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Treatment with cisplatin concomitantly with radiotherapy for head and neck squamous cell carcinoma

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Background

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Clinical Registries (RKKP). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high quality cancer care across the Danish healthcare system. The guideline content is approved by the disease-specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer

The target users of this guideline are health care professionals working in the Danish healthcare system. The guideline consists of systematically prepared statements that can be used as a decision-making support tool by healthcare professionals and patients, when deciding on appropriate and correct care in a specific clinical situation.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome and sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The clinical practice guideline contains central recommendations (chapter 1) and a description of the scientific evidence (chapters 3+4). Recommendations marked A are the strongest, whereas recommendations marked D are the weakest. For further information on strength of evidence see the ”Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations”, https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. Please see the table of contents for page reference.
Information on the national integrated cancer pathways – descriptions of the patient journey through the healthcare system – can be accessed at the Danish Health Authority website: https://www.sst.dk/

Development of this clinical practice guideline has been funded by The Danish Health Authority (National Cancer Plan IV) and the Danish Clinical Registries (RKKP).

1. Anbefalinger - DA (Quick Guide)

Indikation

- **Indikationen for konkomitant kemoradioterapi med cisplatin er udstukket af den Danske Hoved-Hals Cancer Gruppe, DAHANCA, og beskrevet i de kliniske retningslinjer publiceret på www.dahanca.oncology.dk.**
- **Indikationerne omfatter nasopharynxcancer, lokal-avanceret planocellulært karcinom i mundhule, oropharynx, hypopharynx og larynx samt ved primærbehandling af patienter med ukendt primærtumor og halsmetastaser (A).**
- **Tilsvarende, men med lavere evidensstyrke (B) gives cisplatin ved planocellulær sinonasal cancer med stor tumorbyrde og ved postoperativ strålebehandling ved tumorer med høj risiko for tilbagefald (ikke radikal operation) eller gennemvækst af lymfeknude) (B).**

Behandling

1. **Konkomitant cisplatin 40 mg/m2 bør gives 5 eller 6 gange med en uges mellemrum under strålebehandling på de af DAHANCA givne indikationer (www.dahanca.oncology.dk) (B)**
2. **Første behandling bør gives på første strålebehandlingsdag, men kan gives indenfor den første uge. Behandling kan gives ambulant, 3-4 timer før strålebehandling (C).**

Understøttende behandling

3. **Hydrering med intravenøs isotonisk saltvand skal gives før og efter cisplatininfusion (se skema A, appendix) (A).**
4. **Intravenøs mannitol kan gives før cisplatininfusion mhp. beskyttelse af nyrerne (se skema A, appendix) (B).**
5. **Magnesium skal gives i forbindelse med cisplatininfusion (se skema A, appendix) (A).**
6. **Forebyggende kvalmebehandling bør gives i hht. lokale retningslinjer, gerne i overensstemmelse med MASCC anbefalingerne (A).**

Screening før behandling

7. **Audiometri bør foretages før første cisplatinbehandling og bør gentages ved tinnitus eller høretab (B).**

8. **Nyrefunktionen skal undersøges før første cisplatinbehandling, enten ved at måle glomerulær filtrationshastighed (GFR) med 51Cr-EDTA eller tilsvarende tracer (f.eks. Technetium-99m DTPA) eller ved at beregne estimeret GFR (eGFR) ud fra kreatinin (A).**

9. **Før hver cisplatinbehandling skal blodprøver undersøges for knoglemarvssuppression, elektrolytforstyrrelser (Na+, K+, Mg++) og nyrefunktion (A).**

Kontraindikationer

10. **Cisplatin bør ikke gives til følgende patienter:**

    - **Patienter med nedsat nyrefunktion (GFR < 50 ml/min) eller nyresygdom (A).**
    - **Knoglemarvsinsufficiens (B).**
    - **Kvinder gravide i første trimester (B).**
    - **Patienter, der af lægen vurderes uegnede, f.eks. grundet almentilstand (B).**

11. **Cisplatin skal overvejes nøje hos:**

    - **Patienter med moderat til svær hørenedsættelse (B).**
    - **Patienter med moderat til svær neuropati (B).**

Recommendations - ENG (Quick Guide)

Indications

- **Indications for cisplatin concomitantly with raditherapy are defined by the Danish Head and Neck Cancer Group, DAHANCA, and described in clinical guidelines published at www.dahanca.oncology.dk.**
- **Indications include nasopharyngeal cancer, locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx, as well as for primary treatment of carcinoma of unkown origin with neck node metastases (A).**
- **Likewise, but with a lower level of evidence (B), cisplatin is indicated in squamous cell sinonasal cancer with extensive tumor burden and in postoperative settings with high risk of recurrent disease (incomplete tumor resection) or with extranodal extension.**

Treatment

1. **Concomitant cisplatin 40 mg/m2 should be given weekly for 5 or 6 cycles during radiation treatment as described by DAHANCA (www.dahanca.oncology.dk) (B).**
2. **The first cycle should be given on the first day of radiotherapy, but may be given within the first week of treatment. Cisplatin may be given as outpatient treatment when possible, and 3-4 hours prior to radiotherapy (C).**

Supportive treatment

3. **Intravenous isotonic saline must be administered before and after cisplatin treatment (see Chart A, appendix) (A).**
4. **Intravenous mannitol may be administered prior to cisplatin infusion adding to the renal protective effect (see Chart A, appendix) (B).**
5. **Magnesium must be administered during cisplatin treatment to reduce the risk of hypomagnesemia (see Chart A, appendix) (A).**
6. **Prophylactic anti-emetics should be given according to local guidelines, preferably in accordance with MASCC recommendations (A).**

Screening prior to treatment

7. **Audiometry should be performed prior to the first cisplatin treatment and should be repeated if the patient experiences either tinnitus or hearing loss (B).**

8. **Renal function must be assessed prior to the first cisplatin treatment, either by measuring glomerular filtration rate (GFR) using 51Cr-EDTA or equivalent radioactive tracers (such as Technetium-99m DTPA) or by using the estimated GFR from blood samples (A).**

9. **Before each cisplatin treatment, blood samples must be drawn and assessed for bone marrow suppression, electrolyte imbalance (i.e. Na+, K+, Mg++), and renal function (A).**

Contraindications

10. **Cisplatin should not be administered to the following patients:**

    - **Patients with reduced renal function (e.g. measured by an estimated by eGFR < 50 ml/min) or pre-existing renal disease (A).**
    - **Insufficient bone marrow function (B).**
    - **Women pregnant in the first trimester (B)**
    - **Patients deemed unfit by the physician, e.g. poor performance status (B).**

11. **Cisplatin should be considered carefully in:**

    - **Patients with moderate to severe hearing impairment (B).**
    - **Patients with moderate to severe neuropathy (B).**

2. Introduction

Head and neck cancer is the seventh most common cancer worldwide with more than 800.000 new cases each year and more than 400.000 deaths (1). In Denmark, approximately 1,300 patients are diagnosed with head and neck cancer each year (Danish Head and Neck Cancer Group, DAHANCA 2018 annual report). Head and neck cancer comprises a diverse group of tumors which primarily arise in the epithelial lining of the nasal and oral cavities, pharynx, and larynx. The majority (>90%) is head and neck squamous cell carcinomas (HNSCC). Primary treatment is either surgery and/or radiotherapy, and in case of large tumor burden or nodal disease, concomitant chemotherapy may be added.
Following treatment, patients often suffer from short and long-term side effects which may cause severe morbidity and reduce quality of life (2, 3). Hence, ensuring the right treatment for the right patient is essential.

Objective

The overall objective of this guideline is to support high quality cancer care across the Danish healthcare system.
The specific objective is to ensure patients with locoregionally advanced head and neck squamous cell carcinoma the optimal treatment appropriate for each individual.

Target population

This guideline is intended to provide information about concomitant cisplatin treatment for patients with locoregionally advanced head and neck squamous cell carcinoma who are candidates for radiation treatment with curative intent, thus, this guideline is not intended for patients with distant metastatic disease.

Target User

This guideline is developed to support clinical decision-making and quality improvement. Thus, the target users are healthcare professionals working in Danish cancer care, primarily physicians and nurses working with head and neck cancer.

3. Scientific evidence

Indications

- **Indications for cisplatin concomitantly with radiotherapy are defined by the Danish Head and Neck Cancer Group, DAHANCA, and described in clinical guidelines published at www.dahanca.oncology.dk.**
- **Indications include nasopharyngeal cancer, locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx, as well as for primary treatment of carcinoma of unkown origin with neck node metastases (A).**
- **Likewise, but with a lower level of evidence (B), cisplatin is indicated in squamous cell sinonasal cancer with extensive tumor burden and in postoperative settings with high risk of recurrent disease (incomplete tumor resection) or with extranodal extension.**

Literature review and evidence description

HNSCC of the oral cavity, oropharynx, hypopharynx, and larynx

Multiple randomized trials have established the benefits of a multimodality approach adding chemotherapy to definitive radiotherapy in the treatment of locoregionally advanced head and neck squamous cell carcinoma (HNSCC).

The updated Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) was published in 2009. This analysis included 16,485 patients (in 87 trials) with squamous cell carcinoma of the head and neck (HNSCC) in the oral cavity, oropharynx, hypopharynx, and larynx and compared definitive locoregional therapy alone (surgery and/or RT) to definitive locoregional therapy in combination with chemotherapy (induction, concurrent, or adjuvant). The vast majority of patients were stage III-IV, thus with locoregionally advanced disease either due to large primary tumor (3/4) or nodal disease (N1+). It should be noted that these trials were conducted prior to the HPV era and thus, data do not differentiate between patients with HPV-positive versus negative tumors (or p16 positive versus negative). However, a subsequent study showed inferior results from radiation with cetuximab compared to radiation and cisplatin (4) [1b]. In the meta-analysis, fifty trials compared radiotherapy to concomitant chemoradiotherapy confirming an absolute survival benefit of 6.5% at 5 years (27.2% to 33.7%) (hazard ratio [HR] 0.81, 95% CI 0.78-0.86) (5) [1a].
The benefit of concomitant chemotherapy was due to its effect on deaths related to head and neck cancer (HR 0.78 [0.73–0.84], p<0.0001) with an absolute difference of 8.6% at 5 years (from 38% to 46.6%) and with no effect on non-cancer deaths (5) [1a].

The meta-analysis showed no significant benefit for induction chemotherapy versus radiotherapy alone [1a], but secondary analyses suggested that concurrent chemoradiotherapy was more effective at preventing locoregional failure, while induction chemotherapy provided a relatively more pronounced effect on distant metastases (5) [2a/b].

No statistically significant differences were observed with different radiotherapy schedules (conventional or altered fractionation). The effect of different combinations of chemotherapy, cisplatin alone, platin + 5-FU, or other combinations did not differ significantly, but monotherapy with any other drug than cisplatin led to inferior benefits and cannot be recommended as standard practice (5) [1a].

As with most clinical trials, patients included were primarily younger patients (below the age of 70) and in Eastern Cooperative Oncology Group (ECOG) performance status 0-1. The analysis of overall survival showed a significant decrease in effect of concomitant chemotherapy with increasing patient age, and no benefit was observed in those over the age of 70. The reason for this is unknown, but several factors may be considered, including older patients are more likely to die from other causes, thereby diluting any observed difference in overall survival from combined treatment, but also the relatively low number of older patients in the studies weakens the statistical power (5).The MACH-NC update could not discern any significant variation of chemotherapy effect according to patient characteristics for event-free survival.

Recently, a retrospective study has shown that neither overall survival, progression-free survival, local control rate, nor distant metastasis-free survival differed between the age-groups, the oldest age-group being ≥75 years. Furthermore, the rate of acute toxicities was not higher for older patients, but is was shown that performance status 2-3 was associated with impaired overall survival rates (6). Therefore, the recommendation is that even in advanced age, treatment decisions should be made according to the general health condition and comorbidity, rather than calendar age alone [2a].
The magnitude of benefit according to tumor site was not evaluated in the MACH-NC analysis, but a subsequent MACH-NC analysis showed that overall survival benefit of chemotherapy was consistent across all tumor locations (oral cavity, oropharynx, hypopharynx, and larynx) (7) [1a]. The 5-year absolute benefit was 8.9%, 8.1%, 5,4%, and 4% for tumors in the oral cavity, oropharynx, larynx, and hypopharynx, respectively. It is noteworthy that the benefit was higher for concomitant chemotherapy for all tumor sites, but not significant in oral cavity and larynx cancer which may be a result of lack of power (7).

Nasopharyngeal cancer (NPC)
Concomitant chemoradiotherapy for all stages of nasopharyngeal cancer (NPC) has been a standard treatment in Denmark since 2003 (as described in the DAHANCA-14 protocol, https://www.dahanca-oncology.dk). The Scandinavian Society for Head and Neck Oncology (www.sshno.org) aims to unify treatment protocols throughout the Nordic countries (Denmark, Sweden, Norway, Finland, and Iceland). A recent review of management and survival outcomes of NPC in these countries shows that the treatment varies between the academic centres in the region regarding radiotherapy technique, chemotherapy regimen, and the use of hypoxic modifiers (8).

An update by the Meta-Analysis of Chemotherapy in Nasopharynx (MAC-NPC) group has confirmed that adding concomitant chemotherapy to radiotherapy improves overall survival in stage II-IV NPC patients by 6% at 5 years. Also, progression-free survival, locoregional control, distant control, as well as cancer-related mortality improved (9) [1a]. Older patients were underrepresented in this meta-analysis; therefore, a recent review has been performed to evaluate the effect of chemoradiotherapy in older adults (majority above 70 years of age) with NPC. They found that chemoradiotherapy was independently associated with improved overall survival in NPC patients ≥ 70 years old (10) [2b].

Carcinoma of Unknown Primary of the Head and Neck (CUP)
No randomized studies have investigated the effect of concomitant chemoradiotherapy for CUP, and treatment differs between centers (11). However, solid evidence exists regarding the beneficial effects of chemotherapy concomitant with radiotherapy as primary treatment for head and neck squamous cell carcinomas with known primary tumor (5, 7) (see section "Head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx" above). Furthermore, chemotherapy concomitant with postoperative radiotherapy has shown survival benefits for patients with high risk of recurrence, i.e. in case of positive margins (R1 resection) or ENE (12-14); thus, an equivalent positive effect in CUP is plausible.

Postoperative concomitant chemoradiotherapy
The first meta-analysis evaluating the use of postoperative concomitant chemoradiotherapy versus radiotherapy for stage III/IV (7th TNM) HNSCC showed improved overall survival and progression-free survival in favor of concomitant chemoradiotherapy, but also more frequent and severe mucosal toxicity (14, 15) [1a]. Comparative analyses revealed that the effect was primarily seen in patients with extra nodal extension (ENE) and/or microscopically involved surgical margins (16) (C/4). Data has been confirmed in an updated meta-analysis (17) [1a]. A 10-year follow up study (of the two largest RCTs in the field showed no significant differences in outcome. However, subgroup analysis of patients who had either microscopically involved resection margins (R1) and/or extracapsular spread of disease (i.e. ENE) showed improved locoregional control and disease-free survival with concurrent administration of chemotherapy. However, as the trial was not designed to address this specific question this observation must be viewed as exploratory and hypothesis-generating rather than as proof of evidence (12, 18) [2b].

Patient values and preferences

No literature on patient values and preferences were found. The effect of adding cisplatin to radiation treatment in head and neck cancer must be weighed against likely side effects. Thus, shared decision making is essential in these situations.

Rationale

Curative treatment for head and neck squamous cell carcinoma includes surgery and/or radiotherapy, but for locally advanced tumors, a multimodality approach may be required. Pursuing improved survival outcomes, different regimes of chemotherapy have been added to definitive radiation treatment over time. Due to considerable heterogeneity of clinical studies, definitive results have been difficult to draw. This relates to factors such as in timing (induction, concomitant, or adjuvant; type of drug(s)), type of systemic treatment (chemotherapy or epidermal growth factor receptor (EGFR) inhibitors); monochemotherapy or different

combinations, as well as differences in dose schedules (low/high, weekly/triweekly); However, due to well-conducted international meta-analyses and national clinical trials by the DAHANCA group, the present guidelines may claim significant validity.

Based on the results of the DAHANCA 5, 6, 7, and 9 trials, different radiotherapy regimes (i.e. conventional, accelerated normofractionated, or hyperfractionated) are recommended for different patients depending on tumor site, extent of disease, but also depending on performance status and general health of the patient (see www.dahanca.oncology.dk for guidelines per tumor site) (2, 19-22).

Based on the trials and literature review, concomitant chemoradiotherapy should be used for fit patients receiving either accelerated normofractionated radiotherapy (i.e. 66-68 Gy, 2 Gy per fraction, 6 fractions per week for 5½ weeks) or postoperative conventional normofractionated radiotherapy (i.e. 60-66 Gy, 2 Gy per fraction, 5 fractions per week for 6-6½ weeks) [1a].

However, concomitant chemotherapy could also be added to accelerated hyperfractionated radiotherapy (i.e. 76 Gy, 56 fractions, 10 fractions per week for 5½ week). The hyperfractionated radiotherapy regime is known to be an effective treatment yielding superior control and survival rates compared to other regimes (19, 23, 24). In the DAHANCA 28a trial, concomitant weekly cisplatin and nimorazole were added to this regime and found to be feasible with an acceptable toxicity profile and encouraging tumor control rates, especially in patients with stage III/IV p16-negative HNSCC (25) [2b].

Comments and considerations

Patient data, treatment, and adverse events are registered in the DAHANCA database. Within the DAHANCA collaboration, trials are continuously being conducted to ensure high quality and safety of HNSCC treatment in Denmark.

Treatment

1. **Concomitant cisplatin 40 mg/m2 should be given weekly for 5 or 6 cycles as described by DAHANCA (www.dahanca.oncology.dk) (B).**

2. **The first cycle should be given on the first day of radiotherapy, but may be given within the first week of treatment. Cisplatin may be given as outpatient treatment when possible, and 3-4 hours prior to radiotherapy (C).**

Literature review and evidence description

Regime

The use of concomitant chemoradiotherapy is reasoned by both direct cytotoxic effect as well as a radiosensitizing effect through different mechanisms (26, 27).

Chemoradiation is superior to radiotherapy alone for both definitive and adjuvant treatment for patients with risk factors (R1 resection or ENE), however, the optimal regime is still debated, and various combinations are being used (28). The effect of different combinations of chemotherapy, cisplatin alone, platin + 5-FU, or other combinations have shown not to differ significantly, but monotherapy with any other drug than cisplatin yields inferior results and cannot be recommended as standard practice (5).

It is often argued that tri-weekly cisplatin 100 mg/m^2 should be the treatment of choice (29-32), though most studies do not show weekly cisplatin 40 mg/m^2 to be inferior, whilst weekly cisplatin doses <40 mg/m^2 are (29-35).

Studies exploring concomitant chemoradiotherapy are mainly combined with conventional radiotherapy (i.e. 2 Gy per fraction, 5 fractions per week), but within the DAHANCA group, accelerated radiotherapy (median treatment time 39 days) has been the standard treatment for years (21) and three cycles of cisplatin given tri-weekly (day 1, 22, and 43) is obviously not amenable with the accelerated regime. Within the DAHANCA collaboration, concomitant weekly cisplatin 40 mg/m^2 is the standard concomitant regime. The DAHANCA 18 trial was conducted to investigate weekly cisplatin, 40 mg/m^2 administered concomitantly to accelerated radiotherapy together with the hypoxic modifier nimorazole (36). The study found the regime to be tolerable with acceptable toxicity and superior survival rates compared with historical data (5, 7, 36-38). The regime is also used internationally, and a retrospective study from the Netherlands found it to be well tolerated and with high treatment compliance (15, 39) [4].

Independent of regime, it has been shown that the cumulative dose of cisplatin is associated with survival benefit, and cumulative dose ≥200 mg/m^2 is recommended (28) [1a].

- Weekly cisplatin 40 mg/m^2 for 5 to 6 weeks, concomitant with any relevant radiotherapy regime should be administered to eligible patients (see patient selection) [2b].
- The first treatment should be given on the first day of radiotherapy, but may be given within the first week. Treatment may be given as outpatient treatment when possible, and 3-4 hours prior to radiotherapy [3].

Treatment of choice for cisplatin in unfit patients (see contraindications) is debatable. Several other chemotherapeutics (e.g. carboplatin, 5-fluorouracil, and paclitaxel) and biological drugs (e.g. cetuximab) have been investigated, showing inferior treatment outcomes when administered as monotherapy with radiation, but sometimes with a more favorable toxicity profile compared to cisplatin (15, 40, 41). However, randomized trials are sparse, and furthermore, the radiotherapy regime in most studies is conventional, thus, the effect of concomitant non-cisplatin drug with conventional radiotherapy versus accelerated radiotherapy is unclear. Recently, a randomized trial comparing accelerated radiotherapy with either daily cetuximab or tri-weekly cisplatin 100 mg/m^2 was published (4). They found that for HPV-positive oropharyngeal cancer patients, radiotherapy plus cetuximab demonstrated inferior overall survival rates and progression-free survival compared to radiotherapy plus cisplatin; toxicity rates were similar (4). A randomized trial comparing conventional radiotherapy with either daily cetuximab or tri-weekly cisplatin 100 mg/m^2 for patients with HPV-positive disease found similar results, inferior tumor control in the cetuximab group and no benefit regarding toxicity (42).

The effect of carboplatin has been evaluated in a meta-analysis comparing the use of cisplatin versus carboplatin concomitant to radiotherapy (43). Five-year overall survival superiority in favor of cisplatin was found, but no significant difference in 3-year locoregional control. Cisplatin caused significant increased nausea and vomiting, nephrotoxicity and hematological toxicity, whilst carboplatin yielded increased hematological toxicity. The results were based on merely three randomized trials, the rest being retrospective or matched-pair studies (43).

Paclitaxel has been investigated in the concomitant setting as well, though, only a few limited studies used paclitaxel as monotherapy (44-46). One study compared weekly cisplatin 30 mg/m2 with paclitaxel 30 mg/m2 and found comparable survival rates and toxicities. The cisplatin dose was, however, inferior to current standard (45).

- Deciding whether a cisplatin-unfit patient should be recommended another concomitant drug must be carefully considered for each individual, based on the reason for cisplatin-unfitness, comorbidity, performance status, age, and patient preference.
- In Denmark, preferred alternative treatment options include: Hyperfractionated radiotherapy alone, concomitant weekly carboplatin, concomitant weekly paclitaxel, or concomitant weekly cetuximab.

Patient values and preferences

No literature on patient values and preferences were found. The effect of adding chemotherapy to radiation treatment in head and neck cancer must be weighed against likely side effects. Thus, shared decision making is essential in these situations.

Rationale

Within the DAHANCA collaboration, concomitant weekly cisplatin 40 mg/m^2 has been the standard concomitant regime for many years for both nasopharyngeal cancer and non-nasopharyngeal cancer of the head and neck. No new data has emerged to justify any changes. The regime is well-known in the clinical setting, well-incorporated, manageable, and reasonably safe if patients are selected rationally. Furthermore, treatment side effects are well-known and often well-managed due to years of clinical experience and collaboration within the group.

The DAHANCA 18 and 28a trials specifically explored the use of weekly cisplatin 40 mg/m^2 for 5-6 weeks concomitantly with accelerated, respectively hyperfractionated radiotherapy, and both confirmed that the regimes are tolerable with acceptable toxicity profiles and high survival rates compared to historical data (5, 7, 25, 36-38).

Comments and considerations

Patient data, treatment, and adverse events are registered in the DAHANCA database. Within the DAHANCA collaboration, trials are continuously being conducted to ensure high quality and safety of HNSCC treatment in Denmark.

Supportive treatment

3. **Intravenous isotonic saline must be administered before and after cisplatin treatment (see Chart A, appendix) (A).**

4. **Intravenous mannitol may be administered prior to cisplatin infusion adding to the nephroprotective effect (see Chart A, appendix) (B).**

5. **Magnesium must be administered during cisplatin treatment to reduce the risk of hypomagnesemia (see Chart A, appendix A) (A).**

6. **Prophylactic anti-emetics should be given according to local guidelines, preferably in accordance with MASCC recommendations (A).**

Literature review and evidence description

Multiple trials have established the safety and benefits of a multimodality approach adding chemotherapy to definitive radiotherapy in the treatment of locoregionally advanced head and neck cancer squamous cell carcinoma (HNSCC). Therefore, concomitant chemotherapy should be recommended to the above mentioned patient groups. However, concomitant chemoradiotherapy is more toxic than radiotherapy alone, hence, it should only be recommended for fit patients.

Frequent side effects from combined treatment are pain, mucositis, dysphagia, and requirement for a feeding tube. Less frequent, but more severe side effects are febrile neutropenia, nephrotoxicity, ototoxicity, and neuropathy and should be managed accordingly (see below) (2, 39, 47).

Hydration and nephrotoxicity

Cisplatin is a highly effective cytotoxic agent, but its use can be limited due to its toxicities, which include nephrotoxicity, ototoxicity, neurotoxicity, nausea and vomiting (48). Nephrotoxicity is a dose-limiting factor and one of the main reasons for not receiving cisplatin or discontinuing treatment; this is especially evident in high-dose cisplatin treatment, but also, though significantly less frequent, when used in lower dose in a weekly setting (33, 35, 39, 49, 50). Cisplatin can also induce electrolyte wasting, which must be supplemented (51).

Renal toxicity from cisplatin is induced from the uptake and activation of platinum within the proximal tubule cells, hence, any measure that reduces cisplatin uptake, or activation by the kidney relative to tumor cells, should reduce risk of nephrotoxicity (52). It is therefore logical that a lower dose given weekly will lower the risk as opposed to high-dose bolus infusions. Underlying kidney disease predispose to acute kidney injury during cisplatin treatment, however, data is limited as patients with underlying kidney disease are usually excluded from clinical studies (52).

Renal function must be assessed prior to the first treatment and before subsequent treatments to determine if cisplatin should be administered or discontinued. Glomerular filtration rate (GFR) is used to measure kidney

function. GFR can be determined by different methods, ^{51}Cr-EDTA clearance often depicted as the reference method. An estimated GFR (eGFR) can be determined using different algorithms, but may not depict GFR as accurately as ^{51}Cr-EDTA clearance, as described recently (53).

At which level of renal impairment cisplatin should be deferred, is unknown. The threshold in most clinical trials is eGFR <50mL/min, which seems reasonable and has been the recommendation in DAHANCA for years.

The primary approach to prevent or at least reduce the risk of nephrotoxicity is the administration of lower doses of cisplatin accompanied by the administration of intravenous isotonic saline prior to and after cisplatin infusion (54). There is no gold standard hydration regime, however, a systematic review of hydration strategies found that 2-4 L administered over two to six hours was effectively nephroprotective (51). Furthermore, adding mannitol to force diuresis, as well as magnesium supplementation, added to the effect (51).

A recent meta-analysis analyzing the efficacy of clinically tested protectives of cisplatin-induced nephrotoxicity found that only magnesium holds nephroprotective effects (55). However, the authors conclude that more studies need to be conducted to confirm these results.

In Denmark, a retrospective study has been performed that indicates a nephroprotective effect of mannitol when 500 mL of mannitol 15% was administered intravenously during cisplatin treatment. There was a significantly smaller decrease in renal function (3.3% in the mannitol group vs 9.7% in the non-mannitol group) measured by ^{51}Cr-EDTA clearance, but none of the patients in the non-mannitol group experienced a decrease of ^{51}Cr-EDTA clearance below the predefined limit of 50 mL/min (56) .

Based on these trials, the recommendations are:

- Intravenous isotonic saline 0.9% must be administered before and after cisplatin treatment [1b].
- Intravenous mannitol may be administered prior to cisplatin infusion adding to the nephroprotective effect [2a].
- Magnesium must be administered during cisplatin treatment to reduce the risk of renal injury and to reduce the risk of hypomagnesemia [1a].

Anti-emetics

Cisplatin is categorized as a highly emetogenic chemotherapeutic drug, that is, the risk of vomiting within the first 24 hours is >90% if the patient does not receive prophylactic anti-emetics (57). Though tri-weekly high-dose cisplatin cause significant more nausea and vomiting than weekly cisplatin, even low-dose cisplatin is highly emetogenic, and prophylactic anti-emetics should be administered (30) [1a].
Prophylactic anti-emetics must be given according to local guidelines, preferably in accordance with MASCC recommendations [1a].

Patient values and preferences

No literature on patient values and preferences were found.

Rationale

The literature review supports the previous DAHANCA guideline regarding cisplatin. Intravenous isotonic saline and magnesium are mandatory, whilst mannitol is not. Historically, mannitol was administered at all DAHANCA centres, but within recent years, some DAHANCA centres stopped using mannitol while some continued, reflecting the somewhat inconsistent data.

At the DAHANCA centres, antiemetics are administered according to local guidelines. Often a combination of a corticosteroid (e.g. prednisolone or dexamethasone), a neurokinin $(NK)_1$-receptor antagonist (e.g. aprepitant) and/or a serotonin $(5\text{-}HT)_3$-receptor antagonist (e.g. palonosetrone) is being used, as recommended by Multinational Association of Supportive Care in Cancer (MASCC) (57).

A treatment chart (Chart A) is depicted in Appendix A.

Comments and considerations

Patient data, treatment, and adverse events are registered in the DAHANCA database. Within the DAHANCA collaboration trials are continuously being conducted to ensure high quality and safety of HNSCC treatment in Denmark.

Screening prior to treatment

7. **Audiometry should be performed prior to the first cisplatin treatment and should be repeated if the patient experiences either tinnitus or hearing loss (B).**

8. **Renal function must be assessed prior to the first cisplatin treatment, either by measuring glomerular filtration rate (GFR) using 51Cr-EDTA or equivalent radioactive tracers (such as Technetium-99m DTPA) or by using the estimated GFR from blood samples (A).**

9. **Before each cisplatin treatment, blood samples must be drawn and assessed for bone marrow suppression, electrolyte imbalance (i.e. Na+, K+, Mg++), and renal function (A).**

Literature review and evidence description

Hearing loss (ototoxicity) is a frequent adverse event during and after cisplatin treatment (58, 59). The outer hair cells within the spiral organ may be damaged, in that the destructive pattern of outer hair cell loss progresses starting at the cochlear base (high frequencies) and progressing upward to the cochlear apex (low frequencies) with each cisplatin infusion (60). Hearing loss is irreversible, and as primarily high frequency loss occurs, it may be problematic for the patient since regular speech is in high frequencies, thus, the patient may lose communication ability without hearing aids (61, 62).

The risk of hearing impairment following cisplatin varies in studies, but may be as high as 66% (61, 63). It is a severe side effect as it may negatively affect quality of life and ability to work, thus, efforts to predict and/or avoid hearing loss are of great importance. Hence, the issue should be addressed prior to initiation of treatment as part of the informed patient decision making. The ability to predict treatment-induced hearing impairment is very important and a prediction model has been reported in a recent study. (64). Consistent with previous studies, it was found that factors predictive of the degree of hearing impairment were high-dose cisplatin, higher radiotherapy dose or tumor site close to the cochlea, older patients, and patients with better hearing at baseline (63, 65, 66).

The use of concomitant chemoradiotherapy can worsen the effects on hearing function. Studies have shown that when using radiotherapy alone, no significant hearing loss is found using doses ≤40 Gy, whilst using concomitant cisplatin 100 and 40 mg/m^2, respectively, yielded significant hearing loss of 21.5 dB and 9.5 dB at 8.000 Hz with low radiation doses (10 Gy). This increased to 38.4 dB and 18.9 dB for high radiation doses (40 Gy) (63).

To reduce the risk of hearing impairment following radiotherapy, dose to the inner ear should be restrained. This may follow recommendations according to the QUANTEC (**qu**antitative **a**nalysis of **n**ormal **t**issue **e**ffects in the **c**linic) review that summarizes the currently available three-dimensional dose-volume outcome data and presents updated normal tissue dose-volume tolerance guidelines (67).

Thus, ototoxicity risk assessment needs to include tumor site as risk increases with sites closer to the inner ear. The DAHANCA standard regime of 40 mg/m^2 is less ototoxic than 100 mg/m^2 (62, 63).

Prior to initiation of cisplatin treatment, hearing must be assessed using audiometry. Normal hearing ranges from 0 to 20 dB in all frequencies; 0 dB being the reference value, where hearing starts. There are no data to support any specific hearing loss threshold where cisplatin in contraindicated. This assessment is individually based and should be discussed with the patient, considering tumor burden, site, prognosis etc.
Audiometry should be performed prior to the first cisplatin treatment and should be repeated if the patient experiences either tinnitus or hearing loss [2b].

The effect of cisplatin on renal function is described above in “Hydration and nephrotoxicity”.
Renal function must be assessed prior to the first cisplatin treatment either by measuring glomerular filtration rate (GFR) using 51Cr-EDTA clearance or an equivalent radioactive tracer (such as Technetium-99m DTPA) or by using the estimated GFR from blood samples (B).

Cytotoxic agents, e.g. cisplatin, are hematotoxic and thus may negatively affect bone marrow function. This may cause anemia, thrombocytopenia, leukopenia, and neutropenia. If immune function deteriorates, the patient may experience febrile neutropenia. If any of these occur, and bone marrow do not recover before the next cycle, the patient may experience symptoms like bleeding, tiredness, tachycardia, dyspnea, and infections. To avoid severe bone marrow suppression, blood samples are obtained weekly.
Before each cisplatin treatment, blood samples must be taken and evaluated for bone marrow suppression, electrolyte imbalance (i.e. Na+, K+, Mg++), renal function (A).

Patient values and preferences

No literature on patient values and preferences were found.

Rationale

Hearing loss is a severe side effect to cisplatin treatment as it may negatively affect quality of life, ability to communicate, and work, thus, efforts to predict and/or avoid hearing loss are of great importance. Hence, the issue should be addressed prior to initiation of treatment as part of the informed patient-decision making.

Comments and considerations

Patient data, treatment, and adverse events are registered in the DAHANCA database. Within the DAHANCA collaboration trials are continuously being conducted to ensure high quality and safety of HNSCC treatment in Denmark.

Contraindications

10. Cisplatin should not be administered to the following patients:

- **Patients with reduced renal function (e.g. measured by an estimated by eGFR below 50 ml/min) or pre-existing renal disease (A).**
- **Insufficient bone marrow function (A).**
- **Women pregnant in the first trimester and women breastfeeding (B)**
- **Patients deemed unfit by the physician, e.g. due to poor performance (B).**

11. Cisplatin should be considered carefully in:

- **Patients with moderate to severe hearing impairment (B).**
- **Patients with moderate to severe neuropathy (B).**

Literature review and evidence description

Reduced renal function and hearing impairment

For literature review regarding renal function and hearing impairment, please see section “Screening prior to treatment”.

Neuropathy

It has been established that a cumulative cisplatin dose of 250–500 mg/m^2 is required to observe mild to severe peripheral neurotoxicity in adult patients, but that preexisting neuropathy may predispose (68). Thus, weekly cisplatin 40 mg/m^2 for five to six weeks will rarely be problematic unless patients have pre-existing neuropathy.

Insufficient bone marrow function

For literature review regarding bone marrow function, please see section “Screening prior to treatment”.

Fertility, pregnancy and breastfeeding

Cisplatin treatment may cause impaired fertility in men (69-71). Most of the literature includes patients with testicular cancer, and to date, no trials have been investigating fertility following head and neck cancer treatment. Due to the rise in HPV-related head and neck cancers, mainly in younger patients, questions about fertility are likely to arise.

It is difficult to extrapolate results from patients with testicular cancer due to differences in age, treatment intensity etc., however, the risk seems to be dose-related, and thus, expected to be lower in patients treated with weekly cisplatin concomitantly with radiotherapy. There may be an increased risk of miscarriages, but most authors have not found any increased risk of major anomalies (e.g. congenital or genetic abnormalities, or perinatal death) in children of male cancer survivors treated with chemotherapy or radiotherapy (70).
No firm recommendation regarding fatherhood following concomitant cisplatin treatment can be given, but presumably, it is safe [3a].

Literature regarding head and neck cancer during pregnancies are scarce. A recent review evaluated the frequency, tumor type, associated factors, and specific biomarkers associated with head and neck cancer during pregnancy, but no data on cisplatin treatment in these patients was published (72). However, cisplatin is frequently used in cervical cancer treatment where cancer during pregnancy is more frequent than in head and neck cancer.
Cisplatin appears to be relatively safe for the fetus. A meta-analysis, primarily of case studies, where patients were treated with cisplatin during the second or third trimester showed that 71 of 88 (81%) infants were born completely healthy. However, there were five cases of hearing loss, cardiac and cerebral malformations, and one child was diagnosed with a rare rhabdomyosarcoma at the age of 5 and one presented with acute myeloid leukemia at 22 months. Thus, for cervical cancer it was concluded that cisplatin may be a favorable choice [3a] (73).
Weekly cisplatin concomitant with radiotherapy during pregnancy may be safe for patients with head and neck cancer in the second and third trimester, however, expected benefit must be weighed against specific risks for both mother and child.

Reports on cisplatin concentrations in breast milk after treatment are sparse and results are conflicting (74). In a recent case report detectable levels of cisplatin were found months after weekly cisplatin for three weeks [4] (75).
Breastfeeding should be avoided.

Patient values and preferences

No literature on patient values and preferences were found.
The effect of adding cisplatin to radiation treatment in head and neck cancer must be weighed against likely side effects. Thus, shared decision making is essential in these situations.

Rationale

The literature review supports the previous DAHANCA guideline regarding contraindications to cisplatin.

Weekly cisplatin 40 mg/m^2 has been used regularly for almost two decades, and the present recommendations are in accordance with the knowledge obtained through clinical experience and research within the DAHANCA group.

Comments and considerations

Patient data, treatment, and adverse events are registered in the DAHANCA database. Within the DAHANCA collaboration, trials are continuously being conducted to ensure high quality and safety of HNSCC treatment in Denmark.

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5. Methods

This guideline is produced on behalf of the Danish Head and Neck Cancer Group (DAHANCA).
The use of cisplatin administered weekly at a dose of 40 mg/m^2 concomitant with radiotherapy has been a standard treatment for locoregionally advanced head and neck cancer patients in Denmark since 2003.

The recommendations are based on literature review and the clinical practice, experience, and expertise within the DAHANCA group throughout this extended time period.

Literature search

No formal search strategy has been performed but relevant widely acknowledged meta-analyses, reviews, and randomized controlled trials have been used.

Evidence assessment

The authors conducted the critical evaluation of the evidence. The recommendations were graded according to Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009).

Articulation of the recommendations

The recommendations were formulated by the authors and consensus were assured within the DAHANCA group before final approval.

Stakeholder involvement

Only the authors and members of the DAHANCA group have been involved in the guideline development.

External review and guideline approval

The guideline has been consulted with the DAHANCA group before final approval at the DAHANCA meeting 12th of March 2020.

Recommendations which generate increased costs

The recommendations in this guideline are not estimated to generate increased costs.

Need for further research

Significant evidence exists that demonstrate survival benefit of chemoradiotherapy over radiotherapy for locoregionally advanced head and neck squamous cell carcinoma. Cisplatin demonstrating superior benefit, though optimal regime remains to be resolved. Furthermore, the optimal alternative treatment option for cisplatin unfit patients remains debatable and should be further investigated.

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  No conflicts of interest.

6. Monitoring

Standards and indicators

The use of cisplatin is registered in the DAHANCA database. Based on predefined indicators of quality each year, a report is conducted in collaboration with RKKP.

Plan for audit and feedback

Ongoing evaluation and feedback will take place at the DAHANCA meetings.
It was not within the scope of this guideline to change treatment recommendations according to specific tumor sites, but national guidelines by tumor site are currently being revised; hence, this guideline will be amended accordingly.

7. Appendix

Cisplatin - Administration, dose, dose modifications, and supportive treatment.

Chart A. Hydration

Label:

Cycle:	Dato:

Infusion fluids / medication	mL	Tid (min)	Start time	Sign.	End time	Sign.	Urine output	Weight
Isotonic saline (NaCl isotonic) + Mg^{2+}4 mmol	1000	60						Start:
Antiemetics								
Mannitol 10% Optional	500	60						
Cisplatin in isotonic saline (NaCl isotonic)	500							
Isotonic saline (NaCl isotonic) + Mg^{2+} 4 mmol	1000	60						End:

The patient must have urinated after pre-hydration and before cisplatin infusion begins.

In case of significant weight gain (e.g. above 1.5-2 kg), the patient should be offered one tablet Furosemide 40 mg.

If blood samples show a tendency to hypomagnesemia, the patient must be offered Mablet 360 mg twice daily, at least day 1-3.

Likewise, if blood samples show hypokalemia, the patient must be given Kaleorid 750 mg twice a day, day 1-3.

The patient must drink at least 2 L of fluids for the next 6 hours after hydration.