netupitant + palonosetron + dexamethasone (NEPA), aprepitant + ondansetron + dexamethasone (AOD), fosaprepitant + ondansetron + dexamethasone (FOD), palonosetron + dexamethasone (PD), aprepitant + granisetron + dexamethasone (AGD), rolapitant + ondansetron + dexamethasone (RGD), fosaprepitant + granisetron + dexamethasone (FGD), granisetron + dexamethasone (GD) ondansetron + dexamethasone (OD). <p>Endpunkt: complete response (CR), no vomiting (NV), no nausea (NN), and the effects of triple regimens on chemotherapy-related adverse events</p> <p>Suchzeitraum (Aktualität der Recherche): keine Angaben, nur auf Englisch</p> <p>Anzahl eingeschlossene Studien/Patienten (Gesamt): 10 RCTs (n=6317)</p> <p>Qualitätsbewertung der Studien: Cochrane Collaboration's "Risk of bias + Jadad scale: The quality scores of the studies ranged from 0 (lowest) to 5 (highest)."</p> <p>Networkanalysis: Bayesian framework</p>
	<p>3. Ergebnisdarstellung</p> <p>Studiencharakteristika</p> <ul style="list-style-type: none"> • 10 studies [12–21] fulfilled the eligibility criteria [...]. The Jadad scores of all of the included studies were calculated to be 4–5, indicating that they were of high quality. <p>Qualitätsbeurteilung der Studien</p> <ul style="list-style-type: none"> • The methodological quality of the included studies was generally good. Across all six domains, approximately 71.6% of the assessments were classified as 'low risk', and 1.7% were

classified as 'high risk'. It is unlikely that the evidence presented in this review was affected by biases associated with performance. However, we cannot exclude the possibility that selection bias was present in some individual trials, since they lacked a description of their allocation. In addition, some uncertainty regarding the risks of bias associated with random sequence generation and with the blinding of outcome assessors was due mainly to insufficient reporting.

Supplementary Table S1: Jadad quality scale

Study	Random sequence generation	Double blind	Incomplete outcome data	Total score
Daniel Campos 2001	2	2	1	5
H. Saito 2012	1	2	1	4
P. J. Hesketh 2014	1	2	1	4
P. J. Hesketh 2003	2	2	1	5
Sant P. Chawla 2001	2	2	1	5
Sergio Poli-Bigelli 2003	2	2	0	4
Steven Grunberg 2011	2	2	0	4
Toshiaki Takahashi 2010	1	2	1	4
Zhihuang Hu 2014	2	2	1	5
Bernardo Rapoport 2015	2	2	1	5

Jadad quality scale: 1–2 total score is for low quality, 3–5 total score is for high quality.



Referenzen

12. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R, Chawla SP, Carides AD, Ianus J, Elmer ME, Evans JK, Beck K, Reines S, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J Clin Oncol.* 2003; 21:4112–4119.
13. Chawla SP, Grunberg SM, Gralla RJ, Hesketh PJ, Rittenberg C, Elmer ME, Schmidt C, Taylor A, Carides AD, Evans JK, Horgan KJ. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer.* 2003; 97:2290–2300.
14. Campos D, Pereira JR, Reinhardt RR, Carracedo C, Poli S, Vogel C, Martinez-Cedillo J, Erazo A, Wittreich J, Eriksson LO, Carides AD, Gertz BJ. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol.* 2001; 19:1759–1767.
15. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, Hipple

- A, Evans JK, Horgan KJ, Lawson F. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer*. 2003; 97:3090–3098.
16. Hesketh PJ, Rossi G, Rizzi G, Palmas M, Alyasova A, Bondarenko I, Lisyanskaya A, Gralla RJ: Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. *Ann Oncol*. 2014; 25:1340–1346.
 17. Saito H, Yoshizawa H, Yoshimori K, Katakami N, Katsumata N, Kawahara M, Eguchi K. Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. *Ann Oncol*. 2013; 24:1067–1073.
 18. Takahashi T, Hoshi E, Takagi M, Katsumata N, Kawahara M, Eguchi K. Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin. *Cancer Sci*. 2010; 101: 2455–2461.
 19. Hu Z, Cheng Y, Zhang H, Zhou C, Han B, Zhang Y, Huang C, Chang J, Song X, Liang J, Liang H, Bai C, Yu S. Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: a randomized, double-blind, placebo-controlled phase III trial. *Support Care Cancer*. 2014; 22:979–987.
 20. Grunberg S, Chua D, Maru A, Dinis J, DeVandry S, Boice JA, Hardwick JS, Beckford E, Taylor A, Carides A, Roila F, Herrstedt J. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol—EASE. *J Clin Oncol*. 2011; 29:1495–1501.
 21. Rapoport BL, Chasen MR, Gridelli C, Urban L, Modiano MR, Schnadig ID, Poma A, Arora S, Kansra V, Schwartzberg LS, Navari RM. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. *Lancet Oncol*. 2015; 16:1079–89.

Ergebnisse

Network analysis

Complete response (CR)

- [...] preventive effect of 8 antiemetic regimens on delayed vomiting, with the outcomes of a total of 6,143 patients being reported
- Netupitant + palonosetron + dexamethasone (NEPA) was the most effective treatment, with an absolute rank of 0.8579
- The ranking from high to low was as follows:
 - aprepitant + ondansetron + dexamethasone (AOD),
 - fosaprepitant + ondansetron + dexamethasone (FOD),
 - palonosetron + dexamethasone (PD),
 - aprepitant + granisetron + dexamethasone (AGD),
 - rolapitant + ondansetron + dexamethasone (RGD),
 - fosaprepitant + granisetron + dexamethasone (FGD),
 - granisetron + dexamethasone (GD) and

- ondansetron + dexamethasone (OD).
- However, the results should be interpreted with caution because most of comparisons among the various regimens did not reach statistical significance.

No vomiting (NV)

- In nine studies, a total of nine antiemetic regimens and 4,835 patients were analyzed.
- The absolute rank of NEPA was 0.8631, which indicates this regimen may be optimal.
- The emetic regimens in decreasing order of absolute rank were as follows: AOD, FOD, AGD, PD, FGD, RGD, OD and GD.
- Again, these findings should be interpreted with caution because most of the comparisons did not reach statistical significance.

No nausea (NN)

- 3,409 patients were analyzed. The FOD regimen was not analyzed in this section because the studies in which it was included did not report the relevant data.
- The efficacy of NEPA was again the best, with an absolute rank of 0.7902.
- In decreasing order, the ranking was as follows: PD, AOD, RGD, OD, AGD, FGD, and GD.
- These results should also be interpreted with caution.

Safety

- The incidences of constipation (23.9%), anorexia (36.3%) and hiccups (35.5%) were the highest in the patients treated with AGD, while the incidence of asthenia (14.3%) was the highest in the patients treated with AOD. The incidence of adverse events (constipation: 0.4%, hiccups: 0.6% and asthenia: 0.4%) was the lowest in patients treated with RGD.

Table 3: Incidence of adverse events in patients treated with different triple antiemetic regimens

Regimen	Constipation	%	Hiccups	%	Asthenia	%	Anorexia	%	Diarrhea	%
OD	95/761	12.5	37/476	7.8	101/761	13.3	62/497	12.5	55/497	11.1
AOD	198/1926	10.3	136/1778	7.6	276/1926	14.3	175/1799	9.7	160/1665	9.6
GD	105/948	11.1	127/1158	11	40/837	4.8	100/241	41.5	61/451	13.5
FGD	23/174	13.2	15/174	8.6	N/A	N/A	N/A	N/A	N/A	N/A
AGD	105/439	23.9	83/234	35.5	31/289	10.7	85/234	36.3	56/445	12.6
PD	N/A	N/A	5/136	3.7	N/A	N/A	3/136	2.2	N/A	N/A
FOD	121/1143	10.6	64/1143	5.6	98/1143	8.6	76/1143	6.7	89/1143	7.8
NEPA	N/A	N/A	7/136	5.1	N/A	N/A	1/136	0.7	N/A	N/A
RGD	2/535	0.4	3/535	0.6	2/535	0.4	N/A	N/A	N/A	N/A
Total	649/5926	11.0%	540/5770	9.4%	548/5491	10%	502/4186	12.0%	421/4201	10.0%

Show are the incidences of adverse events in patients treated with the indicated regimens. Total incidences of constipation, hiccups, asthenia, anorexia and diarrhea are shown at the bottom of the table. N/A, no adequate data in relevant trials.

	<p>Limitations to the study (Anmerkung des Autors)</p> <p>[...] We could not perform subgroup analysis of specific cancer types because data on cancer types were lacking in the included studies. Thus, we could not clearly determine whether the efficacies of the triple regimens differed based on the cancer type.</p>
	<p>4. Anmerkungen/Fazit der Autoren</p> <p>With respect to CR, NV and NN, NEPA had the best preventive effect against cisplatin-based chemotherapy-induced delayed nausea and vomiting. The safety of NEPA was also better, making it worthy of recommendation. AOD ranked second, second and third, respectively, for CR, NV and NN, which also indicates superior preventative effects. [...] And although RGD offers no advantage with respect to delayed vomiting, it effectively prevents delayed nausea and is relatively safe to use. Thus, the RGD regimen deserves the attention of clinicians and patients for its ability to prevent severe constipation, hiccups, asthenia and/or delayed nausea.</p> <p>5. Anmerkung FB Med: AM teilweise nicht zugelassen.</p>
<p>Zhang Y et al., 2017 [15].</p> <p>Neurokinin-1 Receptor Antagonist-Based Triple Regimens in Preventing Chemotherapy-Induced Nausea and Vomiting: A Network Meta-Analysis</p>	<p>1. Fragestellung</p> <p>Neurokinin-1 receptor antagonists (NK-1RAs) are widely used for chemotherapy-induced nausea and vomiting (CINV) control in patients with highly emetogenic chemotherapy (HEC) and/or moderately emetogenic chemotherapy (MEC). Whether the efficacy and toxicity of antiemesis are different among various NK-1RA-based triple regimens is unknown.</p> <p>2. Methodik</p> <p>Population: patients with highly emetogenic chemotherapy (HEC) and/or moderately emetogenic chemotherapy (MEC).</p> <p>HEC, such as anthracycline plus cyclophosphamide (AC) or cisplatin, and MEC, such as carboplatin or oxaliplatin, were defined according to the National Comprehensive Cancer Network Antiemesis Guideline Version 2, 2016</p> <p>Intervention: NK-1RA based triple antiemetic regimens. NK-1RA was used at the standard dose. NK-1RA + serotonin receptor antagonists [5HT3RA] + dexamethasone</p> <p>Komparator: duplex regimen (5HT3RA + dexamethasone)</p> <p>Endpunkt: The assessment of efficacy and toxicity occurred during the first cycle of chemotherapy</p> <ul style="list-style-type: none"> • The proportions of patients with complete responses (CRs) • No clinically significant nausea in the acute (0–24 hours after chemotherapy)

- Delayed (>24–120 hours after chemotherapy)
- Overall (0–120 hours) phases
- The toxic outcome was defined as treatment-related adverse events (TRAEs).

Suchzeitraum (Aktualität der Recherche): bis Februar 2016

Anzahl eingeschlossene Studien/Patienten (Gesamt): 35 RCTs/prospective trials (n=25727)

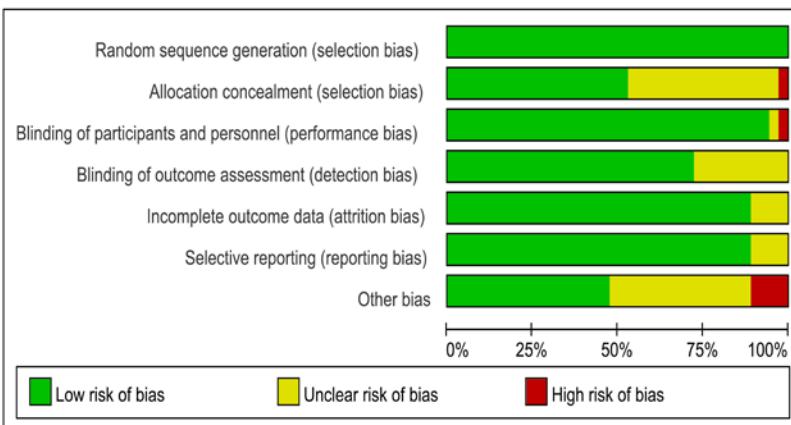
Qualitätsbewertung der Studien: Cochrane risk of bias

Heterogenität: I²

3. Ergebnisdarstellung

Studiencharakteristika

- We identified 1796 records using the search strategy and included 35 studies (17–51), including 36 trials involving 18 889 cancer patients using NK-1RA-based triple antiemetic regimens (NK-1RA+5HT3RA+dexamethasone, n=12051) or conventional duplex control regimen (5HT3RA+dexamethasone, n = 6838) to control for CINV in this meta-analysis



Ergebnisse

Pair-Wise Meta Analyses for Antiemetic Efficacy and Toxicity

Table 2. Binary comparison of NK-1RA-based triple regimens vs conventional duplex regimens for antiemetic efficacy and toxicity measures as complete response and treatment-related adverse events

Outcome	No. of trials (No. of participants)	References	OR* (95% CI) in random model	Effect size		Heterogeneity χ^2
				Z	P†	
Overall phase CR (Total)	30 (15 427)	(17-27,29-31,33-36,39-48,51)	1.70 (1.56 to 1.85)	12.23	<.001	.13
Acute phase CR (Total)	28 (15 142)	(17,19-27,29-31,33-36,39,41-48,51)	1.53 (1.36 to 1.71)	7.32	<.001	.14
Delayed phase CR (Total)	27 (14 340)	(17,19-25,27,29-31,33-36,39,41-48,51)	1.68 (1.53 to 1.84)	11.35	<.001	.13
Overall phase CR (HEC)	17 (9425)	(17-23,26-27,29,31,34,36,39,45,46)	1.72 (1.53 to 1.93)	9.21	<.001	.08
Acute phase CR (HEC)	16 (9273)	(17,19-23,26,27,29,31,34,36,39,45,46)	1.52 (1.32 to 1.75)	5.74	<.001	.09
Delayed phase CR (HEC)	15 (8471)	(17,19-23,27,29,31,34,36,39,45,46)	1.73 (1.53 to 1.96)	8.54	<.001	.07
Overall phase CR (MEC)	10 (3776)	(24,33,35,40-44,48,51)	1.68 (1.39 to 2.03)	5.38	<.001	.23
Acute phase CR (MEC)	9 (3643)	(24,33,35,41-44,48,51)	1.54 (1.16 to 2.03)	3.03	.002	.54
Delayed phase CR (MEC)	9 (3643)	(24,33,35,41-44,48,51)	1.62 (1.37 to 1.93)	5.59	<.001	.37
TRAЕ	19 (11 507)	(17-22,25,26,30,31,33,34,36,39,45-47,51)	1.09 (0.97 to 1.22)	1.40	.16	.65

*Represents OR_{triplex/duplex} in cancer patients using NK-1RA-based triple regimens or conventional duplex regimens in preventing chemotherapy-induced nausea and vomiting. CI = confidence interval; CR = complete response; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; OR = odds ratio; TRAE = treatment-related adverse event; NK-1RA = neurokinin-1 receptor antagonist.

†Two-sided test for pooled analysis (Z test).

‡Two-sided test for heterogeneity (χ^2).

- NK-1RAs-based triple regimens showed statistically significantly superior antiemetic effect in overall, acute, and delayed phase CRs compared with conventional duplex regimens in overall patients, patients with HEC, and patients with MEC. Similar results were found when “no clinically significant nausea” was the toxicity investigated
- [...] no statistically significant difference of TRAE was found between NK-1RA-based triple regimens and duplex control regimen.
- We used funnel plots to assess the publication bias of the literature in this study. All the shapes of the funnels were close to symmetric, and no publication bias was found according to Begg’s test and Egger’s test ($P > .05$).

Network A (Triple antiemetic therapy and conventional duplex regime)

- According to the data based on network A, various NK-1RAs based triple regimens (aprepitant, casopitant, fosaprepitant, netupitant, and rolapitant) shared equivalent antiemetic effect in overall, acute, and delayed phase CRs without statistically significant differences in odds ratios.
- In all patients and patients with HEC, almost all NK-1RAs-based triple regimens showed statistically significantly higher CRs in all phases vs duplex control regimen ($OR_{\text{duplex/triple}} = 0.47-0.66$), while only netupitant based triple regimen had a statistically nonsignificant superior antiemetic efficacy compared with duplex control regimen in terms of acute phase CR.
- [...] in patients with MEC, only aprepitant-based triple regimen showed a statistically significantly better antiemetic effect than duplex control regimen in all outcome measures of efficacy (OR

	<p>duplex/triple = 0.52, 95% CI = 0.34 to 0.68).</p> <ul style="list-style-type: none"> • We observed no statistically significant difference in the antiemetic effect of TRAE among different NK-1RA-based triple regimens vs the duplex control regimen <p><u>Network B (palonosetron-based triple regimen and first-generation 5HT3RAs-based triple regimen)</u></p> <ul style="list-style-type: none"> • [...] the antiemetic efficacy of palonosetron-based triple regimens was similar to first generation 5HT3RAs-based triple regimens for CRs in all phases. <p><u>Network C (NK-1RA-based triple antiemetic regimens and conventional duplex control regimens with various doses of dexamethasone)</u></p> <p>Different doses of dexamethasone (low-dose D, <20 mg; moderate-dose D, 20–39 mg; high-dose D, >39 mg) in combination with NK-1RA plus 5HT3RA showed no statistically significant difference in terms of CRs in all phases.</p> <p>Anmerkungen des Autors bezüglich der Netzwerkanalyse:</p> <ul style="list-style-type: none"> • All the network meta-analyses in our study were used in both the consistency model and the inconsistency model. The variances of those two models were roughly equal. As a result, inconsistency did not appear to be present, and we used the consistency model to show our results. • Our study is not without limitations. First, the lack of connections in the networks made the results dependent on only a few studies so that some of the presented estimates were based exclusively on indirect evidence. Second, we were not able to extract specific patients' data on HEC or MEC in some of the included studies that enrolled mixed patients. Third, we could not compare netupitant-based triple regimen and rolapitant-based triple regimen with other NK-1RAs-based triple regimens.
	<p>4. Anmerkungen/Fazit der Autoren</p> <p>[...] Our study confirmed that different NK-1RAs-based triple regimens were associated with an equivalent effect on CINV control in all the phases.</p> <p>Various NK-1RAs-based triple regimens had superior antiemetic effect than duplex control regimen in patients with HEC.</p> <p>Only aprepitant based triple regimen showed better CINV control compared with duplex control regimen in patients receiving MEC.</p> <p>Moreover, palonosetron and first-generation 5HT3RAs might share equivalent effect on CINV control in the combination of NK-1RAs and dexamethasone. A lower dose of dexamethasone might be applied when used with NK-1RAs and 5HT3RAs.</p> <p>5. Anmerkung FB Med: AM teilweise nicht zugelassen.</p>

<p>Abdel-Rahman O et al., 2016 [1].</p> <p>Neurokinin-1 inhibitors in the prevention of nausea and vomiting from highly emetogenic chemotherapy: a network meta-analysis</p>	<p>1. Fragestellung This network meta-analysis aims to provide a detailed comparative assessment of the efficacy of regimes containing one of the NK-1 inhibitors (aprepitant, fosaprepitant, rolapitant, casopitant, netupitant) in the prevention of CINV from highly emetogenic chemotherapy.</p>
	<p>2. Methodik</p> <p>Population: Patients on highly emetogenic chemotherapy Intervention: rolapitant' or 'aprepitant' or 'casopitant' or 'fosaprepitant' or 'netupitant' Komparator: siehe Intervention Endpunkte: Complete Response (CR), rate of no significant nausea and rate of no emesis. The three outcome measures were principally evaluated in the overall phase (i.e. from 0 to 120h after chemotherapy) Suchzeitraum (Aktualität der Recherche): September 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 19 RCT (n=6788). Non-English language records were excluded. Qualitätsbewertung der Studien: Jadad Scale Netzwerkanalyse: Bayesian approach</p>
	<p>3. Ergebnisdarstellung Studiencharakteristika</p> <ul style="list-style-type: none"> • Hence, 19 studies were included in the final analysis; 12 phase III studies and 7 randomized phase II studies • Four studies evaluated rolapitant-based regimens, one study evaluated a netupitant/palonosetron (palono) (NEPA)-based regimen, three studies evaluated aprepitant/palono-based regimens, 10 studies evaluated aprepitant/ondansetron (ondan) or granisetron (grani)-based regimens (one of which is the NEPA randomized study), two studies evaluated casopitant-based regimens and two studies evaluated fosaprepitant-based regimens. • All patients were enrolled in studies evaluating highly emetogenic chemotherapy and thus have adequate haematological, hepatic and renal functions.

Table 2. Jadad quality scale of the included studies.

Study	Randomization	Blinding	An account of all patients	Total score
Schnadig <i>et al.</i> [2015]	1	2	0	3
Rapoport <i>et al.</i> [2015]	2	2	1	5
Rapoport <i>et al.</i> [2015], HEC1	2	2	1	5
Rapoport <i>et al.</i> [2015], HEC2	2	2	1	5
Gralla <i>et al.</i> [2014]	2	2	1	5
Grunberg <i>et al.</i> [2009]	2	2	1	5
Roila <i>et al.</i> [2009]	2	2	1	5
Schmitt <i>et al.</i> [2014]	2	2	1	5
Hu <i>et al.</i> [2014]	2	2	1	5
Wenzell <i>et al.</i> [2013]	2	0	1	3
Stiff <i>et al.</i> [2013]	2	2	1	5
Takahashi <i>et al.</i> [2010]	2	2	1	5
De Wit <i>et al.</i> [2003]	2	2	1	5
Schmoll <i>et al.</i> [2006]	2	2	1	5
Hesketh <i>et al.</i> [2003]	2	2	1	5
Poli-Bigelli <i>et al.</i> [2003]	2	2	1	5
Herrington <i>et al.</i> [2008]	2	2	1	5
Saito <i>et al.</i> [2014]	2	2	1	5
Ando <i>et al.</i> [2015]	2	0	1	3

Ergebnisse

Indirect comparison for the overall phase of CR (from 0 to 120 h after chemotherapy)

- [...] The majority of the regimens containing NK-1 inhibitors [including NEPA, aprepitant/palono/dexamethasone (dexa), casopitant/ grani or ondan/dexa, aprepitant/ondan/dexa] are better than regimens not containing them (palono/dexa, ondan/dexa, grani/dexa) in terms of achieving a CR in the overall phase
- Other interdrug indirect comparisons among the neurokinin inhibitors themselves suggested that casopitant/grani or ondan/dexa and aprepitant/ grani or ondan/dexa are better than rolapitant/ ondan or grani/dexa in terms of CR achievement
- None of the other interdrug indirect comparisons indicated statistically significant differences between the other neurokinin inhibitors and provided a crude efficacy arrangement for neurokinin inhibitors in terms of ability to achieve CR rates.

Indirect comparison of the overall phase of rate of no significant nausea (from 0 to 120 h after chemotherapy).

- None of the interdrug indirect comparisons indicated statistically significant differences between the evaluated regimens and the relevant league table provided a crude efficacy arrangement for neurokinin inhibitors in terms of their ability to achieve a higher rate of no significant nausea (Figure 3a–c).

Anmerkung des Autors bezüglich Heterogenität:

	<p>The principal weakness of this meta-analysis is the presence of some degree of heterogeneity among included studies. Proper sensitivity analyses and meticulous review of all published data have been conducted to overcome this. Moreover, the network meta-analysis has some inherent limitations in performing indirect comparisons mainly due to selection biases.</p> <p><u>Referenzen:</u></p> <p>[Schnadig et al. 2014; De Wit et al. 2003; Hesketh et al. 2003; Poli-Bigelli et al. 2003; Schmoll et al. 2006; Herrington et al. 2008; Grunberg et al. 2009; Roila et al. 2009; Takahashi et al. 2010; Saito et al. 2013; Stiff et al. 2013; Wenzell et al. 2013; Gralla et al. 2014; Hu et al. 2014; Schmitt et al. 2014; Ando et al. 2015; Rapport et al. 2015a; Rapport et al. 2015b].</p>
	<p>4. Anmerkungen/Fazit der Autoren</p> <p>The indirect comparison from this analysis revealed that the majority of the regimens containing NK-1 inhibitors (including NEPA, aprepitant/palono/dexa, casopitant/grani or ondan/dexa, aprepitant/ondan/dexa) are better than regimens not containing them (palono/dexa, ondan/dexa, grani/dexa) in terms of achieving a CR in the overall phase. However, none of the other interdrug indirect comparisons revealed significant differences in terms of rates of no significant nausea.</p>
<p>Dos Santos LV et al., 2012 [2].</p> <p>Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review</p>	<p>1. Fragestellung</p> <p>We planned this systematic review with meta-analysis to evaluate the overall effectiveness and safety of NK1R antagonists in the prevention of CINV and have reported it according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.</p> <p>2. Methodik</p> <p>Population: cancer patients receiving chemotherapy, regardless of its emetogenic potential.</p> <p>Intervention: Addition of NK1R antagonists (oral or i.v., 1 day, >1 day) to standard antiemetic regimens (including a 5-HT3 antagonist plus dexamethasone)</p> <p>Komparatoren: adequate antiemetic therapy (dual therapy)</p> <p>Endpunkte:</p> <ul style="list-style-type: none"> • Complete response (CR) during the overall period of assessment (ie, during the acute and delayed phases after chemotherapy; 0–24 hours and 24–120 hours, respectively). <ul style="list-style-type: none"> • CR was defined as the absence of vomiting or retching and the absence of the need for rescue antiemetic drugs. • CR in the acute and delayed phases was a secondary outcome. Symptoms that appeared within the first 24 hours after administration of chemotherapy were classified as acute and those that appeared from 24 to 120 hours after

	<p>the administration of chemotherapy were considered as delayed.</p> <ul style="list-style-type: none"> • Nausea and vomiting during the acute, delayed, and overall periods. • Nausea was classified according to a 100-mm visual analogical scale (VAS), where 0 mm correlates to absence of nausea and 100 mm correlates to the worst possible nausea experienced by the patient. • In this classification, patients with a visual analogical scale less than 5 mm were classified as having “no nausea,” and patients with a visual analogical scale less than 25 mm were classified as having “no (clinically) significant nausea.” • Adverse events <p>Suchzeitraum (Aktualität der Recherche): bis Ende 2010</p> <p>Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 (n=8740) No language restrictions.</p> <p>Qualitätsbewertung der Studien: The data extraction form included the following items: [...] methodological characteristics of the RCTs (method of randomization, allocation concealment, blinding, drop-out description, calculation of the sample size, intention-to-treat principle, funding source) [...] The characteristics directly related to the risk of bias were analyzed in subgroups to test their impact on the estimation of the effect size.</p> <p>Heterogenität: I²</p>
	<h3>3. Ergebnisdarstellung</h3> <h4>Studiencharakteristika</h4> <ul style="list-style-type: none"> • Seventeen studies (21,36–38,40–42,44–50,52,55,57) were eligible for quantitative synthesis and analysis, comprising 8740 patients- • All studies were reported in English (21,36–38,40–42,44–50,52,55,57), and all but one were multicentered (55). • Only three studies used intention-to-treat analysis (36,41,49); however, the drop-out rate for the remaining studies was less than 5% (21,37,38,40,42,44–48,50,52,55,57). • Three studies used ondansetron, an active antiemetic agent, in place of a placebo in the control arm from day 2 to the last day of therapy (48,50,52). Nine studies decreased the dexamethasone dose in the experimental arm in an attempt to prevent pharmacokinetic interaction with NK1R antagonists (41,42,46–50,52,57). • All studies were blinded. <h4>Qualität der Studien</h4> <ul style="list-style-type: none"> • There was no strong evidence of publication bias (Egger test: $P = .09$). All efficacy outcomes were corrected for publication bias using the “trim and fill” method, and no major impact on the effect size was found. • The methodological characteristics of the selected trials included in this meta-analysis had no impact on the results

obtained, as confirmed by a sensitivity analysis that we performed.

Trial	No. of patients	Randomization method and allocation concealment		Blinding/ placebo controlled	Drop-out description ITT*	Funding	Predetermined alpha-error and power	Reference
		Adequate	Unclear					
Navari (1999)	159	Adequate	Yes	Yes	No Unclear		Yes	[21]
Hesketh (1999)	61	Unclear	Yes	Yes	No Pharm Company only		Yes	[45]
Campos (2001)	351	Adequate	Yes	Yes	No Pharm Company plus other sources		Yes	[37]
Chawla (2003)	381	Adequate	Yes	Yes	No Pharm Company only		Yes	[38]
de Wit (2003)	202	Adequate	Yes	Yes	No Pharm Company only		Yes	[40]
Hesketh (2003)	530	Adequate	Yes	Yes	No Pharm Company only		Yes	[46]
Poli-Bigelli (2003)	569	Adequate	Yes	Yes	No Pharm Company only		Yes	[47]
Warr (2005)	886	Adequate	Yes [#]	Yes	No Pharm Company only		Yes	[52]
Schmoll (2006)	489	Adequate	Yes [#]	Yes	No Pharm Company only		Yes	[50]
Joshi (2007)	36	Unclear	Yes	No	Unclear		No	[55]
Arpomwrat (2009)	723	Adequate	Yes	Yes	Yes Pharm Company only		Yes	[36]
Gore (2009)	46	Unclear	Yes	Yes	Yes Pharm Company only		No	[41]
Grunberg (2009)	810	Adequate	Yes	Yes	No Pharm Company only		Yes	[42]
Henstedt (2009)	1933	Adequate	Yes	Yes	No Pharm Company only		Yes	[44]
Rolla (2009)	493	Adequate	Yes	Yes	Yes Pharm Company only		Yes	[49]
Rapport (2010)	848	Adequate	Yes [#]	Yes	No Pharm Company only		Yes	[48]
Takahashi (2010)	453	Adequate	Yes	Yes	No Pharm Company only		Yes	[57]

* All studies that excluded patients from efficacy analysis after randomization were not considered as intention-to-treat (ITT) studies. Chawla [38] and De Wit [40] double-counted some patients, and two arms of Campos et al. [37] were excluded, so the total number of subjects in these studies was 8950 and the number of subjects analyzed in the meta-analysis was 8740.

† This study was probably funded by a pharmaceutical company.
‡ Active agent control in the delayed phase.

Ergebnisse

CR in the overall phase (13 studies, n= 8173).

- The frequency of vomiting, retching, or use of rescue medication was statistically significantly decreased among patients who received NK1R antagonists compared with the standard therapy ($OR = 0.51$, 95% CI = 0.46 to 0.57, $P < .001$).
- In the experimental arm, 3759 of 5252 patients (72%) had a complete response in the overall phase, whereas only 1569 of 2921 (54%) patients in the control arm did ($P < .001$).
- Among patients given aprepitant, 1459 of 2268 (64.3%) had a CR vs 977 of 1972 (49.5%) in the control arm. Among patients given casopitant, 1985 of 2575 (77.1%) had a CR vs 542 of 865 (62.6%) in the control arm.

Acute phase (15 studies, n= 8376).

- There was a statistically significant greater frequency of CR among patients who received NK1R antagonists compared with patients who did not receive them ($OR = 0.56$, 95% CI = 0.48 to 0.65, $P < .001$).

Delayed phase (15 studies, n=8375):

- There was again a statistically significantly greater frequency of CR among patients who received NK1R antagonists (OR = 0.48, 95% CI = 0.42 to 0.56, $P < .001$).

Other Endpoints

- Rate of emesis, no nausea, no substantial nausea in all phases: The addition of a NK1R antagonist was superior to the control arm. secondary endpoints (no emesis in the delayed phase and no nausea in the acute and delayed phases), the effect size could not be estimated because of the heterogeneity seen among trials. We chose not to pool the data because we could not identify the reasons for such findings.

Subgroup analysis für CR: HEC, MEC

- HEC: 54-73%, OR = 0.46, 95% CI: 0.40 – 0.53, $P < 0.001$
- MEC: 54-71%, OR = 0.59, 95% CI: 0.51 – 0.67, $P < 0.001$
- Considering that the control arms for highly and moderately emetogenic chemotherapy were not dissimilar, the differences suggest that the addition of a NK1R antagonist yields a superior magnitude of impact favoring their use in highly emetogenic chemotherapy schedules ($P_{interaction} = .015$).

Safety (Details siehe Anhang)

- [...] incidence of severe infection increased from 2% to 6% in the NK1R antagonist group (three RCTs with a total of 1480 patients; OR = 3.10; 95% CI = 1.69 to 5.67, $P < 0.001$).

Referenzen

21. Navari RM, Reinhardt RR, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 Antiemetic Trials Group. *N Engl J Med.* 1999;340(3):190–195.
36. Arpornwirat W, Albert I, Hansen VL, Levin J, Bandekar RR, Grunberg SM. Phase 2 trial results with the novel neurokinin-1 receptor antagonist casopitant in combination with ondansetron and dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving moderately emetogenic chemotherapy. *Cancer.* 2009;115(24):5807–5816.
37. Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol.* 2001;19(6):1759–1767.
38. Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer.* 2003;97(9):2290–2300.
40. de Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol.* 2003;21(22):4105–4111.
41. Gore L, Chawla S, Petrilli A, et al.; Adolescent Aprepitant in Cancer Study Group. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. *Pediatr Blood Cancer.* 2009;52(2):242–247.
42. Grunberg SM, Rolski J, Strausz J, et al. Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2009;10(6):549–558.

	<p>44. Herrstedt J, Apornwirat W, Shaharyar A, et al. Phase III trial of casopitant, a novel neurokinin-1 receptor antagonist, for the prevention of nausea and vomiting in patients receiving moderately emetogenic chemotherapy. <i>J Clin Oncol.</i> 2009;27(32):5363–5369.</p> <p>45. Hesketh PJ, Gralla RJ, Webb RT, et al. Randomized phase II study of the neurokinin 1 receptor antagonist CJ-11,974 in the control of cisplatin-induced emesis. <i>J Clin Oncol.</i> 1999;17(1):338–343.</p> <p>46. Hesketh PJ, Grunberg SM, Gralla RJ, et al.; Aprepitant Protocol 052 Study Group. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. <i>J Clin Oncol.</i> 2003;21(22):4112–4119.</p> <p>47. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al.; Aprepitant Protocol 054 Study Group. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. <i>Cancer.</i> 2003;97(12):3090–3098.</p> <p>48. Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. <i>Support Care Cancer.</i> 2010;18(4):423–431.</p> <p>49. Roila F, Rolski J, Ramlau R, et al. Randomized, double-blind, dose-ranging trial of the oral neurokinin-1 receptor antagonist casopitant mesylate for the prevention of cisplatin-induced nausea and vomiting. <i>Ann Oncol.</i> 2009;20(11):1867–1873.</p> <p>50. Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. <i>Ann Oncol.</i> 2006;17(6):1000–1006.</p> <p>55. Joshi AJ, Singh H, Chawla S. Prevention of chemotherapy induced delayed nausea and vomiting with aprepitant in patients receiving highly emetogenic-five day cisplatin regimens. <i>J Clin Oncol.</i> 2007;25(18s):suppl, abstr 14125.</p> <p>57. Takahashi T, Hoshi E, Takagi M, Katsumata N, Kawahara M, Eguchi K. Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin. <i>Cancer Sci.</i> 2010;101(11):2455–2461.</p>
	<p>4. Schlussfolgerungen der Autoren</p> <ul style="list-style-type: none"> • In conclusion, NK1R antagonists, including aprepitant and casopitant, improved control of CINV in the acute, delayed, and overall phases for patients who received highly and moderately emetogenic chemotherapy. CINV control in the acute phase seemed to be a surrogate for CINV control in the delayed phase. • Our results demonstrate that cancer patients who receive moderately emetogenic chemotherapy derive an overall benefit from using NK1R antagonists, similar to patients who receive highly emetogenic chemotherapy, however, in lower magnitude. <p><i>Anmerkung FB Med:</i></p> <ul style="list-style-type: none"> • Alle Patienten (sowohl HEC als auch MEC) wurden in die Metaanalyse eingeschlossen. • Studien durch Pharmaunternehmen gesponsert.
Simino GP et al., 2016 [11].	<p>1. Fragestellung</p> <p>The goal of the present systematic review was to assess the efficacy, safety, and effectiveness of serotonin antagonists used as antiemetic agents in cancer patients undergoing CT, comparing the</p>

Efficacy, safety and effectiveness of ondansetron compared to other serotonin-3 receptor antagonists (5-HT3RAs) used to control chemotherapy-induced nausea and vomiting: systematic review and meta-analysis	<p>first antiemetic agent of this class, i.e. ondansetron (OND), with granisetron (GRA), tropisetron (TROP), dolasetron (DOL), and palonosetron (PALO).</p> <p>2. Methodik</p> <p>Population: adults with cancer undergoing CT</p> <p>Intervention: Ondansetron (OND)</p> <p>Komparator: Granisetron (GRA), tropisetron (TROP), dolasetron (DOL), and palonosetron (PALO).</p> <p>Endpunkt:</p> <ul style="list-style-type: none"> • Proportion of patients with partial response and failure (absence of complete response) for acute nausea (AN) and acute vomiting (AV) (0–24 h after the beginning of CT infusion, assessed as separate outcomes). • partial response and failure (absence of complete response) for delayed nausea (DN) and delayed vomiting (DV) (from 24 h to 7 days after the beginning of CT infusion; anticipatory nausea and vomiting (prior to CT administration); • adverse effects. <p>Suchzeitraum (Aktualität der Recherche): August 2015; Studies in Portuguese, English, and Spanish</p> <p>Anzahl eingeschlossene Studien/Patienten (Gesamt): 26 studies (23 RCTS, 3 observational), 8813 Patienten</p> <p>Qualitätsbewertung der Studien:</p> <ul style="list-style-type: none"> • Modified Jadad scale: 0–2 = poor quality/risk of bias; 3–4 = appropriate quality/moderate risk of bias; and 5–9 = high quality/low risk of bias. • Cochrane Collaboration's tool for assessing risk of bias in randomized clinical trials
	<p>3. Ergebnisdarstellung</p> <p>Studiencharakteristika</p> <ul style="list-style-type: none"> • The studies had been published from 1993 to 2013, and all of them were in English. Altogether, in the meta-analysis we assessed 8813 patients of the RCTs, of which 3875 used OND, 2850 GRA, 175 TROP, 674 DOL, and 539 PALO. In the meta-analysis of effectiveness, we assessed 475 patients, of which 268 used OND and 207 GRA. • The OND intervention versus GRA intervention had been assessed in 12 studies [32–42] (outcomes assessed: AN; DN; AV; and DV). Three of them [35,36,41] had compared OND intervention with TROP intervention (outcomes assessed: AN; DN; AV; and DV), four studies [43–47] had compared OND intervention with DOL intervention (outcomes assessed: AV and DV), and six studies [48–53] had compared OND intervention with PALO intervention (outcomes assessed: AN; DN; AV; and DV). <p>Qualitätsbeurteilung</p>

- Of the 23 RCTs, 15 [33,34,36,39–48,50,51] had high methodological quality and low risk of bias, 7 [32,35,37,49,52,53] were classified as having appropriate methodological quality and moderate risk of bias, and one study [38] had poor methodological quality and high risk of bias.
- The assessment of risk of bias showed that 75% of the studies had low risk of bias or uncertain risk. High risk of bias was related to 'allocation concealment' in three studies [35,43,51], 'blinding of participants and professionals' in one study [35], and 'selective reporting of the outcome' in one study [41].
- Conflict of interest: The presence of conflict of interest was considered when the study claimed to be funded or conducted by authors who belonged to the pharmaceutical industry and had received some benefit from it. Of the studies presented, 10 had conflicts of interest [33,39,40,42,44,45,47,48,50,52].

Referenzen

32. Gebbia V, Cannata G, Testa A. Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting. *Cancer*. 1996;74:1945–1952.
33. Gralla RJ, Navari RM, Hesketh PJ, et al. Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. *J Clin Oncol*. 1998;16:1568–1573.
34. Italian Group for Antiemetic Research. Ondansetron versus granisetron, both combined with dexamethasone, in the prevention of cisplatin-induced emesis. *Ann Oncol*. 1995;6:805–810.
35. Jantunen IT, Muuronen TT, Kataja VV, et al. 5-HT3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy - a randomised study. *Eur J Cancer*. 1993;29:1669–1672.
36. Kalaycio M, Mendez Z, Pohlman B, et al. Continuous-infusion granisetron compared to ondansetron for the prevention of nausea and vomiting after high-dose chemotherapy. *J Cancer Res Clin Oncol*. 1998;124:265–269.
37. Martoni A, Angelelli B, Guaraldi M, et al. An open randomised crossover study on granisetron versus ondansetron in the prevention of acute emesis induced by moderate dose cisplatin-containing regimens. *Eur J Cancer*. 1996;32:82–85.
38. Massida B, Ionta MT. Prevention of delayed emesis by a single intravenous bolus dose of 5-HT3-receptor-antagonist in moderately emetogenic chemotherapy. *J Chemother*. 1996;8:237–242.
39. Navari F, Gandara D, Hesketh P, et al. Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin-induced emesis. *J Clin Oncol*. 1995;13:1242–1248.
40. Perez EA, Hesketh P, Sandbach J, et al. Comparison single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: a multicenter, double-blind, randomized parallel study. *J Clin Oncol*. 1998;16:754–760.
41. Ruff P, Paska W, Goedhals L, et al. Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: a multicenter double-blind, randomized, parallel-group study. *Oncology*. 1994;51:113–118.
42. Stewart A, McQuade B, Cronje JD, et al. Ondansetron compared with granisetron in the prophylaxis of cyclophosphamide-induced emesis in outpatients: a multicentre, double-blind, doubledummy, randomised, parallel-group study. *Emesis study group for ondansetron and granisetron in breast cancer patients. Oncology*. 1995;52:202–210.
43. Marty M, Kleisbauer JP, Fournel P, et al. Is navoban (tropisetron) as effective as zofran (ondansetron) in cisplatin-induced emesis? The French

- Navoban Study Group. Anticancer Drugs. 1995;suppl1:615– 621.
44. Fausser AA, Duclos B, Chemaissani A, et al. Therapeutic equivalence of single oral doses of dolasetron mesilate and multiple doses of ondansetron for the prevention of emesis after moderately emetogenic. Chemotherapy. 1996;32A:1523–1529.
 45. Hesketh P, Navari R, Grote T, et al. Double-blind, randomized comparison of the antiemetic efficacy of intravenous dolasetron mesylate and intravenous ondansetron in the prevention of acute cisplatin-induced emesis in patients with cancer. Dolasetron comparative chemotherapy-induced emesis prevention group. J Clin Oncol. 1996;14:2242–2249.
 46. Kim JS, Baek JY, Park SR, et al. Open-label, randomized comparison of the efficacy of intra-venous dolasetron mesylate and ondansetron in the prevention of acute and delayed cisplatin-induced emesis in cancer patients. Cancer Res Treat. 2004;36:372–376.
 47. Lofters WS, Pater JL, Zee B, et al. Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed nausea and vomiting due to moderately emetogenic chemotherapy. J Clin Oncol. 1997;15:2966–2973.
 48. Aapro MS, Grunberg SM, Manikhas GM, et al. A phase III, doubleblind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol. 2006;17:1441–1449.
 49. Dong X, Huang J, Cao R, et al. Palonosetron for prevention of acute and delayed nausea and vomiting in non-small-cell lung carcinoma patients. Med Oncol. 2011;28:1425–1429.
 50. Gralla R, Lichinitser M, Van Der Vegt S. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a doubleblind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol. 2003;14:1570–1577.
 51. Kaushal J, Gupta MC, Kaushal V, et al. Clinical evaluation of two antiemetic combinations palonosetron dexamethasone versus ondansetron dexamethasone in chemotherapy of head and neck cancer. Singapore Med J. 2010;51:871–875.
 52. Mattiuzzi GN, Cortes JE, Blamble DA, et al. Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy- induced nausea and vomiting in patients with acute myelogenous leukemia. Cancer. 2010;116:5659–5666.

Ergebnisse:

Anmerkung FB Med: Keine Unterteilung in hoch/moderat (oder niedrig) ematogene Chemotherapie

Table 3. Meta-analysis of interventions outcomes and adverse effects in the studies.

Intervention	Outcomes	Study (reference)	n	Relative risk (95% CI)	p-Value	I^2 (%)	p-Value
Randomized clinical trials							
OND vs.	AN	10 [32–34,37–42]	4917	1.02 [0.96, 1.09]	0.53	0	0.44
GRA	DN	3 [32,38]	364	1.02 [0.79, 1.31]	0.90	37	0.20
	AV	12 [32–42]	5066	0.97 [0.91, 1.03]	0.27	8	0.37
	DV	3 [32,38]	198	1.18 [0.88, 1.59]	0.27	0	0.66
Adverse effect	Headache	6 [34,36,37,40–42]	2885	1.21 [0.99, 1.47]	0.06	0	0.74
	Constipation	5 [34,37,40–42]	2840	1.02 [0.64, 1.63]	0.94	29	0.23
	Diarrhea	4 [36,37,40,41]	1586	1.01 [0.62, 1.66]	0.96	17	0.31
	Dizziness	2 [40,41]	1417	1.83 [1.19, 2.81]	0.006	0	0.64
	Weakness	2 [34,40]	2051	0.73 [0.25, 2.12]	0.57	72	0.06
	Heartburn	2 [34,40]	2051	1.03 [0.62, 1.72]	0.90	0	0.98
OND vs. TROP	AN	2 [38,43]	240	0.82 [0.51, 1.31]	0.41	64	0.10
	DN	2 [38,43]	240	1.31 [0.95, 1.81]	0.10	8	0.30
	AV	3 [35,38,43]	531	1.16 [0.96, 1.40]	0.12	0	0.77
	DV	2 [38,43]	240	1.00 [0.79, 1.28]	0.98	0	0.46
Adverse effect	Headache	2 [35,43]	491	1.31 [0.97, 1.78]	0.08	84	0.01
OND vs.	AV	4 [44–47]	1371	0.85 [0.73, 0.98]	0.02	21	0.28
DOL	DV	2 [46,47]	660	0.93 [0.83, 1.05]	0.26	0	0.33
Adverse effect	Headache	3 [44,45,47]	1270	0.84 [0.71, 0.98]	0.03	0	0.96
	Constipation	2 [44,47]	859	1.22 [1.00, 1.49]	0.05	0	0.41
	Diarrhea	4 [44–47]	1375	0.48 [0.34, 0.68]	<0.0001	0	0.78
	Fever	2 [44,45]	574	1.91 [0.29, 12.51]	0.50	49	0.16
	Anxiety	2 [44,47]	859	1.62 [0.70, 3.79]	0.26	12	0.29
	Fatigue	2 [44,47]	859	0.93 [0.45, 1.92]	0.84	17	0.27
OND vs. PALO	AN	4 [49,51–53]	254	1.14 [0.78, 1.66]	0.50	0	0.84
	DN	4 [49,51–53]	254	1.25 [1.01, 1.56]	0.04	0	0.44
	AV	6 [38,48–50,52]	1072	1.28 [1.02, 1.59]	0.03	13	0.33
	DV	6 [38,48–51,53]	1072	1.31 [1.01, 1.69]	0.04	72	0.003
Adverse effect	Headache	4 [48–50,52]	1002	1.31 [0.83, 2.08]	0.25	0	0.95
	Constipation	3 [48–50]	859	0.88 [0.47, 1.65]	0.70	0	0.42
	Diarrhea	3 [48,49,52]	628	1.68 [0.41, 6.95]	0.47	Not applicable	-
	Dizziness	2 [49,50]	463	4.89 [0.85, 28.32]	0.08	0	0.70

Subgroup analysis: emetic potential of the chemotherapeutic drug

Acute nausea.

- For the HEC subgroup, the comparison of OND with GRA showed no efficacy difference in five studies [32–34,37,39], as well as in the MEC subgroup [32,38]. One study [41] had assessed patients with diverse emetic potential and other study had assessed participants with MEC and HEC (OND vs. TROP). Two studies [38,43] had only assessed MEC.
- In the HEC subgroup, regarding the comparison of OND with PALO, the studies showed no statistically significant difference in efficacy of the drugs, as well as in the MEC subgroup.

Acute vomiting.

- In the HEC subgroup [32–34,36,37,39], the comparison of OND with GRA showed greater OND efficacy
→ RR (M-H, random, 95% CI) = 0.92 [0.85, 1.00], p = 0.04, and I² = 0%.
- In the MEC subgroup, there was no statistically significant difference between these drugs. The studies that had compared OND with TROP [35,38,43] had only addressed patients submitted to MEC.
- In the comparison of OND with DOL, the HEC subgroup [45,46]

	<p>showed no efficacy difference. However, in the MEC subgroup, OND exhibited greater efficacy than DOL in the control of AV \rightarrow RR (M-H, random, 95% CI) = 0.77 [0.64, 0.91], p = 0.003, and I² = 0%.</p> <ul style="list-style-type: none"> The comparison of OND with PALO in the HEC subgroup [48,49,53] showed no efficacy difference between the drugs for this outcome. In the MEC subgroup [50–52], PALO exhibited greater efficacy than OND \rightarrow RR (M-H, random, 95% CI) = 1.57 [1.15, 215], p = 0.004, and I² = 0%. <p>Delayed nausea</p> <ul style="list-style-type: none"> The RCTs had assessed 958 participants. The comparisons had been OND versus GRA (three studies) [32,32,36] and OND versus TROP (two studies) [38,43], which showed no statistically significant difference (p = 0.90 and 0.10, respectively). The comparison of OND with PALO (four studies) [49,51–53] showed greater PALO efficacy for this outcome (p = 0.004). Statistical heterogeneity in the three comparisons of the studies had been low. When we excluded the MEC studies from the meta-analysis for the DN outcome, the comparison of OND with GRA did not modify the statistical relevance. When the MEC studies [51,52] that had compared OND with PALO were excluded, there was greater PALO efficacy and heterogeneity \rightarrow RR (M-H, random, 95% CI) = 1.24 [0.75, 2.04], p = 0.41, and I² = 60%. <p>Subgroup analysis: Conflict of interest</p> <p>Acute vomiting</p> <ul style="list-style-type: none"> In the subgroup with conflict of interest that had compared OND with PALO, the latter showed less efficacy, RR (M-H, random, 95% CI) = 1.28 [0.96, 1.70], p = 0.10, and I² = 38%. <p><i>Anmerkung FB Med: Nur Unterschiede bei dem oben genannten Endpunkt gefunden.</i></p>
	<p>4. Anmerkungen/Fazit der Autoren</p> <ul style="list-style-type: none"> In the present meta-analysis, ondansetron had similar efficacy than granisetron and tropisetron, and greater than dolasetron in cancer patients undergoing HEC, MEC. Palonosetron exhibited greater efficacy than ondansetron, reducing the occurrence of delayed nausea, acute vomiting and delayed vomiting. However, in the assessment of the ‘conflict of interest’ subgroup, palonosetron lost efficacy when compared with ondansetron for the acute vomiting outcome. In the subgroup that had received prior chemotherapy, there was not statistical significance that favored palonosetron. In the sensitivity assessment, when studies that assessed MEC were excluded from the meta-analysis, palonosetron was also less effective than ondansetron. <p>5. Hinweise durch FB Med</p>

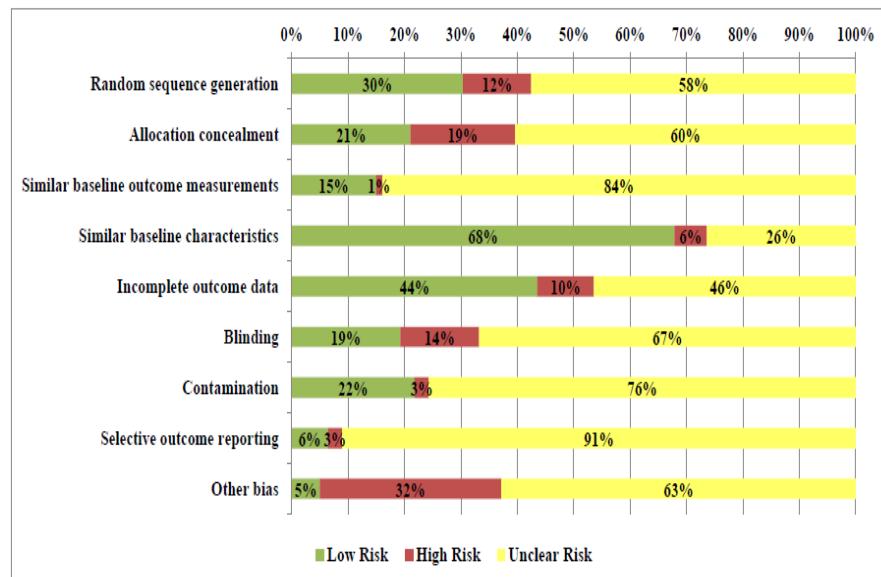
	<ul style="list-style-type: none"> • Unklar, ob bzw. welche antiemetogene Therapie eingesetzt wurde. • AEs: Keine Unterteilung in Subgruppen • Studien durch Pharmaunternehmen gesponsert: Subgruppenanalyse zeigt geringere Wirksamkeit bei Palonosetron beim Endpunkt AN nach Auslassen der relevanten Studien. • AM teilweise nicht zugelassen.
Tricco A et al., 2016 [12]. Comparative safety and effectiveness of serotonin receptor antagonists in patients undergoing chemotherapy: a systematic review and network meta-analysis	<p>1. Fragestellung Our objective was to examine the comparative safety and effectiveness of 5-HT3 receptor antagonists (e.g., dolasetron, granisetron, ondansetron, palonosetron, tropisetron) alone or combined with steroids for patients undergoing chemotherapy.</p> <p>2. Methodik</p> <p>Population: patients of any age undergoing chemotherapy Intervention 5-HT3 receptor antagonist (i.e., dolasetron, granisetron, ondansetron, palonosetron, ramosetron, tropisetron) alone or combined with steroids (dexamethasone, methylprednisolone, prednisone) Komparator: With each other or placebo Endpunkt</p> <ul style="list-style-type: none"> • The primary [...] was the number of patients experiencing arrhythmia. • Secondary outcomes [...]: QTc prolongation, QRS interval prolongation, death, sudden cardiac death, delirium, no nausea, no vomiting, no CINV, and severe vomiting. <p>Suchzeitraum (Aktualität der Recherche): 11th December 2015 Studies published in languages other than English were excluded. Anzahl eingeschlossene Studien/Patienten (Gesamt): 299 studies (n=58412). RCTs and Non-RCTs Qualitätsbewertung der Studien:</p> <ul style="list-style-type: none"> • Risk of bias using the Cochrane Effective Practice and Organisation of Care risk-of-bias tool [28]. <p>Heterogenität: I^2 Netzwerk-Metaanalyse: [...] frequentist framework with a random-effects model assuming a common within-network heterogeneity variance across all comparisons [...]</p> <p>3. Ergebnisdarstellung Studiencharakteristika</p> <ul style="list-style-type: none"> • The included studies were published between 1985 and 2015, with the largest proportion (based on 5-year intervals) appearing between 1995 and 1999, and nearly half were conducted in Europe [...]. More than 80% of the studies used an RCT design and more than 40% involved multiple centers. • The most commonly examined 5-HT3 receptor antagonist was ondansetron. More than 60% of the studies were limited to

adults (age \geq 18 years) [...] Lung cancer was the most common diagnosis, and more than half of the chemotherapy regimens included cisplatin. Concomitant radiotherapy was reported in less than 5% of the studies.

Anmerkung FB Med: Patientencharakteristika (Tumorart und Chemotherapie) siehe Anhang

Qualitätsbeurteilung der Studien

Appendix D. Aggregate Cochrane EPOC risk-of-bias appraisal results



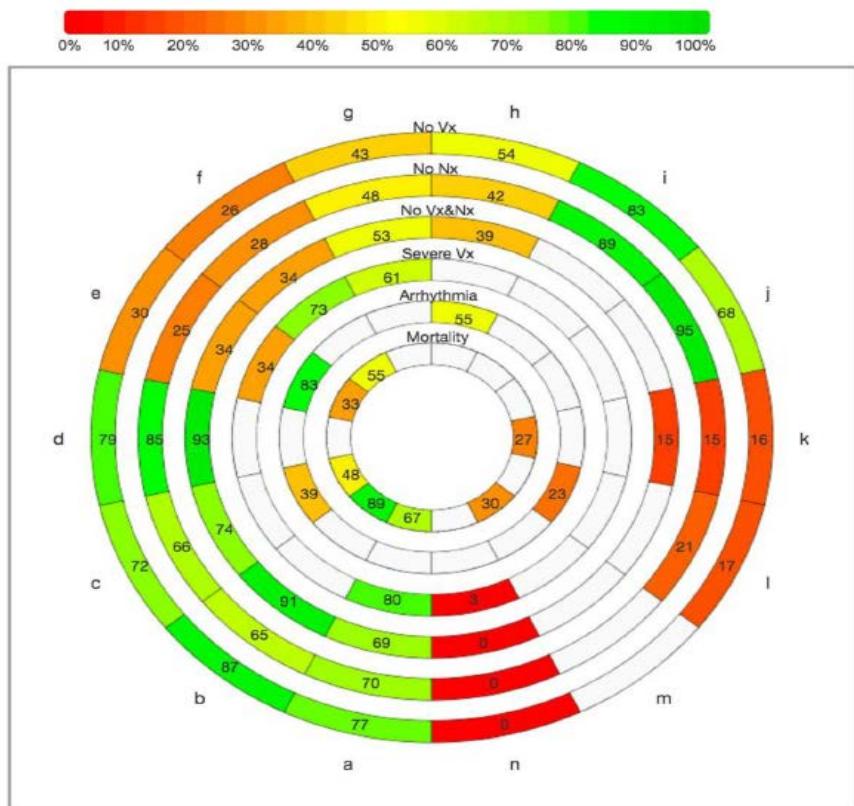
Abbreviations: EPOC - Effective Practice and Organisation of Care; High Risk - high risk of bias; Low Risk - low risk of bias; Unclear Risk - unclear risk of bias

- Overall, more than half of the studies were assessed as unclear on all of the following components: random sequence generation, allocation concealment, baseline outcome measure similarities between treatment groups, blinding, contamination, selective outcome reporting, and other bias.
- With regard to sources of funding, 153 of the 299 studies did not report the source of funding, 127 were funded by pharmaceutical companies, 17 were publicly funded, and two reported no funding was received.
- Reporting bias and small-study effects were not observed across the comparison-adjusted funnel plots for all outcomes

Ergebnisse

Rank Heat plot

Anmerkung FB Med: [...] each sector is colored according to the ranking of the particular treatment at the corresponding outcome. [...] The red color corresponds to the smallest SUCRA value (0%), values near the middle of the scale are yellow, and the green color corresponds to the highest SUCRA value (100%). A.A. Veroniki et al. / Journal of Clinical Epidemiology 76 (2016) 193e199 195



Treatments
a: ONDA+STER
b: PALO+STER
c: GRAN+STER
d: RAMO+STER
e: GRAN
f: ONDA
g: RAMO
h: PALO
i: TROP+STER
j: DOLA+STER
k: TROP
l: DOLA
m: METO+DEX
n: PLAC

Outcomes
Circles from outside in refer to :
1st: No Vx
2nd: No Nx
3rd: No Vx&Nx
4th: Severe Vx
5th: Arrhythmia
6th: Mortality
White sectors refer to treatments without data on the outcome within the circle.

Arrhythmia

- NMA for the primary outcome of arrhythmia was attempted using three RCTs ($n = 627$ adults) investigating dolasetron, granisetron, palonosetron, and/or granisetron + dexamethasone.
- The NMA showed no statistically significant effects [...] The safest treatment according to the SUCRA was granisetron (83% probability, Fig. 3: Rank Heat plot).

Mortality

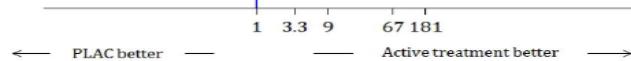
- NMA for the secondary outcome of mortality was conducted with eight RCTs ($n = 4823$ adults) investigating dolasetron, granisetron, ondansetron (usual care), palonosetron, tropisetron, granisetron + dexamethasone, metoclopramide + dexamethasone, ondansetron + dexamethasone, and/or

	<p>palonosetron + dexamethasone.</p> <ul style="list-style-type: none"> The safest treatment according to the SUCRA was palonosetron + dexamethasone (93% probability, Fig. 3). <p><u>QTc prolongation</u></p> <ul style="list-style-type: none"> four RCTs investigating dolasetron + dexamethasone, granisetron, granisetron + dexamethasone, ondansetron (usual care), ondansetron + dexamethasone, palonosetron, and palonosetron + dexamethasone ($n = 3358$ children and adults, Fig. 2). The safest treatment according to the SUCRA was palonosetron + dexamethasone (83% probability). (Fig. 3) <p><u>Other safety parameter</u></p> <ul style="list-style-type: none"> <u>Sudden cardiac death:</u> [...] ondansetron and ondansetron + dexamethasone ($n=213$ patients, $OR= 2.73$, 95% CI = 0.11–67.80). $p=n.s.$ <u>Delirium:</u> no statistically significant results for any of the treatment comparisons <ul style="list-style-type: none"> metoclopramide + dexamethasone versus granisetron ($n=361$ patients, $OR = 4.14$, 95% CI = 0.86–19.93), metoclopramide + dexamethasone versus granisetron + dexamethasone ($n = 478$ patients, $OR = 4.07$, 95% CI = 0.85–19.59), granisetron versus granisetron + dexamethasone ($n = 597$ patients, $OR = 0.98$, 95% CI = 0.01–7.10). <u>QRS interval prolongation</u> (more than 24 h of chemotherapy): ondansetron administered on days 1–7 plus dexamethasone vs. dolasetron + dexamethasone: resulted in statistically significantly fewer patients experiencing a prolonged QRD interval ($OR = 0.29$, 95% CI = 0.19–0.48). <p><u>Number of patients without vomiting</u></p> <ul style="list-style-type: none"> [...] 71 RCTs ($n = 16,300$ adults, 12 treatments plus placebo). All of the treatments were statistically significantly superior to placebo for this outcome.
--	--

Appendix O. No. of patients without vomiting – RCTs only

Reference treatment: PLAC

Treatment Effect	OR 95%CI 95%PrI
TROP	11.03 (4.28,28.47) (3.37,36.18)
DOLA	12.75 (5.01,32.43) (3.94,41.30)
ONDA	14.12 (5.97,33.40) (4.63,43.06)
GRAN	15.70 (6.61,37.28) (5.13,48.03)
RAMO	19.52 (7.62,50.03) (5.99,63.63)
PALO	26.53 (10.41,67.63) (8.18,86.10)
DOLA+STER	32.55 (11.02,96.12) (8.84,119.90)
GRAN+STER	35.27 (14.31,86.95) (11.18,111.29)
ONDA+STER	36.93 (14.95,91.23) (11.68,116.73)
RAMO+STER	39.39 (12.80,121.23) (10.31,150.49)
TROP+STER	41.11 (11.34,149.11) (9.28,182.16)
PALO+STER	47.86 (17.68,129.55) (14.01,163.44)



Abbreviations: CI - confidence interval; OR - odds ratio; PrI - prediction interval; RCT - randomized controlled trial

DOLA - dolasetron; GRAN - granisetron; ONDA - ondansetron; PALO - palonosetron; PLAC - placebo; RAMO - ramosetron; STER - steroid; TROP - tropisetron

- In another subgroup analysis including 69 RCTs and 15,742 patients who received *cisplatin chemotherapy* (12 treatments plus placebo); [...] dolasetron + steroid and tropisetron + steroid both had a higher SUCRA (89% probability) than palonosetron + steroid (78% probability).

Number of patients without vomitting more than 24 h after chemotherapy

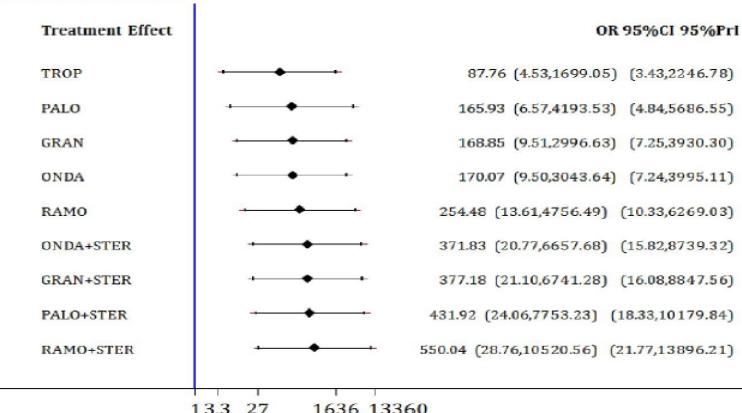
- A subgroup analysis was conducted with 45 RCTs involving only adults ($n = 8845$ patients, 26 treatments plus placebo). [...]
- Dolasetron + steroid on day 1 had the highest SUCRA (94% probability) along with palonosetron + steroid on day 1 (94% probability).

Number of patients without CINV

- NMA for 27 RCTs involving 10,924 adults (nine treatments plus placebo).

Appendix R. No. of patients without CINV – RCTs only

Reference treatment: PLAC



Abbreviations: CI - confidence interval; CINV – chemotherapy-induced nausea and vomiting; OR - odds ratio; PrI - prediction interval; RCT - randomized controlled trial

GRAN - granisetron; PALO - palonosetron; PLAC - placebo; ONDA - ondansetron; STER - steroid; TROP - tropisetron;

Similar results were observed in another subgroup analysis including 15 RCTs and 5250 patients receiving *cisplatin* chemotherapy (nine treatments plus placebo).

Number of patients without CINV at more than 24 h after chemotherapy

- 26 RCTs (n = 8851 patients, 22 treatments plus placebo)
- Ramasetron on day 1 and at least one subsequent day had the highest SUCRA (90% probability), followed by tropisetron + steroid on day 1 and at least one subsequent day (88% probability)

Number of patients experiencing severe vomiting defined as vomiting five times or more) within 24 h after chemotherapy.

- 11 RCTs, 1364 adults, and six treatments plus placebo were included. [...]
- Ondansetron + steroid had the highest SUCRA (80% probability), followed closely by ondansetron (73% probability).

4. Fazit der Autoren

From this study, we conclude that most 5-HT3 receptor antagonists alone or combined with steroids decrease the occurrence of nausea and/or vomiting. Most 5-HT3 receptor antagonists were relatively safe when compared with each other, yet none of the studies compared active treatment with placebo for harms. Dolasetron + dexamethasone may prolong the QTc compared to ondansetron + dexamethasone [...].

5. Hinweise durch FB Med

	<ul style="list-style-type: none"> • Keine Unterteilung in MEC und HEC. • Therapieoptionen: Chemotherapie, OP. • Teilweise verschiedene Patientenpopulationen zusammen untersucht (u.a. Alter <18 Jahre) • AM teilweise nicht zugelassen.
Tricco A et al., 2015 [13]. Interventions to decrease the risk of adverse cardiac events for patients receiving chemotherapy and serotonin (5-HT3) receptor antagonists: a systematic review	<p>1. Fragestellung We aimed to determine whether diagnostic interventions can be implemented to mitigate the risk of adverse cardiac events associated with 5-HT3 receptor antagonists for patients undergoing chemotherapy or surgery through a systematic review.</p> <p>2. Methodik Population: studies of patients of all ages receiving 5-HT3 antagonist receptors for nausea and vomiting symptoms post-surgery or after chemotherapy will be included. Studies on all forms of chemotherapy will be included, as well as studies on patients who are chemotherapy-naïve or have received chemotherapy previously. Intervention: 5-HT3 antagonist <i>Anmerkung FB Med: Ursprüngliche Intervention der Fragestellung: strategies to mitigate cardiac risk amongst these patients, such as electrocardiography, telemetry, adjustment of antiarrhythmics, and electrolyte monitoring and replacement, will be included. + Komparator: placebo or supportive care will be eligible comparators.</i> Endpunkt: arrhythmia and secondary outcomes are sudden death, QT prolongation, PR prolongation, all-cause mortality, nausea, and vomiting Suchzeitraum (Aktualität der Recherche): nicht genannt Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 Studien (256 Patienten) Qualitätsbewertung der Studien: Cochrane Effective Practice and Organisation of Care Risk of Bias Tool and the McHarm tool for reporting adverse events</p> <p>3. Ergebnisdarstellung</p> <p>Studiencharakteristika The study conduct period was 2000 and 2002 in the randomized clinical trials [19,20] and not reported in the non-randomized clinical trial [18] that was published in 1996 (Table 1). The trials were conducted in the United States [18], multiple European countries [19], and South Korea [20].</p>

Table 1 Study characteristics

Reference	Study period, country	Study design, # of patients	5-HT3 dose/day	Intervention, examination timing	Outcomes examined
Hesketh [18]	NR, USA	Non-RCT, 44	IV dolasetron 1.2 mg/kg, 1.8 mg/kg, 2.4 mg/kg 30 mins before chemotherapy	ECG, 1–2 hrs and 24–48 hrs	PR, QT
Gralla [19]	August 2000 to October 2001, Germany, Italy, UK, Netherlands, Russia	RCT, 98	IV palonosetron 0.25 mg, IV palonosetron 0.75 mg, IV ondansetron 32 mg 30 mins before chemotherapy	ECG, 15 mins, 24 hrs, 1 wk	Mortality, QT
Kim [20]	April 2002 to October 2002, South Korea	RCT, 114	IV dolasetron 100 mg 30 mins before and 200 mg p.o. 2–5 days after chemotherapy, IV ondansetron 8 mg 30 mins before and IV ondansetron 16 mg 2–4 hrs plus an additional 16 mg/day p.o. 2–5 days after chemotherapy	ECG, 15 mins, 24 hrs, 1 wk	ECG findings unspecified

ECG: electrocardiogram; IV: intravenous; NR: not reported; Non-RCT: non-randomized clinical trial; p.o.: administered orally; RCT: randomized controlled trial.

Table 2 Patient characteristics

Reference	% female	Mean age in years (SD) [range]	Cancer site (%)	Common chemotherapeutic agents* (%)
Hesketh [18]	71	Median 54 (NR) [25–81]	Breast (55), other (45)	Doxorubicin (15), cyclophosphamide (26), 5-FU (43), vincristine (23), methotrexate (14)
Gralla [19]	72	55 (11) [18–NR]	Breast (57), lung (80 < bladder (5), colon (4), rectal (3), small-cell lung (3), gastric (3))	Cyclophosphamide (63), doxorubicin (48), cisplatin (18), methotrexate (16), carboplatin (12)
Kim [20]	37	55.6 (11) [18–NR]	Lung (26), gastric (11), other (29)	5-FU plus cisplatin (27), cisplatin plus the following: taxol, docetaxel, etoposide and ifosfamide, etoposide, gemcitabine, docetaxel plus 5-FU (73)

NR: not reported; SD: standard deviation. *received by >10% of patients.

Qualitätsbeurteilung der Studien

Table 3 Appraisal of risk of bias, according to Cochrane Effective Practice and Organization of Care risk-of-bias tool [16]

Criterion	Hesketh [18]	Gralla [19]	Kim [20]
Random sequence generation	High	Unclear	Unclear
Allocation concealment	High	Low	High
Similar baseline outcome measures	Unclear	Low	Low
Similar baseline characteristics	Low	Low	Low
Incomplete outcome data	Low	Low	Low
Blinding	High	Low	High
Contamination	Unclear	Unclear	Unclear
Selective outcome reporting	Unclear	Unclear	Unclear
Other bias	High	Low	Low

Referenzen

18. Hesketh PJ, Gandara DR, Hesketh AM, Facada A, Perez EA, Webber LM, et al. Dose-ranging evaluation of the antiemetic efficacy of intravenous dolasetron in patients receiving chemotherapy with doxorubicin or cyclophosphamide. *Support Care Cancer*. 1996;4:141–6.
19. Gralla R, Lichinitser M, Van Der Vegt S, Sleeboom H, Mezger J, Peschel C, et al. Palonosetron improves prevention of chemotherapy-induced nausea and

vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol. 2003;14:1570–7.

20. Kim JS, Baek JY, Park SR, Choi IS, Kim SI, Kim DW, et al. Open-label, randomized comparison of the efficacy of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed cisplatin-induced emesis in cancer patients. Cancer Res Treat. 2004;36:372–6.

Ergebnisse

Arrhythmia

- None of the included trials reported data on arrhythmia, our primary outcome of interest. However, all three trials reported no clinically relevant differences in ECG findings among the patients receiving the 5-HT₃ receptor antagonists examined.

Sudden cardiac death and all-cause mortality

- Mortality was reported in one of the trials [19]. One withdrawal due to a serious adverse event (pulmonary embolism resulting in death) occurred in the ondansetron group and three other deaths occurred, yet the number of deaths per treatment group was not reported. All deaths were deemed as unlikely or definitely unrelated to the study medications [19].
- Although mortality was not specifically reported, no patients dropped out due to mortality in the other two trials [18,20].

Table 4 QT and PR prolongation

Author, year	Treatment (dose, time of treatment)		
Hesketh [18]	Dolasetron (1.2 mg/kg, BC)	Dolasetron (1.8 mg/kg, BC)	Dolasetron (2.4 mg/kg, BC)
QT prolongation*	11 ms	27 ms	39 ms
PR prolongation†	1 ms	10 ms	22 ms
Gralla [19]	Palonosetron (0.25 mg, BC)	Palonosetron (0.75 mg, BC)	Ondansetron (32 mg, BC)
QT prolongation*	1 ms	2 ms	5 ms
PR prolongation	NS	NS	NS
Kim [20]	Dolasetron (100, BC+ 800 mg, AC)	Ondansetron (8 mg, BC + 80 mg, AC)	
QT prolongation	NS	NS	
PR prolongation	NS	NS	

AC: after chemotherapy treatment; BC: before the start of chemotherapy treatment; NS: not significant. *mean change from baseline; †median change from baseline.

	<p>4. Anmerkungen/Fazit der Autoren In our systematic review, we did not find any clinically relevant changes in the QT interval between different dosages of dolasetron [18] or between palonosetron and ondansetron [19] or dolasetron and ondansetron [20]. Furthermore, we did not find any other significant differences in other ECG changes between these 5-HT3 receptor antagonists at 15 minutes, 1–2 hours, 24 hours, and 1 week post-administration. However, this does not suggest that these agents do not cause cardiac harm [...]</p> <p>5. Anmerkung FB Med: AM teilweise nicht zugelassen</p>
Whiting P et al., 2015 [14].	<p>1. Fragestellung To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.</p>
Cannabinoids for Medical Use A Systematic Review and Meta-analysis	<p>2. Methodik Population: Patients on chemotherapy Intervention: Nabilon Komparator Chlorpromazin, Alizapride, Domperidon, Prochlorperazin Endpunkte: Nausea, vomiting, retching, number of vomiting episodes, appetite, Physician global impression, duration of vomiting, complete response (vomiting, retching, nausea), partial response (vomiting, retching) Suchzeitraum (Aktualität der Recherche): till April 2015 without language restriction Anzahl eingeschlossene Studien/Patienten (Gesamt): Insgesamt: 28RCTs (n=1772), 14 RCTs mit Nabilon, Anzahl Patienten unbekannt Qualitätsbewertung der Studien: GRADE (Grading of Recommendations Assessment, Development and Evaluation)</p>
	<p>3. Ergebnisdarstellung Studiencharakteristika</p> <ul style="list-style-type: none"> • Nausea and vomiting due to chemotherapy was assessed in 28 studies (37 reports; 1772 participants).<i>Fourteen studies assessed nabilone [...]</i> • Eight studies included a placebo control, 3 of these also included an active comparator, and 20 studies included only an active comparator. The most common active comparators were prochlorperazine (15 studies), chlorpromazine (2 studies) and domperidone (2 studies). Other comparators (alizapride, hydroxyzine, metoclopramide and ondansetron) were evaluated in single studies. • Of all 28 studies, risk of bias was high for 23 or unclear for 5.

Referenzen

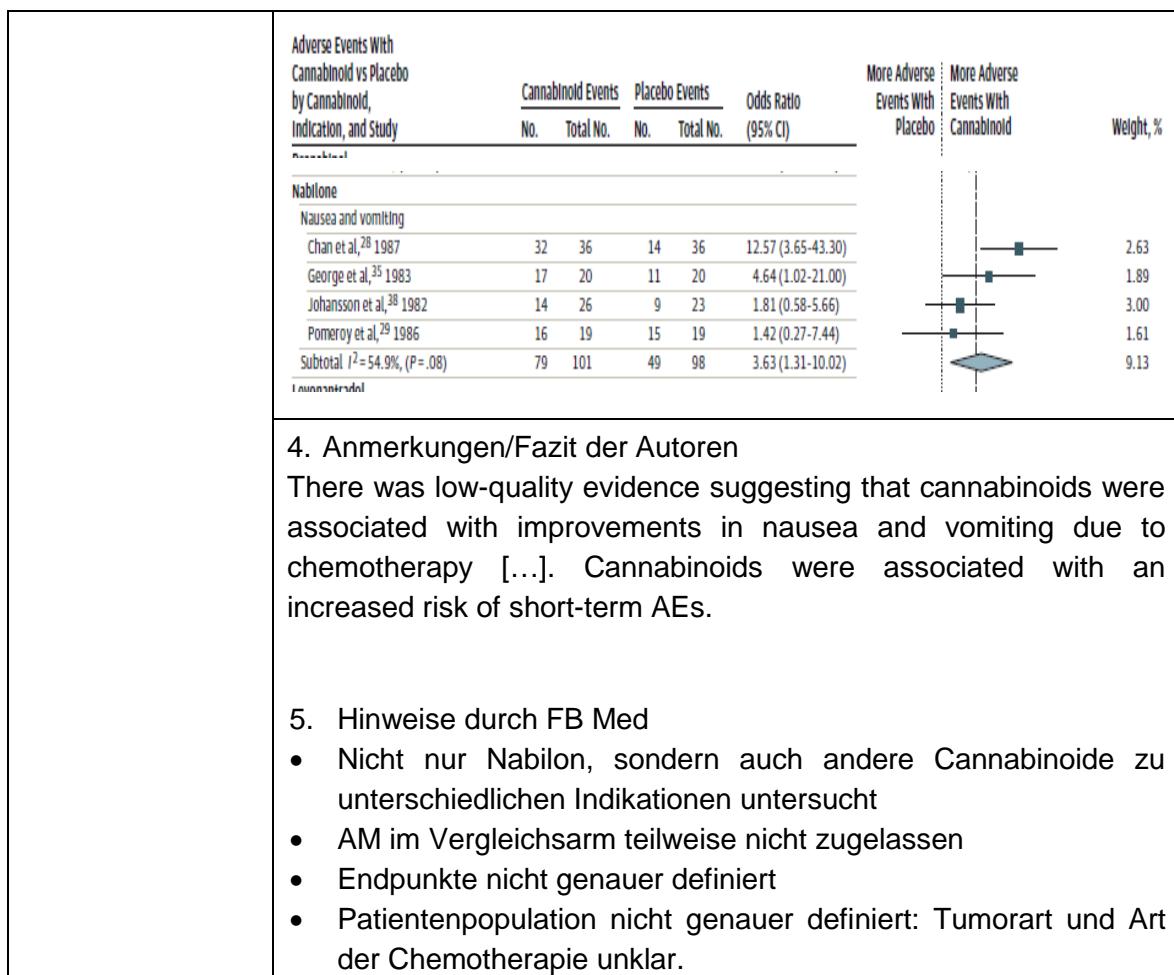
28. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics*. 1987;79 (6):946-952.
29. Pomeroy M, Fennelly JJ, Towers M. Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. *Cancer Chemother Pharmacol*. 1986;17(3): 285-288.
31. Niederle N, Schütte J, Schmidt CG. Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. *Klein Wochenschr*. 1986;64(8):362-365.
32. Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. *Am J Clin Oncol*. 1985;8(4):336-340.
35. George M, Pejovic MH, Thuaire M, Kramar A, Wolff JP. [Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin]. *Biomed Pharmacother*. 1983;37(1): 24-27.
36. Jones SE, Durant JR, Greco FA, Robertone A. A multi-institutional phase III study of nabilone vs placebo in chemotherapy-induced nausea and vomiting. *Cancer Treat Rev*. 1982;9(suppl B):45-48.
37. Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota CH, Rieth TE. Double-blind, randomized, crossover trial of nabilone vs placebo in cancer chemotherapy. *Cancer Treat Rev*. 1982;9(suppl B):39-44.
38. Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. *Cancer Treat Rev*. 1982;9(suppl B):25-33.
40. Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. *J Clin Pharmacol*. 1981;21(8-9 suppl):64S-69S.
42. Steele N, Gralla RJ, Braun DWJr, Young CW. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. *Cancer Treat Rep* 1980;64(2-3):219-224.
45. Ahmedzai S, Carlyle DL, Calder IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. *Br J Cancer*. 1983;48(5):657-663.
51. Levitt M. Nabilone vs placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. *Cancer Treat Rev*. 1982;9(suppl B) 49-53.
52. Chan HS, MacLeod SM, Correia JA. Nabilone vs prochlorperazine for control of cancer chemotherapy-induced emesis in children. *Proc Am Soc Clin Oncol*. 1984;3:108.
57. Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N Engl J Med*. 1979;300(23):1295- 1297.

Ergebnisse

Nausea and Vomiting Due to Chemotherapy

All studies suggested a greater benefit of cannabinoids compared with both active comparators and placebo, but these did not reach statistical significance in all studies.

Safety



Leitlinien

<p>Leitlinienprogramm Onkologie et al., 2016 [6].</p>	<ul style="list-style-type: none"> • Ziel ist eine flächendeckende Umsetzung einer multidisziplinären, qualitätsgesicherten und sektorenübergreifenden Versorgung des onkologischen Patienten in den Bereichen der Supportiven Therapie • Die Leitlinie richtet sich an die eigentlich Betroffenen, Patienten und deren Angehörige im Sinne der Partizipation und Förderung der Alltagsautonomie durch Information und Beratung.
<p>Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe, & Arbeitsgemeinschaft der Wissenschaftlich Medizinischer Fachgesellschaften (AWMF).</p>	<p>Methodik</p> <p>Grundlage der Leitlinie</p> <ul style="list-style-type: none"> • Die Leitlinienbewertung erfolgte mit DELBI (Deutsches Instrument zur methodischen Leitlinien-Bewertung, Fassung 2005/2006, © AWMF, ÄZQ 2008). • Die konsentierten Schlüsselfragen wurden aufgrund einer orientierenden Vorrecherche im Kick-Off- Meeting folgenden Evidenzkategorien zugeteilt: <ul style="list-style-type: none"> • Evidenzbasiert mit systematischer de novo Recherche, • Leitlinienadaptation evidenzbasierten Leitlinien • Konsensbasiert durch Expertenkonsens der Mandatsträger ohne systematische Recherche • Zur Diskussion, Konsensfindung und Abstimmung [...] 2 Konsensuskonferenzen einberufen, die unter der Moderation der AWMF-zertifizierten Leitlinienberater [...] durchgeführt wurden. • Beiden Konsensuskonferenzen wurde eine Online-Vorabstimmung vorangestellt. Hierbei wurden alle für die Konsensuskonferenz vorbereiteten Empfehlungen/ Statements den Mitgliedern per E-Mail zugesandt. • Suchzeitraum Suche am 01.06.2014, Update 11/2015 • Ausgehend von den Kriterien der evidenzbasierten Medizin wurden systematische Reviews, die mindestens 2 randomisiert kontrollierten Studien (RCTs) einschlossen als Sekundärquellen verwendet, ebenso evidenzbasierte Leitlinien. Als Primärquellen wurden – wenn vorhanden – RCTs bevorzugt. Falls zu einer Thematik kein RCT oder Review vorhanden war, wurden Studien mit höherem Verzerrungspotential (z.B. Beobachtungsstudien, Kohortenstudien, Fallstudien) einbezogen.
	<p>LoE: Schema der Evidenzgraduierung nach Oxford (Version 2009)</p> <p>Anmerkung Fb Med: Schema siehe Anhang</p> <p>Sowie GRADE bei externen Recherche</p>

Tabelle 4: Evidenzgraduierung nach GRADE (http://www.gradeworkinggroup.org)		
Qualität de Evidenz	Beschreibung	Symbol
Hohe Qualität	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.	⊕⊕⊕⊕
Moderate Qualität	Wir haben mäßig viel Vertrauen in den Effektschätzer: der wahre Effekt ist wahrscheinlich nahe bei dem Effektschätzer, aber es besteht die Möglichkeit, dass er relevant verschieden ist.	⊕⊕⊕⊖
Geringe Qualität	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.	⊕⊕⊖⊖
Sehr geringe Qualität	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.	⊕⊖⊖⊖

GoR		
Tabelle 5: Schema der Empfehlungsgraduierung		
Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	Soll
B	Empfehlung	Sollte
O	Empfehlung offen	Kann

Freitext/Empfehlungen/Hinweise	
Empfehlung 1: Hoch emetogene medikamentöse Tumorthерапie	
5.3.	Evidenzbasierte Empfehlung
Empfehlungsgrad	Akute Phase:
A	Bei einer eintägigen medikamentösen Tumorthерапie mit einem Emesisrisiko > 90% soll vor der medikamentösen Tumorthерапie eine Prophylaxe mit einem 5-HT ₃ -RA, einem NK ₁ - RA und Dexamethason erfolgen.
Empfehlungsgrad	Verzögerte Phase:
A	Bei einer eintägigen medikamentösen Tumorthерапie mit einem Emesis Risiko > 90% soll für weitere 2-4 Tage nach Ende der hoch emetogenen Therapie eine Prophylaxe mit Dexamethason erfolgen. War der NK ₁ - RA Aprepitant Bestandteil der Primärprophylaxe, ist dieser für 2 weiteren Tage mit 80 mg täglich zu applizieren. Die Gabe von Fosaprepitant oder Netupitant/Palonosetron erfolgt nur am Tag 1 der medikamentösen Tumorthерапie.
Level of Evidence	Literatur für die akute und verzögerte Phase: (Nakamura, Taira et al. 1999, Campos, Pereira et al. 2001, Chawla, Grunberg et al. 2003, Hesketh, Grunberg et al. 2003, Poli-Bigelli, Rodrigues-Pereira et al. 2003, Warr, Hesketh et al. 2005, Schmoll, Aapro et al. 2006, Rapoport, Jordan et al. 2010, Takahashi, Hoshi et al. 2010, Saito, Yoshizawa et al. 2013, Aapro, Rugo et al. 2014, Hesketh, Rossi et al. 2014, Hu, Cheng et al. 2014)
Abstimmung im Plenum	Konsens
Abk.: 5-HT ₃ -RA - 5-Hydroxytryptamin3-Rezeptorantagonist, NK ₁ - RA - Neurokinin-1-Rezeptor-Antagonist	
Hintergrund:	

	<p>Für die antiemetische Prophylaxe war seit den frühen 90iger Jahren die Kombination aus einem 5-HT₃-RA und Dexamethason als Standard etabliert (Jantunen, Kataja et al. 1997, Jordan, Hinke et al. 2007) Im Jahr 2003 wurden die NK₁-RA in die klinische Praxis eingeführt und gehören bei der Prävention der hoch emetogenen Chemotherapie mittlerweile ebenfalls zum Standardvorgehen.</p> <p>Empfehlung 2: Moderat emetogene medikamentöse Tumortherapie</p> <table border="1"> <tr> <td style="background-color: #fca864;">5.4.</td><td>Evidenzbasierte Empfehlung</td></tr> <tr> <td>Empfehlungsgrad</td><td>Akute Phase:</td></tr> <tr> <td style="background-color: #fca864;">A</td><td>Bei einer medikamentösen Tumortherapie mit einem Emesisrisiko > 30-90 % (Ausnahme Carboplatin, s. nächste Empfehlung) soll vor der Chemotherapie eine Prophylaxe mit einem 5-HT₃- RA und Dexamethason erfolgen.</td></tr> <tr> <td>Empfehlungsgrad</td><td>Verzögerte Phase:</td></tr> <tr> <td style="background-color: #fca864;">B</td><td>Bei einer medikamentösen Tumortherapie mit bekanntem emetogenen Potential in der verzögerten Phase (Oxaliplatin, Doxorubicin, Cyclophosphamid und Bendamustin) sollte die Gabe von Dexamethason an den Tagen 2 bis 3 erfolgen.</td></tr> <tr> <td style="background-color: #fca864;">O</td><td>Bei anderen medikamentösen Tumortherapien mit einem moderaten Emesisrisiko kann auf eine antiemetische Prophylaxe an den Tagen 2-3 verzichtet werden.</td></tr> <tr> <td>Level of Evidence</td><td>Literatur für die akute und verzögerte Phase : (www.mascc.org 2016) (Jantunen, Kataja et al. 1997, Hesketh, Sanz-Altamira et al. 2012)</td></tr> <tr> <td style="background-color: #fca864;">1a</td><td></td></tr> <tr> <td style="background-color: #fca864;">EK</td><td>Bendamustin</td></tr> <tr> <td>Abstimmung im Plenum</td><td>Konsens</td></tr> <tr> <td style="background-color: #fca864;">5.5.</td><td>Evidenzbasierte Empfehlung</td></tr> <tr> <td>Empfehlungsgrad</td><td>Akute Phase:</td></tr> <tr> <td style="background-color: #fca864;">A</td><td>Bei einer carboplatinhaltigen Chemotherapie (ab AUC ≥ 4) soll vor deren Applikation eine Prophylaxe mit einem 5-HT₃-Rezeptorantagonist und Dexamethason erfolgen.</td></tr> <tr> <td>Empfehlungsgrad</td><td>Zusätzlich kann die Gabe eines NK₁-RA erfolgen.</td></tr> <tr> <td style="background-color: #fca864;">O</td><td></td></tr> <tr> <td>Empfehlungsgrad</td><td>Verzögerte Phase:</td></tr> <tr> <td style="background-color: #fca864;">B</td><td>Bei einer carboplatinhaltigen Chemotherapie (ab AUC ≥ 4) sollte eine antiemetische Prophylaxe mit Dexamethason an den Tagen 2-3 erfolgen.</td></tr> <tr> <td>Empfehlungsgrad</td><td>Falls der NK₁- RA Aprepitant Bestandteil der Primärprophylaxe war, soll dieser für 2 weitere Tage mit 80 mg täglich appliziert werden. Die Gabe von Fosaprepitant oder Netupitant/Palonosetron erfolgt nur am Tag 1 der Carboplatintherapie.</td></tr> <tr> <td>Level of Evidence</td><td>Für die akute und verzögerte Phase. De novo: (Gralla, Jordan et al. 2010, Tanioka, Kitao et al. 2013, Ito, Karayama et al. 2014, Hesketh, Schwartzberg et al. 2015, Yahata, Kobayashi et al. 2015)</td></tr> <tr> <td style="background-color: #fca864;">1a</td><td></td></tr> <tr> <td>Abstimmung im Plenum</td><td>Konsens</td></tr> <tr> <td></td><td>Abk.: 5-HT₃-RA - 5-Hydroxytryptamin3-Rezeptorantagonist, NK₁- RA - Neurokinin-1-Rezeptor-Antagonist</td></tr> <tr> <td></td><td>Hintergründe</td></tr> </table>	5.4.	Evidenzbasierte Empfehlung	Empfehlungsgrad	Akute Phase:	A	Bei einer medikamentösen Tumortherapie mit einem Emesisrisiko > 30-90 % (Ausnahme Carboplatin, s. nächste Empfehlung) soll vor der Chemotherapie eine Prophylaxe mit einem 5-HT ₃ - RA und Dexamethason erfolgen.	Empfehlungsgrad	Verzögerte Phase:	B	Bei einer medikamentösen Tumortherapie mit bekanntem emetogenen Potential in der verzögerten Phase (Oxaliplatin, Doxorubicin, Cyclophosphamid und Bendamustin) sollte die Gabe von Dexamethason an den Tagen 2 bis 3 erfolgen.	O	Bei anderen medikamentösen Tumortherapien mit einem moderaten Emesisrisiko kann auf eine antiemetische Prophylaxe an den Tagen 2-3 verzichtet werden.	Level of Evidence	Literatur für die akute und verzögerte Phase : (www.mascc.org 2016) (Jantunen, Kataja et al. 1997, Hesketh, Sanz-Altamira et al. 2012)	1a		EK	Bendamustin	Abstimmung im Plenum	Konsens	5.5.	Evidenzbasierte Empfehlung	Empfehlungsgrad	Akute Phase:	A	Bei einer carboplatinhaltigen Chemotherapie (ab AUC ≥ 4) soll vor deren Applikation eine Prophylaxe mit einem 5-HT ₃ -Rezeptorantagonist und Dexamethason erfolgen.	Empfehlungsgrad	Zusätzlich kann die Gabe eines NK ₁ -RA erfolgen.	O		Empfehlungsgrad	Verzögerte Phase:	B	Bei einer carboplatinhaltigen Chemotherapie (ab AUC ≥ 4) sollte eine antiemetische Prophylaxe mit Dexamethason an den Tagen 2-3 erfolgen.	Empfehlungsgrad	Falls der NK ₁ - RA Aprepitant Bestandteil der Primärprophylaxe war, soll dieser für 2 weitere Tage mit 80 mg täglich appliziert werden. Die Gabe von Fosaprepitant oder Netupitant/Palonosetron erfolgt nur am Tag 1 der Carboplatintherapie.	Level of Evidence	Für die akute und verzögerte Phase. De novo: (Gralla, Jordan et al. 2010, Tanioka, Kitao et al. 2013, Ito, Karayama et al. 2014, Hesketh, Schwartzberg et al. 2015, Yahata, Kobayashi et al. 2015)	1a		Abstimmung im Plenum	Konsens		Abk.: 5-HT ₃ -RA - 5-Hydroxytryptamin3-Rezeptorantagonist, NK ₁ - RA - Neurokinin-1-Rezeptor-Antagonist		Hintergründe
5.4.	Evidenzbasierte Empfehlung																																														
Empfehlungsgrad	Akute Phase:																																														
A	Bei einer medikamentösen Tumortherapie mit einem Emesisrisiko > 30-90 % (Ausnahme Carboplatin, s. nächste Empfehlung) soll vor der Chemotherapie eine Prophylaxe mit einem 5-HT ₃ - RA und Dexamethason erfolgen.																																														
Empfehlungsgrad	Verzögerte Phase:																																														
B	Bei einer medikamentösen Tumortherapie mit bekanntem emetogenen Potential in der verzögerten Phase (Oxaliplatin, Doxorubicin, Cyclophosphamid und Bendamustin) sollte die Gabe von Dexamethason an den Tagen 2 bis 3 erfolgen.																																														
O	Bei anderen medikamentösen Tumortherapien mit einem moderaten Emesisrisiko kann auf eine antiemetische Prophylaxe an den Tagen 2-3 verzichtet werden.																																														
Level of Evidence	Literatur für die akute und verzögerte Phase : (www.mascc.org 2016) (Jantunen, Kataja et al. 1997, Hesketh, Sanz-Altamira et al. 2012)																																														
1a																																															
EK	Bendamustin																																														
Abstimmung im Plenum	Konsens																																														
5.5.	Evidenzbasierte Empfehlung																																														
Empfehlungsgrad	Akute Phase:																																														
A	Bei einer carboplatinhaltigen Chemotherapie (ab AUC ≥ 4) soll vor deren Applikation eine Prophylaxe mit einem 5-HT ₃ -Rezeptorantagonist und Dexamethason erfolgen.																																														
Empfehlungsgrad	Zusätzlich kann die Gabe eines NK ₁ -RA erfolgen.																																														
O																																															
Empfehlungsgrad	Verzögerte Phase:																																														
B	Bei einer carboplatinhaltigen Chemotherapie (ab AUC ≥ 4) sollte eine antiemetische Prophylaxe mit Dexamethason an den Tagen 2-3 erfolgen.																																														
Empfehlungsgrad	Falls der NK ₁ - RA Aprepitant Bestandteil der Primärprophylaxe war, soll dieser für 2 weitere Tage mit 80 mg täglich appliziert werden. Die Gabe von Fosaprepitant oder Netupitant/Palonosetron erfolgt nur am Tag 1 der Carboplatintherapie.																																														
Level of Evidence	Für die akute und verzögerte Phase. De novo: (Gralla, Jordan et al. 2010, Tanioka, Kitao et al. 2013, Ito, Karayama et al. 2014, Hesketh, Schwartzberg et al. 2015, Yahata, Kobayashi et al. 2015)																																														
1a																																															
Abstimmung im Plenum	Konsens																																														
	Abk.: 5-HT ₃ -RA - 5-Hydroxytryptamin3-Rezeptorantagonist, NK ₁ - RA - Neurokinin-1-Rezeptor-Antagonist																																														
	Hintergründe																																														

	<p><u>Hat ein NK1-RA einen Stellenwert bei moderat emetogener Chemotherapie?</u></p> <ul style="list-style-type: none"> • Moderat emetogene Chemotherapie „alle“: <p>[...] Patienten (n = 1000) mit moderat emetogener Chemotherapie (AC-basierte Chemotherapie ausgeschlossen) einschloss, [...] (Weinstein, Jordan et al. 2016) Verglichen wurde die 3-fach Kombination Fosaprepitant, Ondansetron, Dexamethason versus Ondansetron und Dexamethason.</p> <p>Der primäre Endpunkt „Complete Response“ in der verzögerten Phase wurde erreicht (78,9 % versus 68,5 %, p < 0,001). Anzumerken ist, dass in dieser Studie > 50 % der Patienten eine carboplatinhaltige Chemotherapie erhielten, sodass die Ergebnisse auch auf diesem Hintergrund interpretiert werden müssen.</p> <p>In der Rapoport Phase-III-Studie von 2010 erfolgte eine post hoc Analyse zu den rein moderat emetogenen Chemotherapien (> 50 % der Patienten erhielten eine AC-basierte Chemotherapie). Von diesen 429 Patienten erzielten 73,9 % eine CR mit der 3-fach Kombination (Aprepitant + Ondansetron + Dexamethason) im Vergleich zu 65,5 % im Kontrollarm (carboplatin-haltige Chemotherapie eingeschlossen). [...]</p> <ul style="list-style-type: none"> • Carboplatinhaltige Chemotherapie <p>Carboplatin zählt zu den stärksten emetogenen Substanzen der moderat emetogenen Risikogruppe. Es ist davon auszugehen, dass die emetogene Potenz von Carboplatin eher unterschätzt wird, zumal zwei Zulassungsstudien zu Carboplatin sehr hohe „nausea and vomiting“ Raten berichtet haben: [...] (Swenerton, Jeffrey et al. 1992, Hannigan, Green et al. 1993) Die Emesisraten lagen bei 84 % für Carboplatin/Cyclophosphamid vs. 97 % für Cisplatin/Cyclophosphamid (p < 0,001) in einer Studie und bei 82 % vs. 91 % (p = 0,007) in der anderen Studie (damalige antiemetische Prophylaxe: Metoclopramid, Diphenhydramin, Prochlorperazin und Dexamethason).</p> <p>Erste Daten zur Wirksamkeit der 3-fach Antiemese kommen von einer Subgruppenanalyse der Rapoport Studie (Gralla, Jordan et al. 2010, Rapoport, Jordan et al. 2010) Hier betrug die „No emesis“ Rate 84 % in der Aprepitant Gruppe vs. 70 % in der 5-HT3RA/Dexamethason Kontrollgruppe. Nachfolgende randomisierte Phase-II- und Phase-III-Studien haben diesen Benefit [...] an den Tagen 1-5 bestätigt (Tanioka, Kitao et al. 2013, Ito, Karayama et al. 2014, Yahata, Sonoda et al. 2014), Subgruppenanalyse der Phase-III-Sicherheitsstudie zum NK1-RA NEPA [...] (Jordan, Gralla et al. 2014) [...]</p> <p>Anzumerken ist, dass in den aufgeführten Studien eine Carboplatindosis AUC \geq 4 verwendet wurde. [...] In den vorliegenden S3 Leitlinien ist die Empfehlung mit einer „kann“ Empfehlung etwas konservativer beschieden worden.</p> <ul style="list-style-type: none"> • Oxaliplatinhaltige Chemotherapie <p>Bei der oxaliplatinhaltigen Chemotherapie sind die Studienergebnisse widersprüchlich (Hesketh, Wright et al. 2012, Nishimura, Satoh et al. 2015).</p> <p>Zu erwähnen ist, dass die Ergebnisse von Hesketh aus einer Studie (n = 710) mit dem nicht zugelassenen NK1-RA Casopitant stammen, der aufgrund von Sicherheitsaspekten und nicht aufgrund fehlender Wirksamkeit nicht zugelassen wurde. Die Complete Response an den Tagen 1-5 im Casopitant Arm war mit 86 % nahezu identisch mit 85 % des Kontrollarms.</p> <p>Ergebnisse der Nishimura Studie [...] Von den 413 eingeschlossenen Patienten betrug die „No Emesis“ Rate im Aprepitant Arm 95,7 % und im Kontrollarm 83,6 % an den Tagen 1-5. Analog zu den MASCC/ESMO 2015 LL erfolgt bei oxaliplatinhaltiger Chemotherapie keine Empfehlung zur Primärprophylaxe mit einem NK1-RA (www.mascc.org 2016).</p> <p><u>Gibt es einen zu bevorzugenden 5-HT3-RA bei moderat emetogener Chemotherapie, seitdem die AC-basierte Chemotherapie als hoch emetogen klassifiziert wurde?</u></p> <p>In den bisherigen internationalen Leitlinien wurde Palonosetron als der zu</p>
--	---

bevorzugende 5-HT3-RA bei moderat emetogener Chemotherapie empfohlen (Roila, Herrstedt et al. 2010, Basch, Prestrud et al. 2011) Dies ist auch noch bei dem fokussierten ASCO Leitlinien Update der Fall (Hesketh, Bohlke et al. 2016). [...] In den aktualisierten MASCC/ESMO Leitlinien wird bei der moderat emetogenen Chemotherapie kein bevorzugter 5-HT3-RA mehr empfohlen, [...]. Hintergrund dieser Empfehlung ist, dass die MASCC/ESMO nunmehr auch die AC-basierte Chemotherapie als hoch emetogen klassifiziert hat. Diese Zulassungsstudien zu Palonosetron inkludierten zu > 60 % Mammakarzinom Patientinnen mit AC-basierter Chemotherapie (Eisenberg, Figueroa-Vadillo et al. 2003, Gralla, Lichinitser et al. 2003) sodass die ursprüngliche Empfehlung nicht aufrechterhalten werden konnte, da der Anteil an rein moderat emetogener Chemotherapie zu gering war (www.mascc.org 2016).

5-HT3-Rezeptor-Antagonisten (5-HT3-RA)

5-HT3-RA sind hoch wirksam in der Prophylaxe von akuter Übelkeit und Erbrechen unter medikamentöser Tumorthерапie

Tabelle 30: 5-HT3-Rezeptor-Antagonisten

5-HT ₃ -RA	Empfohlene Dosis intravenös	Empfohlene Dosis oral
Granisetron*	1 mg	2 mg
Ondansetron	8 mg	16 mg
Palonosetron	0,25 mg	0,5 mg
Tropisetron	5 mg	5 mg

*auch als transdermales Pflaster mit 3,1 mg/24 h im Handel.

- In direkt vergleichenden Studien zwischen den 5-HT3-RA zeigte sich weitgehende Äquieffektivität bezüglich der Prophylaxe von akuter Übelkeit und Erbrechen bei hoch und moderat emetogener Tumorthерапie. In der Prophylaxe des verzögerten Erbrechens ist ihr Stellenwert eher als gering einzuschätzen. Eine Ausnahme stellt Palonosetron dar, das auch in der verzögerten Phase wirksam ist.
- Nebenwirkungen, die als Substanzklasseneffekte bei mehr als 5 % der Patienten in großen randomisierten Studien auftraten, sind Kopfschmerzen (10-20 %), Obstipation (10-20 %), Diarrhoe (5-15 %), Anorexie, Fatigue und Fieber. In den meisten Fällen lagen die Nebenwirkungen im Schweregrad 1 und 2. Unter der Therapie mit 5-HT3-RA kann es zu asymptotischen und transienten EKG Veränderungen mit Verlängerung der PR- und der QTc Zeit sowie zur Verbreiterung des QRS Komplexes kommen. Diese EKG Veränderungen sind nicht für Palonosetron beschrieben (Morganroth, Flaharty et al. 2015).

Neurokinin₁-Rezeptor-Antagonisten (NK₁-RA)

NK1-RA sind besonders wirksam in der Prophylaxe von verzögterer Übelkeit und Erbrechen unter medikamentöser Tumorthерапie.

Tabelle 31: NK1-Rezeptor-Antagonisten

NK1-RA	Applikation	Empfohlene Dosis	Tag
Aprepitant	oral	125 mg	1
		80 mg	2-3
Fosaprepitant	intravenös	150 mg	1
'Netupitant + Palonosetron (NEPA)	oral	300 mg + 0,5 mg	1

*in fixer Kombination mit Palonosetron 0,5 mg

- Bisher liegen keine Ergebnisse randomisierter Studien zum direkten Vergleich der Wirksamkeit von Netupitant vs. Aprepitant und Fosaprepitant vor. In der Sicherheits-Phase-III-Studie zu Netupitant/Palonosetron (NEPA) ist z.B. Aprepitant als Observationsarm mitgelaufen, ein prädefinierter Wirksamkeitsvergleich war nicht vorgesehen (Gralla, Bosnjak et al. 2014).
- NK1-RA sind gut verträglich. Weil sie in der Regel in Kombination mit 5-HT3-Rezeptor-Antagonisten und Dexamethason eingesetzt werden, sind medikamentenspezifische Nebenwirkungen nicht immer klar zuzuordnen.
- Nebenwirkungen, die bei mehr als 5 % der Patienten in großen randomisierten Studien unter Aprepitant und Fosaprepitant auftreten, sind Fatigue (17 %) und Aufstoßen (14 %). Eine relativ spezifische Nebenwirkung ist der Schluckauf (4,5 %). Unter der Therapie kann es zu einem asymptomatischen Anstieg von Leberenzymen kommen. Die fixe Kombination Netupitant/Palonosetron (NEPA) ist ebenfalls gut verträglich. Hauptnebenwirkungen sind Kopfschmerzen (3,6 %), Obstipation (3,0 %) und Fatigue (1,2 %).
- Alle drei in Europa zugelassenen NK1-RA sind moderate Cytochrom 3A4 (CYP3A4)-Inhibitoren. Daher ist bei kombinierter Anwendung mit Dexamethason, welches ebenfalls über CYP3A4 metabolisiert wird, die Dosis von Dexamethason zu halbieren. Diese Empfehlung trifft jedoch ausschließlich auf die 20 mg Dexamethason-Dosierung zu, nicht aber auf die 8 mg oder 12 mg Dexamethason-Gaben. [...]

Kortikosteroide

Steroide werden sowohl für die Prophylaxe der akuten als auch der verzögerten Form des Erbrechens eingesetzt (Ioannidis, Hesketh et al. 2000, Grunberg 2007). [...] Da in fast allen großen randomisierten Studien Dexamethason als Kortikosteroid verwendet wurde, gilt Dexamethason als Standard.

Tabelle 32: Kortikosteroide - Dexamethason					
	Risikogruppe	Ziel	Applikation	Empfohlene Dosis ²	Tag
Hoch emetogen	Akute Übelkeit und Erbrechen	oral oder intravenös	1 x 20 mg oder 1x 12 mg ¹		1
	Verzögerte Übelkeit und Erbrechen	oral oder intravenös	1x 8 mg		2-4
Moderat emetogen	Akute Übelkeit und Erbrechen	oral oder intravenös	1 x 8 mg		1
	Verzögerte Übelkeit und Erbrechen	oral oder intravenös	1 x 8 mg		2-3
Gering emetogen	Akute Übelkeit und Erbrechen	oral oder intravenös	1 x 4-8 mg		1

¹wenn in Kombination mit Aprepitant, Fosaprepitant oder Netupitant/ Palonosetron (NEPA)

² die Äquivalenzdosis von 8 mg Dexamethason sind 50-80 mg Prednison bzw. Prednisolon

- Die Kombination aus einem Setron und einem Kortikoid ergibt einen Effektzugewinn von 10-30 % gegenüber der Setron-Monotherapie. Der Vorteil einer Kombinationstherapie konnte bereits in zahlreichen Studien und auch Metaanalysen belegt werden (Roila, Tonato et al. 1991, Ioannidis, Hesketh et al. 2000).
- Akute Nebenwirkungen der prophylaktischen Gabe von Dexamethason sind häufig. In einer prospektiven Studie mit Fokus auf die Nebenwirkungen wurden Schlafstörungen (45 %), Verdauungsbeschwerden (27 %), innere Unruhe (27 %), gesteigerter Appetit (19 %), Gewichtszunahme (16 %), Akne (15 %) und eine Gesichtsrötung beobachtet (Vardy, Chiew et al. 2006).

Metoclopramid (MCP)

- [...] MCP kann zur Prophylaxe von Übelkeit und Erbrechen bei gering emetogener Tumorthерапie eingesetzt werden [...]
- Nebenwirkungen sind Müdigkeit, Durchfall und innere Unruhe. Seltener, aber belastende Nebenwirkungen sind extrapyramidale Bewegungsstörungen und tardive Dyskinesie, die häufiger bei jungen Patienten beobachtet werden. [...]

Cannabinoide

- In einer Übersichtsarbeit wird die Überlegenheit der oralen Cannabinoide (wie z.B. Dronabinol, Nabilon) gegenüber den damals konventionellen Medikamenten wie Metoclopramid oder Haloperidol bei Chemotherapie induziertem Erbrechen dargestellt (Tramer, Carroll et al. 2001). Zu berücksichtigen ist, dass die Spannweite möglicher Nebenwirkungen über Sedation und Euphorie bis zu Halluzination und Dysphorie reicht.

| NCCN et al., 2016 [7]. National Comprehensive | The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis are intended to provide an overview of the treatment principles for preventing chemotherapy - or RT-induced vomiting and nausea, and recommendations for antiemetic prophylaxis according to the emetogenic potential of anti-tumor |

Cancer Network	therapies.
Antiemesis Version 2.16	<p>Methodik</p> <p>Grundlage der Leitlinie</p> <ul style="list-style-type: none"> • Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen • Repräsentativität der Gremien unklar • ob formalisierte Konsensusverfahren angewendet werden ist unklar – • Diskussion der Literatur und Empfehlungen im Expertenpanel • industriefinanziert • Suchzeitraum: September 2015 <p>GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert.</p>
	<p>NCCN Categories of Evidence and Consensus</p> <p>Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.</p> <p>Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.</p> <p>Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.</p> <p>Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.</p> <p>All recommendations are category 2A unless otherwise noted.</p>
	Freitext/Empfehlungen/Hinweise

	<p>HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION^{f,g}</p> <p>DAY 1: Select option A, B, or C (order does not imply preference) DAYS 2, 3, 4:</p> <p>Start before chemotherapy:^h</p> <p>A: Neurokinin-1 (NK1) antagonist-containing regimen (netupitant, see option B);^{i,j} select one agent from each of the following groups (any combination of an NK1 antagonist + 5-HT3 antagonist + steroid [category 1]):</p> <ul style="list-style-type: none"> • NK1 antagonist: <ul style="list-style-type: none"> ➤ Aprepitant 125 mg PO once ➤ Fosaprepitant 150 mg IV once ➤ Rolapitant 180 mg PO once^k AND • Serotonin (5-HT3) antagonist:^j <ul style="list-style-type: none"> ➤ Dolasetron 100 mg PO once ➤ Granisetron 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy ➤ Ondansetron 16–24 mg PO once or 8–16 mg IV once ➤ Palonosetron 0.25 mg IV once AND • Steroid;^{j,l} <ul style="list-style-type: none"> ➤ Dexamethasone 12 mg^m PO/IV once <p>B: Netupitant-containing regimen:^{i,j,n,o}</p> <ul style="list-style-type: none"> ➤ Netupitant 300 mg/palonosetron 0.5 mg PO once ➤ Dexamethasone 12 mg^m PO/IV once <p>C: Olanzapine-containing regimen:^{i,j,p}</p> <ul style="list-style-type: none"> ➤ Olanzapine 10 mg PO ➤ Palonosetron 0.25 mg IV once ➤ Dexamethasone 20 mg^m IV once 	<p>A:^q</p> <ul style="list-style-type: none"> • If aprepitant PO given day 1, then <ul style="list-style-type: none"> ➤ Aprepitant 80 mg PO daily on days 2, 3 AND ➤ Dexamethasone 8 mg^m PO/IV daily on days 2, 3, 4 • If fosaprepitant given day 1, then <ul style="list-style-type: none"> ➤ No further NK1 antagonist is needed on days 2, 3 AND ➤ Dexamethasone 8 mg^m PO/IV once on day 2, 8 mg PO/IV twice daily on days 3, 4 • If rolapitant given day 1, then <ul style="list-style-type: none"> ➤ No further NK1 antagonist is needed on days 2, 3 AND ➤ Dexamethasone 8 mg^m PO/IV twice daily on days 2, 3, 4 <p>B:</p> <ul style="list-style-type: none"> ➤ Dexamethasone 8 mg^m PO/IV daily on days 2, 3, 4 <p>C:</p> <ul style="list-style-type: none"> ➤ Olanzapine 10 mg PO daily on days 2, 3, 4
	<p>MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION^{f,g}</p> <p>DAY 1: Select option A, B, or C (order does not imply preference) DAYS 2 and 3:</p> <p>Start before chemotherapy:^h</p> <p>A:</p> <p>Serotonin (5-HT3) antagonist + steroid (category 1) ± NK1 antagonist^{i,j} (netupitant, see option B)</p> <ul style="list-style-type: none"> • Serotonin (5-HT3) antagonist (Select one):^j <ul style="list-style-type: none"> ➤ Dolasetron 100 mg PO once ➤ Granisetron 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy ➤ Ondansetron 16–24 mg PO once or 8–16 mg IV once ➤ Palonosetron 0.25 mg IV once (preferred) AND • Steroid^j <ul style="list-style-type: none"> ➤ Dexamethasone 12 mg^m PO/IV once <p>WITH/WITHOUT</p> <ul style="list-style-type: none"> • NK1 antagonist: ^{j,r} ➤ Aprepitant 125 mg PO once ➤ Fosaprepitant 150 mg IV once ➤ Rolapitant 180 mg PO once^s (category 1) <p>B:</p> <p>Netupitant-containing regimen:^{i,j,n}</p> <ul style="list-style-type: none"> ➤ Netupitant 300 mg/palonosetron 0.5 mg PO once^r ➤ Dexamethasone 12 mg^m PO/IV once <p>C:</p> <p>Olanzapine-containing regimen:^{i,j,p}</p> <ul style="list-style-type: none"> ➤ Olanzapine 10 mg PO ➤ Palonosetron 0.25 mg IV once ➤ Dexamethasone 20 mg^m IV once 	
<p>Roila L. et al., 2017 [8].</p> <p>2016 updated MASCC/ESMO consensus recommendations:</p>	<p>An update of the recommendations for the prophylaxis of acute and delayed emesis induced by moderately emetogenic chemotherapy published after the last MASCC/ESMO antiemetic consensus conference in 2009 has been carried out.</p> <p>Methodik</p> <p>Grundlage der Leitlinie</p> <ul style="list-style-type: none"> • Update: Update vom Jahr 2009 • Suchzeitraum: January 1, 2009 to January - 6, 2015 	

**Prevention of
nausea and
vomiting following
moderately
emetogenic
chemotherapy**

+

**Roila F et al., 2017
[9].**

**Erratum to: 2016
updated
MASCC/ESMO
consensus
recommend-
ations:
Prevention of
nausea and
vomiting following
moderately
emetogenic
chemotherapy**

- LoE und GoR: ESMO

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Sonstige methodische Hinweise

Konsentfindung unklar.

Freitext/Empfehlungen/

Table 1 Recommendations for moderately emetogenic chemotherapy

Chemotherapy	Recommendations		MASCC level of scientific confidence/level of consensus	ESMO level of evidence / grade of recommendation
	Old	New		
MEC				
Acute	Palo + Dex	5HT3 + Dex	Moderate / moderate	II / B
Delayed	Dex ^a	Dex ^a	Low / moderate	III / C
		None ^b	No confidence possible / high	IV / D
CARBOPLATIN				
Acute	Palo + Dex	NK1 + 5-HT3 + DEX	Moderate / moderate	II / B
Delayed	Dex ^a	Apre ^c	Moderate / moderate	II / B

MEC moderately emetogenic chemotherapy, Palo palonosetron, Dex dexamethasone, Apre aprepitant

^a only in patients with known potential for delayed emesis

^b the steroid can be considered only in patients receiving MEC with known potential for delayed emesis

^c only in patients receiving aprepitant 125 mg on day 1

Is palonosetron the preferred 5-HT3 RA for MEC?

Updated recommendation: For the prevention of acute emesis in MEC-treated patients, a 5-HT3 receptor antagonist plus dexamethasone is recommended

Conclusion: There are insufficient data to support palonosetron as

	<p>the preferred 5-HT3 receptor antagonist for MEC.</p> <p>Referenzen:</p> <ol style="list-style-type: none"> PopovicM, Warr DG, Deangelis C, et al. (2014) Efficacy and safety of palonosetron for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis of randomized controlled trials. <i>Support Care Cancer</i> 22:1685–1697 Geling O, EichlerHG (2005) Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. <i>J Clin Oncol</i> 23:1289–1294 <p>Which MEC chemotherapy regimens require prophylaxis for delayed nausea or vomiting? Is multiday oral dexamethasone the preferred treatment?</p> <p><u>Updated recommendation:</u> In patients receiving MEC chemotherapy with known potential for delayed emesis (e.g., oxaliplatin, doxorubicin, cyclophosphamide), the use of dexamethasone for days 2–3 can be considered. No routine prophylaxis for delayed emesis can be recommended for all other patients receiving MEC chemotherapy.</p> <p><u>Conclusion:</u> No new data have emerged that allow the identification of patients at sufficiently high risk of delayed emesis to warrant prophylaxis. Previous data has demonstrated that some but not all patients may have reduced nausea or vomiting with the addition of dexamethasone beyond 24 h.</p> <p>Referenzen:</p> <ol style="list-style-type: none"> Italian Group for Antiemetic Research (2000) Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. <i>N Engl J Med</i> 342:1554–1559 Inoue A, Yamada Y, Matsumura Y, et al. (2003) Randomized study of dexamethasone treatment for delayed emesis, anorexia and fatigue induced by irinotecan. <i>Support Care Cancer</i> 11:528–532 Hesketh PJ, Bosnjak SM, Nikolic V, et al. (2011) Incidence of delayed nausea and vomiting in patients with colorectal cancer receiving irinotecan-based chemotherapy. <i>Support Care Cancer</i> 19:2063–2066 Lindley C, Goodin S, McCune J, et al. (2005) Prevention of delayed chemotherapy-induced nausea and vomiting after moderately high to highly emetogenic chemotherapy: comparison of ondansetron, prochlorperazine, and dexamethasone. <i>Am J Clin Oncol</i> 28:270–276 <p>Which MEC patients should receive prophylaxis with an NK1 RA?</p> <p><u>Updated recommendation:</u></p> <ul style="list-style-type: none"> A combination of an NK1 receptor antagonist, 5-HT3 receptor antagonist, and dexamethasone is recommended for the prophylaxis of emesis induced by carboplatin-based chemotherapy. No studies evaluated specifically the role of an antiemetic prophylaxis for the prevention of delayed emesis induced by carboplatin.
--	---

	<ul style="list-style-type: none"> If aprepitant 125 mg is used on day 1, aprepitant 80 mg on days 2–3 for the prevention of delayed emesis is recommended. If other NK1 receptor antagonists are used on day 1, no additional prophylaxis for delayed emesis prevention is suggested <p><u>Conclusion:</u> Data presented from six randomized trials including carboplatin suggest a moderate benefit from adding an NK1 receptor antagonist to dexamethasone and a 5-HT3 receptor antagonist.</p> <p><u>Referenzen</u></p> <ol style="list-style-type: none"> Rapoport B, Jordan K, Boice JA, et al. (2010) Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. <i>Support Care Cancer</i> 18:423–431 Weinstein C, Jordan K, Green SA, et al. (2016) Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy: results of a randomized, double-blind phase III trial. <i>Ann Oncol</i> 27:172–178 Gralla RJ, Rapoport BL, Jordan K, et al. (2010) Assessing the magnitude of antiemetic benefit with the addition of the NK1 receptor antagonist aprepitant for all platinum agents: analysis of 1872 patients in prospective randomized clinical phase III trials. <i>J Clin Oncol</i> 28:650s abstract 9057 Jordan K, Gralla R, Rossi G, et al. (2014) Is the addition to an NK1 receptor antagonist beneficial in patients receiving carboplatin? Supplementary data with NEPA, a fixed dose combination of netupitant and palonosetron. <i>Support Care Cancer</i> 22: 107s abstract 0162 Hesketh PJ, Schnadig ID, Schwartzberg LS, et al. (2016) Efficacy of the neurokinin-1 receptor antagonist rolapitant in preventing nausea and vomiting in patients receiving carboplatin-based chemotherapy. <i>Cancer</i> 122:2418–2425 Tanioka M, Kitao A, Matsumoto K, et al. (2013) A randomized, placebo controlled, double-blind study of aprepitant in nondrinking women younger than 70 years receiving moderately emetogenic chemotherapy. <i>Br J Cancer</i> 109:859–865 Yahata H, Kobayashi H, Sonoda K, et al (2016) Efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting with a moderately emetogenic chemotherapy regimen: a multicenter, placebo-controlled, double-blind, randomized study in patients with gynecologic cancer receiving paclitaxel and carboplatin. <i>Int J Clin Oncol</i> 21(3):491–7. doi:10.1007/s10147-015-0928-y Ito Y, Karayama M, Inui N, et al. (2014) Aprepitant in patients with advanced non-small-cell lung cancer receiving carboplatin-based chemotherapy. <i>Lung Cancer</i> 84:259–264
Herrstedt J et al., 2016 [4]. MASCC/ESMO 2016 Updated MASCC/ESMO Consensus Recommendation s: Prevention of Nausea and	<p>This review summarizes the recommendations for the prophylaxis of nausea and vomiting in adults receiving highly emetogenic chemotherapy (HEC) which includes cisplatin, mechlorethamine, streptozocin, cyclophosphamide >1500 mg/m², carmustine, dacarbazine, and the combination of an anthracycline and cyclophosphamide (AC) administered to women with breast cancer.</p> <p>Methodik</p> <p><u>Grundlage der Leitlinie</u></p> <p>Update von 2009</p> <p>Suchzeitraum January 01, 2009, through June 01, 2015</p> <p>LoE oder GoR ESMO</p>

**Vomiting
Following High
Emetic Risk
Chemotherapy**

Update von 2009

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Sonstige methodische Hinweise

Konsentfindung unklar

Freitext/Empfehlungen/Hinweise

Recommendations:

Table 2 Recommendations: antiemetic agents to prevent nausea and vomiting induced by high emetic risk chemotherapy in adults

Setting	Recommendation	MASCC level of confidence	MASCC level of consensus	ESMO level of evidence	ESMO grade of recommendation
Prevention of acute nausea and vomiting following non-AC chemotherapy of high emetic risk	A three-drug regimen including single doses of a 5-HT ₃ -receptor antagonist, dexamethasone, and an NK ₁ receptor antagonist (aprepitant, fosaprepitant, netupitant ^a , or rolapitant), given before chemotherapy is recommended	High	High	I	A
Prevention of delayed nausea and vomiting following non-AC chemotherapy of high emetic risk	In patients receiving non-AC highly emetogenic chemotherapy treated with a combination of an NK ₁ receptor antagonist ^b , a 5-HT ₃ -receptor antagonist, and dexamethasone to prevent acute nausea and vomiting, dexamethasone on days 2–4 is suggested to prevent delayed nausea and vomiting	High	Moderate	I	B
Prevention of acute nausea and vomiting following anthracycline-cyclophosphamide-based chemotherapy of high emetic risk	In women with breast cancer, a three-drug regimen including single doses of a 5-HT ₃ -receptor antagonist, dexamethasone, and an NK ₁ receptor antagonist (aprepitant, fosaprepitant, netupitant ^a , or rolapitant), given before chemotherapy is recommended ^c .	High	High	I	A
Prevention of delayed nausea and vomiting following anthracycline-cyclophosphamide-based chemotherapy of high emetic risk	In women with breast cancer treated with a combination of a 5-HT ₃ -receptor antagonist, dexamethasone and a NK ₁ receptor antagonist to prevent acute nausea and vomiting, aprepitant or dexamethasone ^d should be used on days 2 and 3 or none if fosaprepitant, netupitant or rolapitant has been used in day 1.	Moderate	Moderate	II	B
The MASCC/ESMO Antiemetics Guidelines Committee has discussed the presently available published data about olanzapine, which suggest that it is an effective antiemetic agent.	Olanzapine may be considered with a 5-HT ₃ -receptor antagonist plus dexamethasone, particularly when nausea is an issue ^e .	Low	Low	II	B

^a Netupitant is administered with palonosetron as part of the fixed-dose oral combination agent NEPA.

^b If aprepitant 125 mg is used on day 1, then dexamethasone 8 mg × 1 (days 2–4) + aprepitant 80 mg × 1 (days 2–3) or dexamethasone 8 mg × 2 (days 2–4) + metoclopramide 20 mg × 4 (days 2–4). Please note that this dosage of metoclopramide derives from a phase III study and some regulatory authorities like EMA now recommend a maximum 0.5 mg/kg total daily dose.

^c If a NK₁-receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT₃-receptor antagonist.

^d If aprepitant 125 mg is used on day 1, then aprepitant 80 mg × 1 (days 2–3) or dexamethasone 4 mg × 2 (days 2–3).

^e Patient sedation may be a concern for the 10-mg dose.

Are there differences among the NK1-receptor antagonists in the prevention of nausea and vomiting following high emetic risk chemotherapy?

Clinical differences

At present, no comparative studies have been carried out to identify differences in efficacy and toxicity between the three NK1-receptor antagonists. Therefore, when available, choice may be dependent on respective convenience and cost.

Conclusion

Cisplatin-based chemotherapy

- The addition of an NK1-receptor antagonist in patients receiving cisplatin chemotherapy increased the complete response on day 1 between 4 and 14 %, on days 2–5 between 8 and 21 %, and on days 1–5 between 8 and 20 % [13, 22–24, 33]. This increase is not only statistically significant but also clinically relevant because of the potential positive impact on the rates of complete response in the first cycle on the subsequent cycles of chemotherapy.

- The magnitude of the differences observed between the studies could be affected by differences in the control arm, (e.g. differences in 5-HT3-receptor antagonist use).
- Furthermore, part of the antiemetic effect days 2–5 could also be due to a dependence effect from day 1 (the better results obtained on day 1, the higher chance of complete responses on days 2–5).

Referenzen

13. Hesketh PJ, Rossi G, Rizzi G, Palmas M, Alyasova A, Bondarenko I, Lisyanskaya A, Gralla RJ (2014) Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. Ann Oncol 25:1340–1346
22. Hesketh PJ, Grunberg SM, Gralla RJ et al (2003) The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. J Clin Oncol 21:4112–4119
23. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD et al (2003) Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 97:3090–3098
24. Schmoll HJ, Aapro MS, Poli-Bigelli S et al (2006) Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 17:1000–1006
33. Rapoport BL, Chasen MR, Gridelli C, Urban L, Modiano MR, Schnadig ID, Poma A, Arora S, Kansra V, Schwartzberg LS, Navari RM (2015) Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. Lancet Oncol 16:1079–1089

AC-treated female patients with breast cancer

The addition of a NK1 receptor antagonist in patients receiving AC chemotherapy for breast cancer increased the complete response on day 1 between 0 and 7 %, on days 2–5 between 6 and 9 % and, on days 1–5 between 8 and 9 % [27, 30, 34]. The improvement in the delayed and overall phases is not only statistically significant but also clinically relevant because of the potential positive impact on the complete response rates in the subsequent cycles of chemotherapy. Similar to the cisplatin studies, the differences in the magnitude of benefit could be influenced by differences in the control arm. Also, as with the cisplatin-based studies, none of the AC chemotherapy studies were designed specifically for the investigation of delayed nausea and vomiting, and a carry-over effect of a day 1 difference cannot be excluded.

Referenzen

27. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD, Raftopoulos H, Grunberg SM, Gabriel M, Rodgers A, Bohidar N, Klinger G, Hustad CM, Horgan KJ, Skobieranda F (2005) Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 23: 2822–2830
30. Aapro M, Rugo H, Rossi G, Rizzi G, Borroni ME, Bondarenko I, Sarosiek T,

Oprean C, Cardona-Huerta S, Lorusso V, Karthaus M, Schwarcbszberg L, Grunberg S (2014) A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol 25:1328–1333

34. Schwartzberg LS, Modiano MR, Rapoport BL, Chasen MR, Gridelli C, Urban L, Poma A, Arora S, Navari RM, Schnadig ID (2015) Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. Lancet Oncol 16: 1071–1078

Other high emetic risk chemotherapy

These agents include mechlorethamine, streptozocin, cyclophosphamide >1500 mg/m², carmustine, and dacarbazine. Since the last update in 2009, a few randomized clinical trials have been published. These studies primarily investigated high dose chemotherapy used in connection with stem cell transplantation and are reviewed elsewhere [41]. The recommendation is to add a NK1 receptor antagonist to the combination of a 5-HT3-receptor antagonist and dexamethasone.

Referenzen

41. Einhorn LH, Rapoport B, Navari R, Herrstedt J, BramesMJ (2016). Antiemetic therapy for multiple-day chemotherapy, high dose chemotherapy, and breakthrough nausea and vomiting: review and consensus statements. Support Care Cancer 24.

Dose-schedule of antiemetic agents to prevent nausea and vomiting induced by high emetic risk chemotherapy in adults

Table 1 Dose-schedule of antiemetic agents to prevent nausea and vomiting induced by high emetic risk chemotherapy in adults

Antiemetics	Single dose given before single day chemotherapy	Doses given days 2–4 after single day chemotherapy	MASCC level of confidence	MASCC level of consensus	ESMO level of evidence	ESMO grade of recommendation
5-HT₃-receptor antagonists						
Ondansetron	Oral: 16 mg ^a IV: 8 mg or 0.15 mg/kg, max 16 mg	All serotonin antagonists are dosed on day 1 only	High High	Moderate High	I I	A A
Granisetron	Oral: 2 mg ^b IV: 1 mg or 0.01 mg/kg Transdermal: 3.1 mg/24 h		High High Moderate	High High High	I I I	A A A
Tropisetron	Oral or IV: 5 mg		Moderate	High	I	A
Dolasetron	Oral: 100 mg		Moderate	High	I	A
Palonosetron	IV: 0.25 mg Oral: 0.50 mg		Moderate Moderate	High High	II II	A A
Dexamethasone	Oral or IV: 20 mg ^c Day 1: High 8 mg bid for 3–4 days ^d Day 2–4: Low	Oral or IV: Day 1: High Day 2–4: High	Day 1: High Day 2–4: Low	Day 1: High Day 2–4: High	Day 1: I Day 2–4: III	Day 1: A Day 2–4: A
NK₁-receptor antagonists						
Aprepitant	Oral: 125 mg ^f	Oral: 80 mg days 2 and 3 ^f	High	High	I	A
Fosaprepitant	IV: 150 mg	None	Moderate	High	II	A
Netupitant	Oral: 300 mg ^g	None	High	High	I	A
Rolapitant	Oral: 180 mg ^h	None	High	High	I	A

^a A schedule of 8 mg × 2 is preferred by some panelists in anthracycline-cyclophosphamide-based chemotherapy

^b A dose of 1 mg is preferred by some panelists

^c 12 mg if the NK₁-receptor antagonist used is (fos)aprepitant or netupitant

^d 8 mg once daily if the NK1-receptor antagonist used is (fos)aprepitant or netupitant

^e If dexamethasone is not available limited data suggest that prednisolone or methylprednisolone can be substituted at doses about 7 and 5 times higher, respectively

^f EMA has approved a single oral dose of 165 mg (and none days 2–3), but no randomized clinical trials have tested this dose schedule

^g Administered in combination with oral palonosetron 0.5 mg in a single capsule (NEPA)

^h Equivalent to 200 mg rolapitant hydrochloride monohydrate

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 16.01.2017

#	Suchfrage
1	MeSH descriptor: [Nausea] explode all trees and with qualifier(s): [Chemically induced - CI, Drug therapy - DT, Prevention & control - PC, Therapy - TH]
2	MeSH descriptor: [Vomiting] explode all trees and with qualifier(s): [Chemically induced - CI, Drug therapy - DT, Prevention & control - PC, Therapy - TH]
3	MeSH descriptor: [Antiemetics] explode all trees
4	nause*:ti or vomit*:ti
5	emesis* or emetic* or antiemetic* or (anti and emetic*) or emetogenic*:ti,ab,kw
6	#1 or #2 or #3 or #4 or #5
7	MeSH descriptor: [Antineoplastic Agents] explode all trees
8	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
9	chemotherap*:ti or (chemotherap* and (related or induced)):ti,ab,kw or "chemotherapy related" or "chemotherapy-induced":ti,ab,kw or CINV:ti,ab,kw
10	#7 or #8 or #9
11	#6 and #9
12	#11 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 17.01.2017

#	Suchfrage
1	(("nausea/chemically induced"[MeSH Terms] OR "nausea/drug therapy"[MeSH Terms] OR "nausea/prevention and control"[MeSH Terms] OR "nausea/therapy"[MeSH Terms]))
2	(("vomiting/chemically induced"[MeSH Terms] OR "vomiting/drug therapy"[MeSH Terms] OR "vomiting/prevention and control"[MeSH Terms] OR "vomiting/therapy"[MeSH Terms]))
3	Antiemetics[Mesh]
4	nause*[Title/Abstract] OR vomit*[Title/Abstract]
5	emesis*[Title/Abstract] OR emetic*[Title/Abstract] OR antiemetic*[Title/Abstract] OR (anti[Title/Abstract] AND emetic*[Title/Abstract]) OR emetogenic*[Title/Abstract]
6	#1 OR #2 OR #3 OR #4 OR #5
7	chemotherap*[Title/Abstract] OR (chemotherap*[Title/Abstract] AND (related[Title/Abstract] OR induced[Title/Abstract])) OR "chemotherapy related"[Title/Abstract] OR "chemotherapy-induced"[Title/Abstract] OR CINV[Title/Abstract]
8	#6 AND #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract] OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR

	(meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract])) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
10	((#9) AND ("2012/01/01"[PDAT] : "2017/01/17"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[Mesh] AND animals[MeSH:noexp])))

Leitlinien in Medline (PubMed) am 17.01.2017

#	Suchfrage
1	(("nausea/chemically induced"[MeSH Terms] OR "nausea/drug therapy"[MeSH Terms] OR "nausea/prevention and control"[MeSH Terms] OR "nausea/therapy"[MeSH Terms]))
2	(("vomiting/chemically induced"[MeSH Terms] OR "vomiting/drug therapy"[MeSH Terms] OR "vomiting/prevention and control"[MeSH Terms] OR "vomiting/therapy"[MeSH Terms]))
3	nause*[Title/Abstract] OR vomit*[Title/Abstract]
4	emesis*[Title/Abstract] OR emetic*[Title/Abstract] OR antiemetic*[Title/Abstract] OR ("anti emetic")*[Title/Abstract] OR emetogenic*[Title/Abstract]
5	#1 OR #2 OR #3 OR #4
6	Antineoplastic Combined Chemotherapy Protocols[MeSH] OR Antineoplastic Agents[MeSH] OR Antiemetics[Mesh] OR Chemoradiotherapy[MeSH] OR Drug Therapy, Combination[MeSH] OR Neurokinin-1 Receptor Antagonists[MeSH] OR Ondansetron[MeSH] OR Serotonin Antagonists[MeSH] OR Serotonin 5-HT3 Receptor Antagonists[MeSH] OR chemotherapy*[Title/Abstract] OR radiochemotherap*[Title/Abstract] OR "CINV"[Title/Abstract] OR cancer[Title]
7	#5 AND #6
8	((#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract]))
9	((#8) AND ("2012/01/01"[PDAT] : "2017/01/19"[PDAT]) NOT ((comment[Publication Type]) OR letter[Publication Type])) NOT (animals[MeSH:noexp] NOT (Humans[Mesh] AND animals[MeSH:noexp])))

Literatur:

1. **Abdel-Rahman O.** Neurokinin-1 inhibitors in the prevention of nausea and vomiting from highly emetogenic chemotherapy: a network meta-analysis. *Ther Adv Med Oncol* 2016;8(5):396-406.
2. **Dos Santos LV, Souza FH, Brunetto AT, Sasse AD, Da Silveira Nogueira Lima JP.** Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. *J Natl Cancer Inst* 2012;104(17):1280-1292.
3. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Netupitant/Palonosetron vom 04. Februar 2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 17.01.2017]. URL: <https://www.g-ba.de/informationen/beschluesse/2489/>.
4. **Herrstedt J, Roila F, Warr D, Celio L, Navari RM, Hesketh PJ, et al.** 2016 Updated MASCC/ESMO Consensus Recommendations: Prevention of Nausea and Vomiting Following High Emetic Risk Chemotherapy. *Support Care Cancer* 2017;25(1):277-288.
5. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Netupitant/Palonosetron - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung); Auftrag A15-28 [online]. Köln (GER): IQWiG; 2015. [Zugriff: 18.01.2017]. (IQWiG-Berichte; Band 336). URL: https://www.iqwig.de/download/A15-28_Netupitant-Palonosetron_Nutzenbewertung-35a-SGB-V.pdf.
6. **Leitlinienprogramm Onkologie, Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlich Medizinischer Fachgesellschaften (AWMF).** Supportive Therapie bei onkologischen PatientInnen; S3-Leitlinie [online]. Registernummer 032 - 054OL. Berlin GER): Arbeitsgemeinschaft der Wissenschaftlich Medizinischer Fachgesellschaften (AWMF); 2016. [Zugriff: 18.01.2017]. URL: <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html>.
7. **National Comprehensive Cancer Network (NCCN).** Antiemesis; Version 2.2016 [online]. Fort Washington (USA): NCCN; 2016. [Zugriff: 12.01.2017]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.
8. **Roila F, Warr D, Hesketh PJ, Gralla R, Herrstedt J, Jordan K, et al.** 2016 updated MASCC/ESMO consensus recommendations: Prevention of nausea and vomiting following moderately emetogenic chemotherapy. *Support Care Cancer* 2017;25(1):289-294.
9. **Roila F, Warr D, Hesketh PJ, Gralla R, Herrstedt J, Jordan K, et al.** Erratum to: 2016 updated MASCC/ESMO consensus recommendations: Prevention of nausea and vomiting following moderately emetogenic chemotherapy. *Support Care Cancer* 2017;25(1):295-296.
10. **Shi Q, Li W, Li H, Le Q, Liu S, Zong S, et al.** Prevention of cisplatin-based chemotherapy-induced delayed nausea and vomiting using triple antiemetic regimens: a mixed treatment comparison. *Oncotarget* 2016;7(17):24402-24414.

11. **Simino GP, Marra LP, Andrade EI, Acurcio Fde A, Reis IA, De Araujo VE, et al.**
Efficacy, safety and effectiveness of ondansetron compared to other serotonin-3 receptor antagonists (5-HT3RAs) used to control chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2016;9(9):1183-1194.
12. **Tricco AC, Blondal E, Veroniki AA, Soobiah C, Vafaei A, Ivory J, et al.**
Comparative safety and effectiveness of serotonin receptor antagonists in patients undergoing chemotherapy: a systematic review and network meta-analysis. *BMC Med* 2016;14(1):216.
13. **Tricco AC, Soobiah C, Hui W, Antony J, Struchkov V, Hutton B, et al.**
Interventions to decrease the risk of adverse cardiac events for patients receiving chemotherapy and serotonin (5-HT3) receptor antagonists: a systematic review. *BMC Pharmacol Toxicol* 2015;16:1.
14. **Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al.**
Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA* 2015;313(24):2456-2473.
15. **Zhang Y, Yang Y, Zhang Z, Fang W, Kang S, Luo Y, et al.** Neurokinin-1 Receptor Antagonist-Based Triple Regimens in Preventing Chemotherapy-Induced Nausea and Vomiting: A Network Meta-Analysis. *J Natl Cancer Inst* 2017;109(2).

Anhang:

Dos Santos LV, Souza FH, Brunetto AT, Sasse AD, Da Silveira Nogueira Lima JP. Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. J Natl Cancer Inst 2012 [2]

Table 3. Reported adverse events for all included studies*

Toxicity	No.	No. at risk (%)	OR (95%CI)†	P‡	P, %	NNH
Anemia		1513	0.97 (0.69 to 1.37)	.87	3	NA
Control group	54	384 (14.1)				
NK1R group	157	1129 (13.9)				
Anorexia		4464	1.07 (0.89 to 1.29)	.45	0	NA
Control group	266	1784 (14.9)				
NK1R group	439	2680 (16.4)				
Asthenia or fatigue		7107	1.23 (1.05 to 1.45)	.01	11	37
Control group	337	2510 (13.4)				
NK1R group	741	4597 (16.1)				
Constipation		8422	0.79 (0.69 to 0.90)	<.001	0	-38
Control group	506	3089 (16.4)				
NK1R group	734	5333 (13.8)				
Death		6074	1.11 (0.73 to 1.70)	.62	0	NA
Control group	40	2336 (1.7)				
NK1R group	59	3738 (1.6)				
Dehydration		2540	0.93 (0.41 to 2.11)	.85	40	NA
Control group	19	1109 (1.7)				
NK1R group	24	1431 (1.7)				
Diarrhea		3857	1.06 (0.87 to 1.30)	.56	0	NA
Control group	193	1589 (12.1)				
NK1R group	303	2268 (13.4)				
Dizziness		1748	1.41 (0.57 to 3.48)	.45	44	NA
Control group	26	505 (5.1)				
NK1R group	70	1243 (5.6)				
Headache		4155	0.84 (0.69 to 1.02)	.08	0	NA
Control group	209	1566 (13.3)				
NK1R group	300	2589 (11.6)				
Hiccups		2708	1.30 (1.03 to 1.64)	.03	0	24
Control group	144	1095 (13.2)				
NK1R group	279	1613 (17.3)				
Infection—severe§		1480	3.10 (1.69 to 5.67)	<.001	0	25
Control group	15	741 (2.0)				
NK1R group	44	739 (6.0)				
Febrile neutropenia		6940	1.11 (0.76 to 1.64)	.59	0	NA
Control group	43	2764 (1.6)				
NK1R group	81	4176 (1.9)				
Neutropenia, grade 3–4		3075	1.08 (0.56 to 2.08)	.82	6	NA
Control group	19	1373 (1.4)				
NK1R group	32	1703 (1.9)				
Neutropenia		5795	1.06 (0.83 to 1.34)	.66	29	NA
Control group	316	1870 (16.9)				
NK1R group	934	3925 (23.8)				
Leukopenia		3257	1.03 (0.82 to 1.30)	.78	5	NA
Control group	139	845 (16.4)				
NK1R group	387	2412 (16.0)				
Severe adverse events		6258	1.06 (0.81 to 1.99)	.69	36	NA
Control group	186	2499 (7.4)				
NK1R group	253	3759 (6.7)				

* N = number; OR = Odds Ratio; 95% CI = 95% confidence interval; NK1R = neurokinin 1 receptor; NNH = number needed to harm; NA = not applicable.

† An OR less than 1 favored the NK1R antagonist group, whereas an OR greater than 1 favored the control arm group.

‡ Odds Ratio (OR) and respective 95% CI were calculated using Mantel-Haenszel random-effects model. P values were from the estimation of effect size (and not from heterogeneity test). P values were two-sided.

§ The definition of severe infection used in this meta-analysis followed NCI-CTCAE v3.0 standardization.

Tricco, AC et al., (2016). Comparative safety and effectiveness of serotonin receptor antagonists in patients undergoing chemotherapy: a systematic review and network meta-analysis [12].

Table 2 Summary of patient characteristics

Patient characteristics	Number of studies (n = 299) ^{a, b}	Percentage of studies
Number of patients	58,412	
Mean (median sample size)	197 (105) ^c	
Mean % female	53.1 ^d	
Age category		
Adults and elderly (aged ≥18 years)	192	64.21
Adults only (aged ≥18 to ≤65 years)	56	18.73
Children only (aged <18 years)	25	8.36
All ages	10	3.34
Children and adults (aged ≤65 years)	8	2.68
Not reported	8	2.68
Cancer type ^e		
Lung and respiratory	144	48.16
Breast	110	36.79
Gynecological	98	32.78
Hematological	91	30.43
Unspecified or unknown	87	29.10
Head and neck	87	29.10
Gastrointestinal	86	28.76
Genitourinary	81	27.09
Sarcoma	47	15.72
Not reported	43	14.38
Nervous system	13	4.35
Skin	11	3.68
Optic	5	1.67
Germ cell	5	1.67
Other	3	1.00
Adenocarcinoma	2	0.67
Musculoskeletal	1	0.33
Chemotherapy details		
Cisplatin administered ^f	177	59.20
Cisplatin dose ≥ 50 mg/m ²	116	38.80
Concomitant radiotherapy	12	4.01
Adjuvant	14	4.68
Neoadjuvant	4	1.34
Patient background details		
History of motion sickness	19	6.35
History of CINV	29	9.70

CINV chemotherapy induced nausea and vomiting

^aIncludes unpublished data from conference abstracts and trial protocols (Adel et al. 2006, Tabel et al. 2006, Trifilio et al. 2006, Carrec et al. 2007, Kadota et al. 2007, Plyush 2011)

^bExcept where indicated otherwise

^cOne study did not report sample size (n = 1)

^dEighteen studies did not report female population size (n = 18)

^eThe majority of studies included patients with different diagnoses

^fIncludes the 116 studies with a cisplatin dose ≥ 50 mg/m²

Leitlinienprogramm Onkologie(2016). Supportive Therapie bei onkologischen PatientInnen; S3-Leitlinie [6].

Tabelle 3: Schema der Evidenzgraduierung nach Oxford (Version März 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with > 80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical centre	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of Level >2 diagnostic studies	SR (with homogeneity) of Level 2b and better studies	SR (with homogeneity) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of	Exploratory cohort study with good reference standards; CDR after derivation, or	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way