Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-025-z Natriumthiosulfat

Stand: März 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Natriumthiosulfat [zur Vorbeugung einer durch Cisplatin-Chemotherapie induzierten Ototoxizität] Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Es sind keine Arzneimittel im Anwendungsgebiet zugelassen.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse im Anwendungsgebiet vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Natriumthiosulfat N.N. Pedmarqsi	Anwendungsgebiet laut Zulassung: Pedmarqsi ist angezeigt für die Vorbeugung einer durch eine Cisplatin-Chemotherapie induzierten Ototoxizität bei Patienten im Alter von 1 Monat bis < 18 Jahren mit lokalisierten, nicht metastasierten, soliden Tumoren.
Es sind keine Arzneimittel im Anwendungsgebiet zugelassen.	

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-025z (Beratung nach § 35a SGB V) Natriumthiosulfat

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	13. Februar 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AYA	adolescent and young adult
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
STS	sodium thiosulfate
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Vorbeugung einer durch eine Cisplatin-Chemotherapie induzierten Ototoxizität.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Cisplatin induzierte Ototoxizität durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 05.02.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 436 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf wurden insgesamt 2 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

3.2 Systematische Reviews

Es konnten keine relevanten systematischen Reviews identifiziert werden.

3.3 Leitlinien

Leitlinienprogramm Onkologie [2]

Aktuell liegt zu der Leitlinie „Supportiven Therapie bei onkologischen PatientInnen“ eine Konsultationsfassung vor. Die Konsultationsphase endete am 21.10.2024. Die finale Fassung der Leitlinie ist derzeit in Erstellung. Als Datum der Fertigstellung wurde der 31.12.2024 angegeben.

NCCN, 2024 [3].

National Comprehensive Cancer Network

Adolescent and Young Adult (AYA) Oncology, version 2.2025

Zielsetzung/Fragestellung

The NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology have been developed as supportive care guidelines and not as treatment guidelines. The purpose of the guidelines is to identify and increase awareness of unique issues in AYA oncology.

Methodik

Grundlage der Leitlinie

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger aktueller Evidenz wird die LL ergänzend dargestellt.

- Grundlage der Leitlinie
- Repräsentatives Gremium unklar.
- Interessenkonflikte und finanzielle Unabhängigkeit unklar.
- Systematische Suche, Auswahl und Bewertung der Evidenz unklar.
- Formale Konsensusprozesse und externes Begutachtungsverfahren unklar.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- electronic search of the PubMed database
- Suchzeitraum: nicht angegeben

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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 indicated.

Empfehlungen

The adolescent and young adult (AYA) oncology patient is defined as an individual aged 15–39 years at the time of initial cancer diagnosis. This definition is based on the National

Cancer Institute (NCI) Progress Review Group recommendations for a national agenda to advance AYA oncology.

Ototoxicity –

Conduct routine evaluations for tinnitus and periodic audiogram to monitor hearing loss associated with platinum-based chemotherapy. Consider sodium thiosulfate (STS) to reduce the risk of ototoxicity associated with cisplatin in patients with localized, non-metastatic, solid tumors. There are concerns about the use of STS in the metastatic setting.[h]

h Orgel E, et al. Lancet Oncol 2022;23:570-572.

Ototoxicity may occur following treatment with platinum-based chemotherapy agents.126 Although this side effect is not considered life-threatening, it can have a detrimental effect on an AYA patient's quality of life. In 2022, the FDA approved the use of sodium thiosulfate (STS) for reducing the risk of ototoxicity associated with cisplatin in pediatric patients ≥1 month of age with localized, non-metastatic solid tumors.127
The approval of this indication was based on data from two open-label, phase 3, randomized controlled trials in pediatric patients with cancer who were treated with cisplatin; the incidence of hearing loss was lower in those who received STS than those who did not receive STS.128,129
However, concerns remain regarding the use of STS in the metastatic setting. A post-hoc analysis of data from the ACCL0431 trial showed that, among patients with disseminated disease, STS was associated with a significantly lower 3-year overall survival rate compared with those who did not receive STS (45% vs. 84%; P = .009).130

Referenzen
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Freyer DR et al., 2020 [1].

Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline

Zielsetzung/Fragestellung

Although a clinical practice guideline is available for ototoxicity surveillance,11 a guideline focused on interventions to reduce ototoxicity is not available for health-care professionals in paediatric oncology. Consequently, our objective was to create a clinical practice guideline for the prevention of cisplatininduced ototoxicity in children and adolescents with cancer.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium;

- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Für formale Konsensusprozesse auf Referenz verwiesen, kein externes Begutachtungsverfahren;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Keine Angaben zur Überprüfung der Aktualität.

Recherche/Suchzeitraum:

- Jan 1, 1980, to May 14, 2019 in MEDLINE, MEDLINE inprocess, MEDLINE e-publications ahead of print, Embase, and the Cochrane Central Register of Controlled Trials

LoE

- Cochrane risk of bias

GoR

- GRADE

Empfehlungen

	Recommendation	Recommendation strength	Evidence quality	Remarks
Recommendation 1	Do not use amifostine for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong	High quality	Benefits of amifostine were not observed in single studies or when trials were synthesised; direct data were available for paediatric patients, thus increasing the quality of the evidence; toxicities of amifostine were considered in making this recommendation
Recommendation 2	Do not use sodium diethyldithiocarbamate for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong	Low quality	Benefits of diethyldithiocarbamate were not observed in single studies or when trials were synthesised; evidence quality was low because all studies were done in adults and estimates were imprecise; toxicities of sodium diethyldithiocarbamate contributed to the strong recommendation against routine administration
Recommendation 3	Use sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic hepatoblastoma	Strong	High quality	Evidence was rated as high quality for consistency, precision, trial quality, and availability of direct data; in making this recommendation, the panel valued the observation that sodium thiosulfate did not reduce survival in the trial conducted specifically in this patient population (SIOPEL 6); the panel was reassured by the absence of effect on survival for patients with non-metastatic cancers in the trial that included multiple cancer types (ACCL0431)
Recommendation 4	Consider sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic cancers other than hepatoblastoma	Weak	Low quality	The panel was more certain about hearing protection because this effect should not differ based on cancer type; although sodium thiosulfate did not reduce survival in children with non-metastatic cancers in the one trial that included multiple cancer types (ACCL0431), the panel appreciated this estimate was susceptible to bias given the post-hoc classification of non-metastatic disease, sub-group analysis, and potential for confounding; thus, inability to evaluate consistency, imprecision, and trial design all contributed to this evidence being considered low quality

Recommendation 5	We suggest sodium thiosulfate not be used routinely for the prevention of cisplatin-induced ototoxicity for children and adolescents with metastatic cancers	Weak	Low quality	In making a weak recommendation against routine use of sodium thiosulfate for patients with metastatic cancers, the panel considered the reduction in survival associated with sodium thiosulfate observed in children with metastatic cancers in the one trial that included multiple cancer types (ACCL0431); however, the panel appreciated this estimate was susceptible to bias given the post-hoc classification of metastatic disease, subgroup analysis, and potential for confounding; thus, inability to evaluate consistency, imprecision, and trial design all contributed to this evidence being considered low quality; the weak (rather than strong) recommendation was influenced by patient representatives who advocated for the importance of discussing sodium thiosulfate as an option with patients and families; given the low-quality evidence, some families might favour administration when balancing their own personal preferences and values
Recommendation 6	Do not use intratympanic middle ear therapy for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer	Strong	Low quality	Although benefits of intratympanic therapy were observed in small single trials, results were inconsistent, and most effects were not considered clinically important; in general, achieving consistent drug exposure to the cochlea using intratympanic therapy is challenging; direct data were scarce in paediatric patients and concerns were raised regarding feasibility of repeated administration in this population
Recommendation 7	Do not alter cisplatin infusion duration, as a means in itself, to reduce ototoxicity in children and adolescents with cancer	Strong	Low quality	Studies comparing different durations of cisplatin infusion often focused on outcomes other than hearing; only two studies targeted ototoxicity and estimates were imprecise; thus, there was considerable uncertainty about the effect of infusion duration on ototoxicity risk

Table 3: Summary of cisplatin-induced ototoxicity prevention recommendations for children and adolescents with cancer

Recommendation 1: do not use amifostine for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer

Our first recommendation was a strong recommendation based on evidence of high quality (table 3).

Amifostine is a reducing agent that is dephosphorylated to its active thiol metabolite; it binds to cytotoxic cisplatin metabolites and scavenges free radicals. Among the five randomized trials of amifostine,29–33 two were paediatric studies that enrolled patients with hepatoblastoma (aged 0–11 years)32 and osteosarcoma (aged 7–15 years;29 table 1). Amifostine did not significantly reduce ototoxicity in any of these
studies. When the data were pooled, amifostine did not reduce any ototoxicity (RR 0·96 [95% CI 0·71–1·29]) or severe ototoxicity (0·85 [0·34–2·12]). None of these studies identified a negative effect of amifostine on survival.31
In formulating the strong recommendation against routine use of amifostine, the panel considered the absence of benefit combined with amifostine-related toxicities. Toxicities included hypocalcaemia, nausea, and hypotension.31,32 Direct data were available in paediatric patients, increasing the quality of the evidence.

Recommendation 2: do not use sodium diethyldithiocarbamate for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer

Our second recommendation was a strong recommendation based on evidence of low quality (table 3).

Diethyldithiocarbamate is a heavy-metal chelating thiol compound.34 The trials included in the analysis evaluated sodium diethyldithiocarbamate (two studies) or its oxidised
product, disulfiram (one). All these studies included only adult patients (table 1).34–36 None of the trials found that administration reduced ototoxicity, and the one study of disulfiram found that the intervention was associated with more ototoxicity ($p<0·005$).35 Table 2 shows that sodium diethyldithiocarbamate was not associated with less severe
ototoxicity (RR 0·73 [95% CI 0·08–6·44]).
The panel made a strong recommendation against routine use of sodium diethyldithiocarbamate for cisplatin-induced ototoxicity because of the absence of efficacy and because of drug-related toxicities, including hyperglycaemia, hypertension, dehydration, and taste alteration.34 Evidence quality was low because all studies were done in adults and because the efficacy estimate was imprecise.

Recommendation 3: use sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic hepatoblastoma

Our third recommendation was a strong recommendation based on evidence of high quality (table 3).

Sodium thiosulfate is a thiol-containing reducing agent and freeradical scavenger. Two trials, one conducted by the International Childhood Liver Tumor Strategy Group (SIOPEL 6)19 and the other by the Children's Oncology Group (ACCL0431),18 compared the addition of sodium thiosulfate with usual care (table 1). SIOPEL 6 enrolled 109 children with standard-risk hepatoblastoma (aged 1 month to 8·2 years) and administered six cycles of cisplatin. The sodium thiosulfate dose of 20 g/m² was administered 6 h after each cisplatin dose. The number of patients with any hearing loss was 18 (33%) of 55 with sodium thiosulfate versus 29 (63%) of 46 without sodium thiosulfate (p=0·002). Survival outcomes were favourable. The 3-year event-free survival was 82% (95% CI 69–90) with sodium thiosulfate versus 79% (65–88) without sodium thiosulfate. 3-year overall survival was 98% (88–100) with sodium thiosulfate versus 92% (81–97) without sodium thiosulfate.

In contrast to SIOPEL 6, ACCL0431 enrolled 125 children with multiple cancer types, prognostic groupings, and treatments.18 The main cancer types represented in this trial were germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, and osteosarcoma. In a post-hoc analysis, localised versus disseminated disease was classified by site investigators.

In ACCL0431, the study authors used the term disseminated to describe patients with brain tumours with positive cerebrospinal fluid. To improve consistency in language, the term metastatic is used in this guideline instead of disseminated. The recommendations refer to patients with non-metastatic disease rather than localized disease to emphasise that patients with regional disease were categorised as localised in ACCL0431. Six enrolled

children had a diagnosis of non-metastatic hepatoblastoma.

In ACCL0431, the sodium thiosulfate dose of 16 g/m² was administered 6 h after each cisplatin dose. Of the 104 patents with evaluable audiological results, the number with hearing loss was 14 (29%) of 49 with sodium thiosulfate versus 31 (56%) of 55 without sodium thiosulfate (p=0·0002). For all patients in ACCL0431, the 3-year event-free survival was 54% (95% CI 40–66) with sodium thiosulfate versus 64% (50–74) without sodium thiosulfate (p=0·36). The 3-yearoverall survival was 70% (56–80) with sodium thiosulfate versus 87% (76–93) without sodium thiosulfate (p=0·07).

The strong recommendation to administer sodium thiosulfate in patients with non-metastatic hepatoblastoma reflects the value placed on hearing protection and highquality evidence. In making this recommendation, the panel valued the observation that sodium thiosulfate did not reduce survival in the trial conducted specifically in children with non-metastatic hepatoblastoma (SIOPEL 6).

The panel was reassured by the absence of effect on survival for patients with non-metastatic cancers enrolled on ACCL0431 (see recommendation 4). The data are most applicable to patients with non-metastatic hepatoblastoma receiving six cycles of cisplatin (as in SIOPEL 6) and thus, the strong recommendation might not be applicable to patients receiving fewer than six cycles of cisplatin.

Recommendation 4: consider sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with non-metastatic cancers other than hepatoblastoma

Our fourth recommendation was a weak recommendation based on evidence of low quality (table 3).

The panel accepted the post-hoc stratified analysis in ACCL0431 and chose to make recommendations for three patient groups: patients with non-metastatic hepatoblastoma, patients with non-metastatic cancers other than hepatoblastoma, and patients with metastatic cancers. Among the 77 patients with non-metastatic cancers enrolled in ACCL0431, the 3-year event-free survival was 60% (95% CI 42–74) with sodium thiosulfate versus 66% (48–78) without sodium thiosulfate (p=0·73) and the 3-year overall survival was 83% (66–92) with sodium thiosulfate versus 89% (74–96) without sodium thiosulfate (p=0·88).

The panel was more certain about hearing protection because this effect should not differ between cancer types. Although sodium thiosulfate did not reduce survival in children with non-metastatic cancers in ACCL0431, the panel appreciated that this estimate was susceptible to bias given the post-hoc classification of non-metastatic disease, sub-group analysis (which can be associated with spurious results),37 and potential for confounding. Thus, inability to evaluate consistency, imprecision, and trial design all contributed to the evidence being of low quality.

These factors resulted in a weak recommendation for sodium thiosulfate administration in children with nonmetastatic cancers other than hepatoblastoma. More research is needed to confirm the efficacy and safety of sodium thiosulfate in this population of children with cancer.

Of note, the two trials (SIOPEL 6 and ACCL0431) used different doses of sodium thiosulfate—16 g/m² and 20 g/m². Thus, either dose could be used but should be administered 6 h after cisplatin. Future research should consider identifying the optimal sodium thiosulfate dosing for this patient population.

Recommendation 5: we suggest sodium thiosulfate not be used routinely for the prevention of cisplatininduced ototoxicity for children and adolescents with metastatic cancers

Our fifth recommendation was a weak recommendation based on evidence of low quality (table 3).

The ACCL0431 trial included 47 patients with a post-hoc designation of metastatic cancers. Among this group, the 3-year eventfree survival was 42% (95% CI 21–61) with sodium thiosulfate versus 61% (39–77) without sodium thiosulfate (p=0·16). The 3-year overall survival was 45% (23–65) with sodium thiosulfate versus 84% (62–94) without sodium thiosulfate (p=0·009).

In making a weak recommendation against routine use of sodium thiosulfate for patients with metastatic cancers, the panel considered the reduction in survival associated with sodium thiosulfate observed in children with metastatic cancers in ACCL0431. However, the panel appreciated that this estimate was susceptible to bias given the post-hoc classification of metastatic disease, subgroup analysis (which can be associated with spurious results),37 and potential for confounding.

Thus, inability to evaluate consistency, imprecision, and trial design all contributed to the evidence being of lowquality. The weak (rather than strong) recommendation against its routine use in this population was influenced by patient representatives on the panel who advocated for the importance of discussing sodium thiosulfate as an option with patients and families. Given the low-quality evidence, some families might favour administration when balancing their own personal preferences and values, which might be affected by their personal financial resources. The panel also recognised that there will be clinical scenarios in which the benefits of sodium thiosulfate administration probably outweigh the risks, such as in a child with blindness. Further, the panel was concerned that a strong recommendation against the use of sodium thiosulfate might limit the investment required to study this drug further in the future. The panel strongly encourages research of sodium thiosulfate in patients with poor prognosis and metastatic cancers so that a negative effect on survival can either be refuted or confirmed.

Recommendation 6: do not use intratympanic middle ear therapy for the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer

Recommendation 6 was a strong recommendation based on evidence of low quality (table 3).

There is great interest in studying local interventions for cisplatin-induced ototoxicity because this approach might eliminate concerns about interference with systemic chemotherapy activity. The overall goal is to deliver medication directly to the cochlea and limit systemic exposure. All included trials administered the agent intratympanically, relying on diffusion from the middle ear compartment through the cochlear round window into the perilymph to achieve this goal. Six randomised trials investigated intratympanic therapy.38–43 Five studies compared intratympanic therapy with usual care in exclusively adult populations, whereas the sixth study compared two intratympanic therapies in a mixed-age population. All studies randomly assigned each ear of the same individual to a study group.

Two studies evaluated intratympanic acetylcysteine, which is an antioxidant and a free radical scavenger.44 One study of 11 patients did not show a benefit of intratympanic acetylcysteine.39 A second study of 20 evaluable patients found significant worsening in thresholds at 8 kHz in control ears but not in ears treated with acetylcysteine.40 Two studies evaluated dexamethasone,38,41 which might reduce the generation of cisplatin-induced reactive oxygen species and inflammation.45 One of these trials evaluated 20 patients and found significantly worse thresholds in control ears compared with ears treated with dexamethasone at both 6 kHz (p=0·0002) and 8 kHz (p=0·009).41 The second trial,38 with 26 patients, did not show a significant difference between ears by American Speech-Language- Hearing Association ototoxicity criteria. However, significant worsening in thresholds at 6 kHz in the control ears but not in the ears treated with dexamethasone was observed.38 When synthesized, mean differences were not significantly different for either acetylcysteine or dexamethasone versus usual care. Another study randomly assigned 120 ears in 60 patients to either intratympanic acetylcysteine or intratympanic dexamethasone.42 The age range of participants was 6–60 years, but the number of paediatric patients enrolled was not stated. This study suggested that acetylcysteine might be better than dexamethasone because zero ears treated with acetylcysteine had tinnitus, versus 20 ears treated with dexamethasone. The study also showed significant worsening in thresholds compared with baseline at 8 kHz in ears treated with dexamethasone but not in ears treated with acetylcysteine. A different study randomly assigned 13

patients receiving concurrent chemotherapy and radiotherapy to receive three administrations of intratympanic sodium thiosulfate gel into either the left or right ear.43 This study was closed early because of poor accrual without showing significant differences in ototoxicity between groups. Only three participants received all three planned sodium thiosulfate treatments, emphasising feasibility concerns. In all studies of intratympanic therapy, differences in thresholds between groups were not considered clinically significant by the panel, even when statistically significant differences were shown. In making a strong recommendation against intratympanic therapy for cisplatin-induced ototoxicity, the panel noted that although benefits of intratympanic therapy were observed in small single trials, results were inconsistent, and most effects were not considered clinically important. Further, there were few direct data in paediatric patients and many concerns were raised regarding feasibility of repeated administration in this population.

In general, it might be challenging to achieve consistent drug exposure to the cochlea using intratympanic therapy because of multiple factors, including variable clearance through the Eustachian tube and inflammation that could affect the extent of diffusion across the round window.46 introduced as an otoprotectant, then the cisplatin infusion will need to be 6 h or less, as was required in the SIOPEL 6 and ACCL0431 trials. Nonetheless, the panel believes that local therapy is an important area of future research (panel).47,48 More effective approaches to achieve consistent delivery of medication into the cochlea are of particular interest. For example, gel formulation installation into the middle ear might result in more sustained concentrations and more consistent delivery across the round window.49 Alternatively, administration directly into the cochlea is being explored, including microneedle array infusion devices placed at the round window48 and otomagnetic administration of nanocapsules containing the drug.47 Future research will be required to evaluate both the efficacy and safety of these approaches.

Recommendation 7: do not alter cisplatin infusion duration, as a means in itself, to reduce ototoxicity in children and adolescents with cancer

Our seventh recommendation was a strong recommendation based on evidence of low quality (table 3).

Only two studies were identified that compared different durations of cisplatin infusion and specified a planned schedule for ototoxicity monitoring that included audiological evaluation. These studies compared continuous infusion of cisplatin over 24 h versus bolus infusion over 1 h50 20 minutes.51 and versus bolus infusion over Synthesis was only possible for any ototoxicity in which no benefit was observed, although the confidence interval was wide, resulting in downgrading of evidence quality. Further, the panel was concerned that many studies that compared different infusion durations were focused on outcomes other than hearing. Together, these issues reduced the ability to determine if infusion duration is associated with ototoxicity risk. Thus, the duration of cisplatin infusion should not be altered, as a means in itself, to reduce ototoxicity. However, if sodium thiosulfate is to be introduced as an otoprotectant, then the cisplatin infusion will need to be 6 h or less, as was required in the SIOPEL 6 and ACCL0431 trials.

Referenzen

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 02 of 12, February 2025) am 04.02.2025

#	Suchschritt
1	MeSH descriptor: [Ototoxicity] explode all trees
2	MeSH descriptor: [Hearing Loss] explode all trees
3	MeSH descriptor: [Cochlea] explode all trees
4	(ototoxicit* OR cochleotoxicit* OR vestibulotoxicit*):ti,ab,kw
5	((otological* OR cochlear OR vestibular OR vestibulocochlear OR auditory) AND toxic*):ti,ab,kw
6	("hearing loss" OR "hearing impairment" OR deafness OR hypoacus* OR hypacus* OR cochlea OR otoprotect*):ti,ab,kw
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	MeSH descriptor: [Cisplatin] explode all trees
9	(cisplatin* OR diamminedichloroplatin* OR dichlorodiammineplatin* OR CDDP OR platin*):ti,ab,kw
10	MeSH descriptor: [Antineoplastic Agents] explode all trees
11	(chemotherap* OR chemoradiotherap* OR radiochemotherap* OR antineoplastic*):ti,ab,kw
12	#8 OR #9 OR #10 OR #11
13	#7 AND #12
14	MeSH descriptor: [Hearing Loss] explode all trees and with qualifier(s): [chemically induced - CI]
15	MeSH descriptor: [Cisplatin] explode all trees and with qualifier(s): [adverse effects - AE]
16	MeSH descriptor: [Antineoplastic Agents] explode all trees and with qualifier(s): [toxicity - TO]
17	#13 OR #14 OR #15 OR #16
18	#17 with Cochrane Library publication date from Feb 2020 to present, in Cochrane Reviews

Leitlinien und systematische Reviews in PubMed am 04.02.2025

verwendete Suchfilter für Leitlinien:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien

#	Suchschritt
1	ototoxicity[mh] OR hearing loss[mh] OR cochlea[mh]
2	ototoxicit*[tiab] OR cochleotoxicit*[tiab] OR vestibulotoxicit*[tiab]
3	(otological*[tiab] OR cochlear[tiab] OR vestibular[tiab] OR vestibulocochlear[tiab] OR auditory[tiab]) AND toxic*[tiab]
4	hearing loss[tiab] OR hearing impairment[tiab] OR deafness[tiab] OR hypoacus*[tiab] OR hypacus*[tiab] OR cochlea[tiab] OR otoprotect*[tiab]
5	#1 OR #2 OR #3 OR #4
6	cisplatin[mh]
7	cisplatin*[tiab] OR diamminedichloroplatin*[tiab] OR dichlorodiammineplatin*[tiab] OR CDDP[tiab] OR platin*[tiab]
8	antineoplastic agents[mh]
9	chemotherap*[tiab] OR chemoradiotherap*[tiab] OR radiochemotherap*[tiab] OR antineoplastic*[tiab]
10	#6 OR #7 OR #8 OR #9
11	#5 AND #10
12	"Hearing Loss/chemically induced"[mh]
13	"Cisplatin/adverse effects"[mh]
14	"Antineoplastic Agents/toxicity"[mh]
15	#11 OR #12 OR #13 OR #14
16	Drug-Related Side Effects and Adverse Reactions[mh]
17	(side[tiab] OR adverse[tiab]) AND (effect*[tiab] OR event*[tiab] OR reaction*[tiab]) OR toxic*[tiab]
18	(#16 OR #17) AND (#6 OR #7)
19	cancer survivors[mh]
20	cancer[ti] AND surviv*[ti]
21	#15 OR #18 OR #19 OR #20
22	(#21) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
23	(#22) AND ("2020/02/01"[PDAT] : "3000"[PDAT])
24	(#23) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
25	(#15) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR

#	Suchschritt
	(("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
26	(#25) AND ("2020/02/01"[PDAT] : "3000"[PDAT])
27	(#26) NOT "The Cochrane database of systematic reviews"[Journal]
28	(#27) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
29	#28 NOT #24

Iterative Handsuche nach grauer Literatur, abgeschlossen am 05.02.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO