Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-08-15-D-172 Netupitant / Palonosetron

Stand: August 2013

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

Netupitant/Palonosetron
zur Prävention von akuter und verzögerter Übelkeit und Erbrechen bei moderater sowie hoch emetogener Chemotherapie

<table>
<tr><th colspan="5">Kriterien gemäß 5. Kapitel § 6 VerfO</th></tr>
<tr><td rowspan="2">Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.</td><td>Serotonin-5HT$_3$-Antagonisten:</td><td>Prokinetika:</td><td>Neurokinin-1(NK1)-Rezeptor-Antagonisten:</td><td>Corticosteroide:</td></tr>
<tr><td>Ondansetron
Granisetron
Tropisetron
Dolasetron
Palonosetron</td><td>Metoclopramid
Domperidon
Alizaprid</td><td>Aprepitant
Fosaprepitant</td><td>Betamethason
Dexamethason
Methylprednisolon
Prednisolon
Prednison</td></tr>
<tr><td>Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.</td><td colspan="4">nicht angezeigt</td></tr>
<tr><td>Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen</td><td colspan="4">Festbetragsgruppen: Stufe:
▪ Serotonin-5HT3-Antagonisten 2
▪ Glucocorticoide, oral 2
▪ Metoclopramid 1
▪ Domperidon 1
▪ Dexamethason 1
▪ Prednisolon 1
▪ Prednison 1

Beschluss vom 9. Juli 2013 zur Einleitung eines Stellungnahmeverfahrens: Festbetragsgruppenbildung Serotonin-5HT3-Antagonisten, Gruppe 1, Stufe 2: Dolasetron, Ondansetron, Granisetron, Tropisetron</td></tr>
<tr><td>Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.</td><td colspan="4">Siehe Recherche und Synopse der Evidenz</td></tr>
</table>

Bei mehreren Alternativen ist die wirtschaftlichere Therapie zu wählen, vorzugsweise eine Therapie, für die ein Festbetrag gilt.	*entfällt*
[…] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	*nicht angezeigt*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Netupitant/Palonosetron n.b. Akynzeo®	Prävention von akuter und verzögerter Übelkeit und Erbrechen, die mit initialen oder wiederholten Behandlungen mit moderat emetogener Chemotherapie assoziiert sind. Prävention von akuter und verzögerter Übelkeit und Erbrechen, die mit initialen oder wiederholten Behandlungen mit hoch emetogener Chemotherapie assoziiert sind.
Ondansetron A04AA01 Zofran®	Übelkeit, Brechreiz und Erbrechen bei Therapie mit Zytostatika und Strahlentherapie.
Granisetron A04AA02 Kevatril®	Kevatril Filmtabletten werden bei Erwachsenen zur Vorbeugung und Behandlung von akuter Übelkeit und Erbrechen in Verbindung mit Chemo- und Strahlentherapie angewendet. Kevatril Filmtabletten werden zur Vorbeugung von verzögerter Übelkeit und Erbrechen in Verbindung mit Chemo- und Strahlentherapie angewendet.
Tropisetron A04AA03 Navoban®	Übelkeit, Brechreiz und Erbrechen bei Therapie mit Zytostatika
Dolasetron A04AA04 Anzemet®	Zur Vorbeugung und Behandlung von Übelkeit und Erbrechen bei zytostatischer Chemotherapie (Behandlung bösartiger Erkrankungen) einschließlich hochdosierten Cisplatins.
Palonosetron A04AA05 Aloxi®	Aloxi ist indiziert zur • 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.

Aprepitant A04AD12 Emend®	Zur Prävention akuter und verzögerter Übelkeit und Erbrechen bei hoch emetogener, auf Cisplatin basierender Chemotherapie bei Erwachsenen. Zur Prävention von Übelkeit und Erbrechen bei moderat emetogener Chemotherapie bei Erwachsenen. EMEND 125mg/80mg wird als Teil einer Kombinationstherapie angewendet (siehe Abschnitt 4.2).
Fosaprepitant A04AD12 IVEmend®	Zur Prävention akuter und verzögerter 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).
Metoclopramid A03FA01 Paspertin®	Hochdosierte Metoclopramidtherapie bei Übelkeit und Erbrechen durch Zytostatika.
Domperidon A03FA03 Domperidon STADA®	Erwachsene • Linderung von Symptomen wie Übelkeit und Erbrechen, Völlegefühl, Oberbauchbeschwerden und Rückfluss (Regurgitation) von Mageninhalt. Kinder • Linderung von Symptomen wie Übelkeit und Erbrechen.
Alizaprid A03FA05 Vergentan®	Zur Vorbeugung bzw. Behandlung von – Erbrechen, Übelkeit und Brechreiz im Zusammenhang mit der Zytostatikatherapie. – Strahlenkater nach Röntgen-, Telekobalt- oder Betatronbestrahlung.
Betamethason H02AB01 CELESTAN® solubile	Onkologie […] Prophylaxe und Therapie von postoperativem und/oder Zytostatika-induziertem Erbrechen im Rahmen antiemetischer Schemata.
Dexamethason H 02 AB 02 Fortecortin®	Prophylaxe und Therapie von postoperativem oder Zytostatika-induziertem Erbrechen im Rahmen antiemetischer Schemata.
Methylprednisolon H02AB04 Methylprednisolon Jenapharm®	Hämatologie/Tumorerkrankungen […] – zusätzlich für Methylprednisolon 4/8/16 mg JENAPHARM®: Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen, Anwendung im Rahmen antiemetischer Schemata.

Prednisolon H02AB06 Decortin H®	Hämatologie/Onkologie: […] – Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen (DS: b bis a), Anwendung im Rahmen antiemetischer Schemata
Prednison H02AB07 Cutason®	Hämatologie/Onkologie: […] – Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen (DS: b bis a), Anwendung im Rahmen antiemetischer Schemata.

Synoptische Evidenzübersicht zur Ermittlung der zVT:

Inhalt

Indikation für die Recherche für Netupitant/Palonosetron:

Prävention von akuter und verzögerter Übelkeit und Erbrechen, die mit initialen oder wiederholten Behandlungen mit moderat emetogener Chemotherapie assoziiert sind.

Prävention von akuter und verzögerter Übelkeit und Erbrechen, die mit initialen oder wiederholten Behandlungen mit hoch emetogener Chemotherapie assoziiert sind.

Berücksichtigte Wirkstoffe/Therapien: Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“.

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenzbasierten systematischen Leitlinien zur Indikation „Übelkeit und Erbrechen bei induzierter Chemotherapie“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 10.07.2013 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AkdÄ, AWMF, GIN, NGC, TRIP, DAHTA. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: DGHO-Onkopedia, NCCN, ESMO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Es wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab insgesamt 383 Treffer, welche anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Die erste Durchsicht ergab 99 eingeschlossene Quellen, die anschließend im Volltext überprüft wurden. Daraus konnten 10 Referenzen, die in die synoptische Evidenz-Übersicht aufgenommen werden.

Abkürzungen	
5-HT3 RAs	Serotonin receptor antagonists (5-HT_3 = 5-hydroxytryptamine-3)
AC	anthracycline combined with cyclophosphamide
HEC	High emetogen chemotherapy
MEC	Moderate emetogen chemotherapy
NK_1,R-Antagonist	Neurokinin-1-Rezeptor-Antagonist
PAL	palonosetron

Cochrane Reviews

Billio et al, 2010 [1] "Serotonin receptor antagonists for highly emetogenic chemotherapy in adults"	1. Fragestellung The primary objective of this review is to investigate the clinical efficacy of different serotonin receptor antagonists (5-HT3 RAs) in the control of acute and delayed emesis induced by highly emetogenic chemotherapy. The secondary objectives are to examine eligible studies for information on adverse events and to assess if there are important differences in the adverse events caused by the different anti-emetic agents. 2. Methodik a. Aktualität der Recherche: Systematische Literaturrecherche im Suchzeitraum 1990-2009 b. Vergleiche/Komparatoren: Vergleich von 5-HT3 RAs untereinander c. Endpunkte Primary outcomes: The primary outcome is acute nausea and vomiting. Secondary outcomes: 1. Delayed nausea and vomiting 2. Adverse effects. Population: adult cancer population 3. Ergebnisdarstellung basierend auf 16 Studien (n=7808) We included 16 RCTs for a total of 7808 participants. Nine of the trials compared granisetron versus ondansetron. No other drug comparison was studied in more than one trial. **Acute vomiting** (8 studies, n= 4256; granisetron versus ondansetron) complete absence of acute vomiting: The pooled OR was 0.89 (95% CI 0.78 to 1.02), favouring ondansetron. There was no statistical heterogeneity among the trials (Chi^2 = 5.69, df = 9, P = 0.77; I^2 = 0%). **Acute nausea** (7 studies, n= 4160; granisetron versus ondansetron) The pooled OR was 0.97 (95% CI 0.85 to 1.10), favouring ondansetron. There was no statistical heterogeneity among the trials (Chi^2 = 6.47, df = 8, P = 0.60; I^2 = 0%). **Total control of acute nausea and vomiting** **(Note:** this outcome refers to the absence of either nausea or vomiting in an individual participant.) (6 studies, n= 2809; granisetron versus ondansetron) The pooled OR was 1.00 (95% CI 0.85 to 1.16). There was no statistical heterogeneity among the trials (Chi^2 = 3.91, df = 6, P = 0.69; I^2 = 0%). **Delayed vomiting** (3 studies, n= 1119; granisetron versus ondansetron)

	The pooled OR was 1.00 (95% CI 0.74 to 1.34). There was no statistical heterogeneity among the trials (Chi^2 = 0.17, df = 2, P = 0.92; I^2 = 0%) **Delayed nausea** (2 studies, n= 1024; granisetron versus ondansetron) The pooled OR was 0.96 (95% CI 0.75 to 1.24) favouring ondansetron. There was no statistical heterogeneity among the trials (Chi^2 = 0.41, df = 1, P = 0.52; I^2 = 0%). **Total control of delayed nausea and vomiting** (2 studies, n= 1045; granisetron versus ondansetron) The pooled OR was 1.00 (95% CI 0.78 to 1.28). There was no statistical heterogeneity among the trials (Chi^2 = 0.10, df = 1, P = 0.75; I^2 = 0%). **Palonosetron plus dexamethasone vs granisetron plus dexamethasone** (1 study, n=1114) • superiority of palonosetron in controlling delayed vomiting (OR 1.45; 95% CI 1.14 to 1.85) and delayed nausea (OR 1.63; 95% CI 1.27 to 2.10). • Complete response for delayed nausea and vomiting was also in favour of the combination palonosetron and dexamethasone (OR 1.63; 95% CI 1.29 to 2.07). **4.** Schlussfolgerungen der Autoren Ondansetron and granisetron appear to be equivalent drugs for the prevention of acute and delayed emesis following the use of highly emetogenic chemotherapy. According to one single trial the combination of palonosetron and dexamethasone was superior to granisetron and dexamethasone in controlling delayed emesis. However, more evidence is needed. Regarding the question of whether there is one serotonin receptor antagonist (5-HT3 RA) to be clearly preferred over the others in the prevention of emesis associated with highly emetogenic chemotherapy, the current answer according to this meta-analysis is no.

Systematische Reviews

Dos Santos, 2012 [2] Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review	1. Fragestellung 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. 2. Methodik a) Systemat.Literaturrecherche im Suchzeitraum bis 2010 b) Vergleiche/Komparatoren Addition of NK1R antagonists to standard antiemetic regimens (including a 5-HT3 antagonist plus dexamethasone) vs adequate antiemetic therapy (dual therapy) c) Population: cancer patients receiving chemotherapy, regardless of its emetogenic potential. d) Endpunkte (primär): proportion of patients who achieved a complete response (CR). 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. e) Metaanalyse: RevMan 5.0 software was used to perform the meta-analysis . The Mantel–Haenszel random-effects method was used to calculate odds ratios (ORs) and the corresponding 95% confidence intervals f) Insgesamt einegschlossen: 17 Studien, n= 8740 3. Ergebnisdarstellung basierend auf insgesamt 17 Studien (n=8740) • 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).

	• CR in the 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). Schlussfolgerungen der Autoren • 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 moderatelyemetogenic 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.
Jin, 2012 [3] Efficacy and safety of aprepitant in the prevention of chemotherapy-induced nausea and vomiting: a pooled analysis.	1. Fragestellung A number of studies have reported that aprepitant has been used to prevent chemotherapy-induced nausea and vomiting. In this study, we aimed to analyze the efficacy and safety of aprepitant, which can provide evidence for aprepitant administration. 2. Methodik a) Systemat. Literaturrecherche im Suchzeitraum bis 2011 b) Vergleiche/Komparatoren aprepitant vs. placebo or no intervention for the prophylaxis of chemotherapy-induced nausea and vomiting c) Population: Patienten, die moderat oder hoch emetogene Chemotherapie erhalten d) Endpunkte: Complete response (CR) e) Ingesamt eingeschlossen: 15 Studien (n=4798) f) All analyses were conducted by using Stata software (Stata SE 10.0). Risk ratios (RRs) and their 95% confidence interval (CI) in respect to the incidence of nausea and vomiting for each study were calculated and pooled by using fixed-effectsmodels (Mantel–Haenszel method). 3. Ergebnisdarstellung basierend auf 15 Studien (n= 4,798; 2,419 in the experimental group and 2,319 in the control group) For the control of nausea and vomiting for highly or moderately emetogenic chemotherapy, aprepitant was given before chemotherapy with or without steroids and 5-HT3 receptor antagonists (palonosetron, ondansetron, or granisetron) according to the protocol used by each trial.

	• The cumulative incidence of emesis was significantly reduced in the aprepitant containing group on the first day [relative risk (RR) =1.13, 95% confidence interval (CI) 1.10–1.16], with no major heterogeneity detected (test for heterogeneity p=0.194). • Similar results were also obtained for delayed nausea and vomiting induced by highly or moderately emetogenic chemotherapy (from days 2 to 5. RR=1.35, 95% CI 1.22–1.48; overall 5 days, RR=1.30, 95% CI 1.22–1.39). 4. Schlussfolgerungen der Autoren In patients receiving moderately or highly emetogenic chemotherapy, the aprepitant-based regimen was superior to the non-aprepitant regimen in preventing CINV in the acute and delayed phases. Anmerkung der FBMed Es wurde keine gesonderte Analyse zum Vergleich der Effekte zwischen MEC und HEC durchgeführt.
Likun, 2011 [4] A systematic review and meta-analysis of intravenous palonosetron in the prevention of chemotherapy-induced nausea and vomiting in adults	1. Fragestellung We performed a systematic review and meta-analysis to evaluate the effectiveness and adverse effects of palonosetron in the prevention of CINV. 2. Methodik a) system. Literaturrecherche im Suchzeitraum 1950 –2010 b) Vergleiche/Komparatoren Palonosetron vs. First-generation 5-HT3-RA c) Population: Patienten, die MEC oder HEC erhoelten d) Endpunkte (primär/sekundär) complete response (CR) of the acute, delayed, and overall phases of CIVN after chemotherapy. Secondary outcomes included adverse effects of palonosetron. e) Statistical Analysis For nonheterogenerous trials, we performed meta-analysis with Review Manager (Revman 4.2) using fixed or random effects models. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A heterogeneity test p > .05 was interpreted as signifying a low level of heterogeneity suitable for meta-analysis. f) Eingesamt eingeschlossen: 8 Studien, n=3592 3. Ergebnisdarstellung • All included studies compared intravenous palonosetron with

	first-generation 5-HT3RA (one compared dolasetron, three compared ondansetron, and four compared granisetron). • Three studies evaluated the effectiveness of both 0.25 and 0.75 mg of palonosetron. Four studies evaluated the effectiveness of 0.25 mg of palonosetron and one evaluated 0.75 mg of palonosetron. • Corticosteroids were used before chemotherapy in two Studies. One study investigated palonosetron combined with dexamethasone. **Effectiveness of Palonosetron Compared with First-Generation 5-HT3RA in Prevention of Acute CINV** • All eight RCTs compared palonosetron with first-generation 5-HT3RA for prevention of acute CINV. • There was no heterogeneity between included studies (p = 0 .80). • Meta-analysis that included 3,592 patients with 3,696 cycles showed that palonosetron reduced the risk of acute CINV by 24% (OR, 0.76; 95% CI, 0.66 – 0.88, p = .0003). • Subgroup analysis showed that there were statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.68; 95% CI, 0.56 – 0.83; p =.0001) and 0.75 mg of palonosetron (OR, 0.82; 95% CI, 0.69 – 0.99; p = .03). **Effectiveness of Palonosetron Compared with First-Generation 5-HT3RA in Prevention of Delayed CINV** • 7 RCTs (n= 3,384; 3,488 cycles) compared palonosetron with first-generation 5-HT3RA in prevention of delayed CINV. • The results showed no heterogeneity (p = .59) in any included studies (OR, 0.62;95% CI, 0.54 – 0.71) in favor of palonosetron (p < .00001). • Subgroup analyses indicated statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.62; 95% CI, 0.51– 0.75; p<.00001) and 0.75 mg of palonosetron (OR, 0.61; 95% CI, 0.52– 0.72; p <.00001). **Effectiveness of Palonosetron Compared with First-Generation 5-HT3RA in Prevention of the Overall Phase of CINV** • Seven RCTs compared palonosetron with first-generation 5-HT3RA in prevention of the overall phase of CINV. • Meta-analysis showed an OR of 0.64 (95% CI, 0.56–0.74) in favor of palonosetron (p < .00001). Subgroup analysis showed statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.62; 95% CI, 0.51– 0.75; p < .00001) and 0.75 mg (OR, 0.65; 95% CI, 0.55– 0.76; p < .00001). **Effectiveness of 0.25 mg of Palonosetron Compared with 0.75 mg of Palonosetron** • Meta-analysis included 3 studies (n = 1,202) showed no statistically significant differences between 0.25 and 0.75 mg of palonosetron in terms of preventing acute CINV (OR,

	1.09; 95% CI, 0.85–1.38; p = .50), delayed CINV (OR, 1.05; 95% CI, 0.83–1.32; p = .68), or overall phase CINV (OR, 1.11; 95% CI, 0.88 –1.40; p = .38). 4. Schlussfolgerungen der Autoren • All but one RCT showed that palonosetron was not superior to first-generation 5-HT3RA for prevention of acute CINV. Our meta-analysis, however, showed that palonosetron was more effective than the first-generation 5-HT3RA in prevention of acute CINV. • We noticed that all the RCTs on prevention of acute CINV were designed for noninferior tests. That might make the sample sizes insufficient to determine differences. Our meta-analysis also demonstrated the superiority of 0.25 mg of palonosetron over first-generation 5-HT3RA in the prevention of acute CINV in HEC.

Leitlinien

American Society of Clinical Oncology (ASCO), 2011 [5] Antiemetics Siehe auch: Basch, 2011 [6] Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update	American Society of Clinical Oncology Clinical Practice Guideline Update 1. Aktualität der Recherche: Suchzeitraum 2006 bis 2009 (Update zu einer älteren Version der LL) 2. Keine Angaben zu GoR oder LoE (Details zum methodischen Vorgehen und ausführliche Informationen zu den ausgewerteten Studien finden sich online in einem separaten Dokument. **Key Recommendations** ● Patients who receive highly emetic chemotherapy regimens should receive the three-drug combination of a neurokinin 1 (NK1) antagonist, 5-hydroxytryptamine-3 (5-HT3) antagonist, and dexamethasone. The three-drug combination of a neurokinin 1 (NK1) receptor antagonist (days 1 through 3 for aprepitant; day 1 only for fosaprepitant), a 5-HT3 receptor antagonist (day 1 only), and dexamethasone (days 1-3 or 1-4) is recommended for patients receiving highly emetogenic chemotherapy. ● The preferred 5-HT3 antagonist for patients who receive moderate emetic chemotherapy regimens is palonosetron; antiemetic treatment includes that agent combined with a corticosteroid. The two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1-3) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT3 serotonin receptor antagonist, preferably granisetron or ondansetron. ● Emesis or nausea despite optimal prophylaxis Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist or adding a dopamine antagonist to the regimen. ● Antiemetic treatment for patients who receive combination chemotherapy should be determined according to the agent with the greatest degree of emetic risk. ● Both dexamethasone and a 5-HT3 antagonist are recommended for patients undergoing high-dose chemotherapy.

<table>
<tr><td rowspan="2">Roila et al, 2010 [7]

Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference</td><td>Leitlinie von European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC)

Systematische Literaturrecherche im Suchzeitraum bis 2009 – Publikation als Ergebnis einer Konsensurkonferenz in Perugia im Jahr 2009

Keine Definition zu GoR und LoE</td></tr>
<tr><td>Antineoplastic agents emetogenicity
Defining the emetogenicity of chemotherapy agents is of value for at least two important reasons. First, such a classification can be used as a framework for defining antiemetic treatment guidelines. Second, it can provide a means for clinical investigators to attain a more precise definition of the emetogenic challenge that is being employed in an antiemetic trial.

<table>
<tr><th colspan="2">Emetogenic potential of <u>i.v.</u> antineoplastic agents</th></tr>
<tr><td>Degree of emetogenicity (incidence)</td><td>Agent</td></tr>
<tr><td>High (>90%)</td><td>Cisplatin
Mechlorethamine
Streptozotocin
Cyclophosphamide ‡1500 mg/m2
Carmustine
Dacarbazine</td></tr>
<tr><td>Moderate (30-90%)</td><td>Oxaliplatin
Cytarabine >1 gm/m2
Carboplatin
Ifosfamide
Cyclophosphamide <1500 mg/m2
Doxorubicin
Daunorubicin
Epirubicin
Idarubicin
Irinotecan
Azacitidine
Bendamustine
Clofarabine
Alemtuzumab</td></tr>
<tr><td>Low (10-30%)</td><td>Paclitaxel
Docetaxel
Mitoxantrone
Doxorubicin HCl liposome Injection
Ixabepilone
Topotecan
Etoposide
Pemetrexed
Methotrexate
Mitomycin
Gemcitabine
Cytarabine 1000 mg/m^2
5-Fluorouracil</td></tr>
</table>
</td></tr>
</table>

	Temsirolimus Bortezomib Cetuximab Trastuzumab Panitumumab Catumaxumab
Minimal (<10%)	Bleomycin Busulfan 2-Chlorodeoxyadenosine Fludarabine Vinblastine Vincristine Vinorelbine Bevacizumab

Emetogenic potential of <u>oral</u> antineoplastic agents	
Degree of emetogenicity (incidence)	Agent
High (>90%)	Hexamethylmelamine Procarbazine
Moderate (30-90%)	Cyclophosphamide Temozolomide Vinorelbine Imatinib
Low (10-30%)	Capecitabine Tegafur Uracil Fludarabine Etoposide Sunitinib Everolimus Lapatinib Lenalidomide Thalidomide
Minimal (<10%)	Chlorambucil Hydroxyurea L-Phenylalanine mustard 6-Thioguanine Methotrexate Gefitinib Erlotinib Sorafenib

prevention of <u>acute</u> nausea and vomiting induced by <u>highly</u> emetogenic chemotherapy

- To prevent acute nausea and vomiting following chemotherapy of high emetic risk a <u>three-drug regimen including single doses of a 5-HT3 receptor antagonist, dexamethasone and aprepitant</u> given before chemotherapy is recommended [High, High] [I, A].
- The principles for use of 5-HT3 receptor antagonists to prevent acute nausea and vomiting induced by chemotherapy of high emetogenic risk are the following: (i) use the lowest tested fully effective dose; (ii) no schedule better than a single dose

	beginning before chemotherapy; (iii) the adverse effects of these agents are comparable; (iv) intravenous and oral formulations are equally effective and safe; (v) give with dexamethasone and an NK1 receptor antagonist beginning before chemotherapy [Moderate, High] [I, A]. **prevention of <u>delayed</u> nausea and vomiting induced by <u>highly</u> emetogenic chemotherapy** • The panel recommended that given the dependence of delayed emesis and nausea on acute antiemetic outcome, optimal acute antiemetic prophylaxis should be employed. In patients receiving cisplatin treated with a combination of aprepitant, a 5-HT3 receptor antagonist and dexamethasone to prevent acute vomiting and nausea, the combination of dexamethasone and aprepitant is suggested to prevent delayed nausea and vomiting, on the basis of its superiority to dexamethasone alone [High, Moderate] [II, A]. • To date, no trials have compared this regimen for delayed emesis with the previous standard treatments (dexamethasone combined with metoclopramide or a 5-HT3 receptor antagonist). **prevention of <u>acute</u> nausea and vomiting induced by <u>moderately</u> emetogenic chemotherapy** • To prevent acute nausea and vomiting induced by non-AC MEC a combination <u>of palonosetron plus dexamethasone is recommended as standard prophylaxis</u> [Moderate, Moderate] [II,B]. • Women receiving a combination of anthracycline plus cyclophosphamide represents a situation with a particularly great risk of nausea and vomiting. To prevent acute nausea and vomiting in these women, a three drug regimen including single doses of a 5-HT3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended [High, High] [I, A]. • If aprepitant is not available women receiving a combination of anthracycline plus cyclophosphamide should receive a combination of palonosetron plus dexamethasone [Moderate, Moderate] [II, B]. **prevention of <u>delayed</u> nausea and vomiting induced by <u>moderately</u> emetogenic chemotherapy** • The panel recommended that patients who receive MEC known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis [High, High] [I, A]. • In patients receiving chemotherapy of moderate emetic risk that does not include a combination of anthracycline plus cyclophosphamide and in which palonosetron is recommended, multiday oral dexamethasone treatment is the preferred treatment for the prevention of delayed nausea and vomiting [Moderate, Moderate] [II, B]. • Therefore, the panel updated the recommendation stating that in these patients aprepitant should be used to prevent delayed nausea and vomiting [Moderate, Moderate] [II, B]

Antiemetic agents to prevent acute emesis induced by HEC in adults

Antiemetics	Single daily dose given before chemotherapy	MASCC		ESMO	
		Level of Consensus	Level of Confidence	Level of Evidence	Grade of Recommendation
Ondansetron	Oral: 24 mg	Moderate	High	I	A
	i.v.: 8 mg or 0.15 mg/kg	High	High	I	A
Granisetron	Oral: 2 mg	High	High	I	A
	i.v.: 1 mg or 0.01 mg/kg	High	High	I	A
Tropisetron	Oral or i.v.: 5 mg	High	Moderate	I	A
Dolasetron	Oral: 100 mg	High	Moderate	I	A
	i.v.:100 mg or 0.18mg/kg	High	High	I	A
Palonosetron	i.v.: 0.25 mg	High	Moderate	II	A
	Oral:0.50 mg	High	Moderate	II	A
Dexamethasone	Oral or i.v.: 12 mg*	High	High	I	A
Aprepitant	Oral: 125 mg	High	High	I	A
Fosaprepitant	i.v.: 115 mg	High	Moderate	II	A

*20 mg if aprepitant is not available. If dexamethasone is not available limited data suggest that prednisolone or methylprednisolone can be substituted at doses about 7 and 5 times higher respectively.

Antiemetic agents to prevent acute emesis induced by MEC in adults

Antiemetics	Single daily dose given before chemotherapy	MASCC		ESMO	
		Level of Consensus	Level of Confidence	Level of Evidence	Grade of Recommendation
Ondansetron	Oral: 16 mg (8 mg b.i.d.)	High	High	I	A
	i.v.: 8 mg or 0.15 mg/kg	High	Moderate	III	B
Granisetron	Oral: 2 mg	High	High	I	A
	i.v.: 1 mg or 0.01 mg/kg	High	High	I	A
Tropisetron	Oral or i.v.: 5 mg	High	Low	III	B
	i.v.: 5 mg	High	Moderate	III	B
Dolasetron	Oral: 100 mg	High	Moderate	II	A
	i.v.:100 mg or 0.18mg/kg	High	Moderate	II	A
Palonosetron	i.v.: 0.25 mg	High	High	I	A
	Oral:0.5 mg	High	Moderate	II	A
Dexamethasone	Oral or i.v.: 8 mg*	High	Moderate	II	A
Aprepitant	Oral: 125 mg	High	Moderate	II	A
Fosaprepitant	i.v.: 115 mg	High	Moderate	II	A

*If dexamethasone is not available limited data suggest that prednisolone or methylprednisolone can be substitued at doses about seven and five times higher, respectively.

Roila, 2011 [8] Delayed emesis: moderately emetogenic chemotherapy (single-day chemotherapy regimens only)	An update of the recommendations for the prophylaxis of delayed emesis induced by moderately emetogenic chemotherapy discussed during the third Perugia Consensus Conference (June 2009) was presented. The review considered new studies published since the second consensus conference (April 2004). System. Literaturrecherche im Suchzeitraum 2004-2009 als Update zu einer Empfehlung aus 2004; Keine Definition von GoR und LoE • Patients who receive moderately emetogenic chemotherapy known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis. MASCC level of confidence: high; level of consensus: high ESMO level of evidence: I; grade of recommendation: A • In breast cancer patients receiving a combination of anthracycline plus cyclophosphamide treated with a combination of aprepitant, a 5-HT3 receptor antagonist and dexamethasone to prevent acute nausea and vomiting, aprepitant should be used to prevent delayed nausea and vomiting. MASCC level of confidence: moderate; level of consensus: moderate ESMO level of evidence: II; grade of recommendation: B • In patients receiving chemotherapy of moderate emetic risk which does not include a combination of anthracycline plus cyclophosphamide and in which palonosetron is recommended for the prophylaxis of acute emesis, multiday oral dexamethasone treatment is the preferred treatment for the prevention of delayed emesis. MASCC level of confidence: moderate; level of consensus: moderate ESMO level of evidence: II; grade of recommendation: B • The optimal duration and dose of dexamethasone have not been defined.
NCCN, 2013 [9] Antiemetics	Leitlinie des National Comprehensive Cancer Network Keine Angaben zur Literaturrecherche oder Methodik im Dokument. Update einer älteren Version der Leitlinie NCCN Categories of Evidence and Consensus : Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. All recommendations are category 2A unless otherwise noted.

	1) <u>High</u> emetic risk i.v. Chemotherapy (start before chemotherapy): • Serotonin (5-HT3) Antagonist Dolasetron Granisetron Ondasetron Palonosetron (preferred; data with palonosetron are based on randomized studies in combination with steroids only) AND • Steroid (Dexamethasone) AND • Neurokinin 1 Antagonist Aprepitant Fosaprepitant (and optional: Lorazepam, H2 Blocker or PPI) 2) <u>Moderate</u> emetic risk i.v. Chemotherapy Day 1(start before chemotherapy): • Serotonin (5-HT3) Antagonist Dolasetron (category 1) Granisetron (category 1) Ondasetron (category 1) Palonosetron (day 1only preferred; data with palonosetron are based on randomized studies in combination with steroids only) AND • Steroid (Dexamethasone) WITH/WITHOUT • Neurokinin 1 Antagonist • Lorazepam • H2 Blocker or PPI Days 2 and 3: • Serotonin (5-HT3) Antagonist monotherapy (unless palonosetron used on day 1) Dolasetron Granisetron Ondasetron OR • Steroid monotherapy OR • Neurokinin 1 Antagonist +- steroid (if oral NK-1 antagonist used on day 1) • Lorazepam • H2 Blocker or PPI
AWMF [10] Diagnostik, Therapie und Nachsorge des Mammakarzinoms	Interdisziplinare S3-Leitlinie des Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. Federführende Fachgesellschaften: Deutsche Krebsgesellschaft e.V. (DKG), Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) (Langversion 3.0 Stand 2012) Informationen zur Methodik im Leitlinienreport:

Aktualität der Recherche: Suchzeitraum 2006-2011 (als Update-Recherche zur Älteren Version der Leitlinie)

Level of Evidence		Studien zu Therapie, Prävention, Ätiologie
1	1a	Qualitativ hochwertiger Systematischer Review (SR) von randomisiert-kontrollierten Studien (RCT) mit geringem Risiko für Verzerrungen
	1b	Einzelne RCT mit geringem Risiko für Verzerrungen
	1c	„Alle oder Keiner "-Prinzip*
2	2a	SR von Kohortenstudien mit geringem Risiko für Verzerrungen
	2b	Einzelne Kohortenstudie mit geringem Risiko für Verzerrungen
	2c	Ergebnisforschung; ökologische Studien
3	3a	SR von Fallkontrollstudien
	3b	Einzelne Fallkontrollstudie
4		Fallserie
5		Expertenmeinung oder basierend auf pathophysiologischen Modellen oder experimenteller Grundlagen-forschung oder „Grundprinzipien"
* Dramatische Effekte, z.B. alle Patienten starben, bevor die Therapie verfügbar war und nach Einführung der Therapie überlebten einige		

Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Syntax
A	Starke Empfehlung	Soll
B	Empfehlung	Sollte
O	Empfehlung offen	Kann

Durch Chemotherapie induzierte Nausea und Vomitus gehören zu den belastendsten Grundsätzlich richtet sich die antiemetische Prophylaxe nach dem emetogenen Potenzial der Zytostatika.

Hoch (Risiko ohne antiemetische Prophylaxe zu erbrechen > 90 %): Cisplatin

Moderat (Risiko ohne antiemetische Prophylaxe zu erbrechen 30–90 %): Carboplatin, Eribulin,Cyclophosphamid (< 1500 mg/m2), Ifosfamid, Cyclophosphamid, per os Mitoxantron (> 12 mg/m2), Doxorubicin, Temozolomid, Epirubicin, Vinorelbin p. o.

Gering (Risiko ohne antiemetische Prophylaxe zu erbrechen 10–30 %): Capecitabine, Methotrexat (> 100 mg/m2),Catumaxomab Mitomycin C, Docetaxel Mitoxantron (< 12 mg/m2), 5-Fluorouracil Paclitaxel, Gemcitabine, Topotecan, Ixabepilon, Trastuzumab, Liposomales Doxorubicin

Minimal (Risiko ohne antiemetische Prophylaxe zu erbrechen < 10 %): Bevacizumab, Vindesin, Hormone, Vinorelbin,Methotrexat (< 100 mg/m2) oder p. o.

Antiemetische Prophylaxe bei Chemotherapie am Tag 1 (akute Phase) und an den Tagen 2–4 (verzögerte Phase) nach den ASCO- und MASCC-Guidelines		
Emetogenes Potenzial	Akute Phase, bis 24 h nach Chemotherapie, Tag 1	Verzögerte Phase, ab 24 h (Tag 2) bis Tag 3 (4) nach Chemo
Hoch	Kombination aus 3 Substanzen: **1. 5-HT_3 RA:** a) Granisetron 2 mg p.o./1 mg i.v. b) Ondansetron 16 mg p.o./8 mg i.v. c)Tropisetron 5 mgp.o./i.v. d) Palonosetron 0,25 mg i.v. + **2. <u>Steroid:</u>** Dexamethason 12mg p.o/i.v. + 3. **<u>Neurokinin-1-Rezeptor-Antagonist:</u>** Aprepitant 125 mg p.o. oder Fosaprepitant 115 mg i.v. (entfallt dann Tage 2 und 3)	Kombination aus 2 Substanzen (kein 5-HT_3 RA): 1. Steroid: Dexamethason 8 mg p.o./i.v. Tage 2 und 3 (ggf. auch 4) + 2. Neurokinin-1-Rezeptor-Antagonist: Aprepitant 80 mg p.o. für Tage 2 und 3 (entfallt wenn Fosaprepitant i.v. an Tag 1)
Moderat	Kombination aus 2 Substanzen: 1. 5-HT_3 RA (Dosen s.o.) a) Palonosetron (bevorzugt) b) Granisetron c) Tropisetron + 2. Steroid: Dexamethason 8 mg p.o/i.v.	Steroid: Dexamethason, 8 mg p.o /i.v. für Tage 2 und 3
	Begrenzte Evidenz liegt für die zusätzliche Verwendung von Aprepitant bei moderat emetogener Chemotherapie vor, bei Auswahl dieser 3er-Kombination ist jeder 5-HT_3 RA geeignet.	
Gering	Steroid: Dexamethason 8 mg p.o/i.v.	keine Routineprophylaxe
Minimal	keine Routineprophylaxe	keine Routineprophylaxe

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 05.07.2013

#	Suchfrage	Treffer
1	MeSH descriptor: [Nausea] explode all trees and with qualifiers: [Prevention & control - PC]	1658
2	MeSH descriptor: [Vomiting] explode all trees and with qualifiers: [Prevention & control - PC]	1906
3	nausea or squeamishness or qualm or queasiness:ti,ab,kw (Word variations have been searched)	17186
4	emesis or vomiting or vomitus or sickness:ti,ab,kw	15652
5	#1 or #2 or #3 or #4	21842
6	chemotherapy-induced or chemotherapy induced or chemotherapy-related or chemotherapy related:ti,ab,kw	7850
7	#6 and #5	512
8	CINV:ti,ab,kw	76
9	#7 or #8	433
10	(antiemetic and treatment) or preventive or prevention* or preventative:ti,ab,kw	101297
11	#9 and #10 from 2008 to2013	187
12	cancer or palliative:ti,ab,kw	69799
13	#11 and #12 from 2008 to 2013	133

Cochrane Reviews [67] | Other Reviews [4] | Clinical Trials [57] | Methods Studies [0] | Technology Assessments [] | Economic Evaluations [3] | Cochrane Groups [2]

→ importiert: 64 Cochrane Reviews, 04 Other Reviews, 00 Technology Assessments

SR/HTA in Medline (PubMed) am 10.07.2013

#	Suchfrage	Treffer
1	"Nausea/prevention and control"[Mesh]	3642
2	“Vomiting/prevention and control"[MeSH Terms]	4619
3	(((nausea[Title/Abstract]) OR squeamishness[Title/Abstract]) OR qualm[Title/Abstract]) OR queasiness[Title/Abstract]	40029
4	(((emesis[Title/Abstract]) OR vomiting[Title/Abstract]) OR vomitus[Title/Abstract]) OR sickness[Title/Abstract]	66026
5	(((#1) OR #2) OR #3) OR #4	81026
6	((((("chemotherapy-induced"[Title/Abstract]) OR (chemotherapy[Title/Abstract] AND induced[Title/Abstract])) OR emetogenic*[Title/Abstract]) OR "chemotherapy-related"[Title/Abstract]) OR (chemotherapy[Title/Abstract] AND related[Title/Abstract])	44732
7	Cancer[Title/Abstract] OR palliative[Title/Abstract]	991409
8	CINV[Title/Abstract]	319
10	((#6) OR #7) OR #8)	1012839
	(#5) AND #10	12564
12	antiemetic agents[MeSH Terms]	6925
13	5HT3[Title/Abstract] OR antiemetic*[Title/Abstract]	5576
14	(#12) OR #13	9752
15	(#10) AND #14	2714
16	(#15) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])	1935
17	(#15) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR	81

	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]))))	
18	(#16) OR #17	163
29	(#18) AND ("2008/07/01"[PDAT] : "2013/07/10"[PDAT])	70

→ nach Dublettenkontrolle importiert: 61 von 70 Treffer

Leitlinien in Pubmed (Medline) am 04.07.2013

#	Suchfrage	Treffer
13	"Nausea/prevention and control"[Mesh]	3640
14	“Vomiting/prevention and control"[MeSH Terms]	4614
15	(((nausea[Title/Abstract]) OR squeamishness[Title/Abstract]) OR qualm[Title/Abstract]) OR queasiness[Title/Abstract]	39997
16	(((emesis[Title/Abstract]) OR vomiting[Title/Abstract]) OR vomitus[Title/Abstract]) OR sickness[Title/Abstract]	65968
17	(((#13) OR #14) OR #15) OR #16	80952
18	((((("chemotherapy-induced"[Title/Abstract]) OR (chemotherapy[Title/Abstract] AND induced[Title/Abstract])) OR emetogenic*[Title/Abstract]) OR "chemotherapy-related"[Title/Abstract]) OR (chemotherapy[Title/Abstract] AND related[Title/Abstract])	44674
19	Cancer[Title/Abstract] OR palliative[Title/Abstract]	990242
20	(#18) AND #19	23276
21	(#20) AND #17	2023
22	(#21) AND (Guideline[ptyp] OR Practice Guideline[ptyp])	4
23	(#21) AND guideline*[Title]	17
24	(#22) OR #23	17
25	(#24) AND ("2008/07/01"[PDAT] : "2013/07/04"[PDAT])	13

→ nach Dublettenkontrolle importiert: 13 von 13 Treffer

Literatur:

1. **Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. Cochrane Database of Systematic Reviews 2010; (1): - CD006272.**

2. **dos Santos LV, Souza FH, Brunetto AT, Sasse AD, Silveira Nogueira Lima JP. Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. Database of Abstracts of Reviews of Effects 2012; (2): 1280-92.**

3. **Jin Y, Wu X, Guan Y, Gu D, Shen Y, Xu Z, Wei X, Chen J. Efficacy and safety of aprepitant in the prevention of chemotherapy-induced nausea and vomiting: a pooled analysis. Support Care Cancer 2012; 20 (8): 1815-22.**

4. **Likun Z, Xiang J, Yi B, Xin D, Tao ZL. A systematic review and meta-analysis of intravenous palonosetron in the prevention of chemotherapy-induced nausea and vomiting in adults. Oncologist 2011; 16 (2): 207-16.**

5. **American Society of Clinical Oncology (ASCO). Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update, Stand: 2011. (US): ASCO 2008; 30 (7): 600-7.http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Guidelines/Clinical+Practice+Guidelines/Antiemetics%3A+American+Society+of+Clinical+Oncology+Clinical+Practice+Guideline+Update, Zugriff am 04.07.2013.**

6. **Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, Chesney M, Clark-Snow RA, Flaherty AM, Freundlich B, Morrow G, Rao KV, Schwartz RN, Lyman GH. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2011; 29 (31): 4189-98.**

7. **Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, Bria E, Clark-Snow RA, Espersen BT, Feyer P, Grunberg SM, Hesketh PJ, Jordan K, Kris MG, Maranzano E, Molassiotis A, Morrow G, Olver I, Rapoport BL, Rittenberg C, Saito M, Tonato M, Warr D. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 2010; 21 Suppl 5 v232-v243.annonc.oxfordjournals.org/content/21/suppl_5/v232.full.pdf, Zugriff am 04.07.2013.**

8. **Roila F, Warr D, Aapro M, Clark-Snow RA, Einhorn L, Gralla RJ, Herrstedt J, Saito M, Tonato M. Delayed emesis: moderately emetogenic chemotherapy (single-day chemotherapy regimens only). Support Care Cancer 2011; 19 Suppl 1 S57-S62.**

9. **National Comprehensive Cancer Network (NCCN). Antiemesis. Fort Washington (CN): NCCN, 2013 http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf, Zugriff am 10.07.2013.**

10. **Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V, Deutschen Krebshilfe e.V. Interdisziplinäre S3-Leitlinie fur die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 3.0, Aktualisierung 2012. (AWMF Leitlinien-Register Nummer 032-045OL): http://www.awmf.org/uploads/tx_szleitlinien/032-045OL_l_S3__Brustkrebs_Mammakarzinom_Diagnostik_Therapie_Nachsorge_2012-07.pdf, Zugriff am 09.08.2012.**