Low dose cisplatin weekly versus high dose cisplatin every three weeks in primary chemoradiation in sarcopenic head and neck cancer patients.

Published: 29-07-2021
Last updated: 19-03-2025

This study has been transitioned to CTIS with ID 2024-514919-10-00 check the CTIS register for the current data. To investigate if the use of weekly low dose cisplatin increases compliance to the planned chemotherapy scheme in LA-HNSCC patients with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Oral soft tissue conditions
Study type	Interventional

Summary

ID

NL-OMON56152

Source
ToetsingOnline

Brief title
CISLOW

Condition

- Oral soft tissue conditions
- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Head and neck therapeutic procedures

Synonym
head and neck cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Cisplatin, Head and Neck Cancer, Sarcopenia, Toxicity

Outcome measures

Primary outcome

The primary outcome parameter is compliance (non CDLT) rate to the proposed cisplatin scheme. Compliance to chemotherapy is defined as the absence of CDLT. CDLT is defined as any toxicity resulting in a cisplatin dose-reduction of >=50%, a postponement of treatment of >=4 days or a definite termination of cisplatin after the first or second cycle of therapy.

Secondary outcome

Secondary outcome parameters are adverse events/toxicity, cumulative cisplatin dose, time to recurrence, 2-year overall survival, costs, quality of life and patient*s preference. The main oncological outcome parameters are time to recurrence and survival. Clinically relevant treatment related toxicity parameters, including specific toxicity that results in significant (grade 3 or 4) toxicity, treatment de-escalation or termination, will be recorded by the treating medical oncologist. Toxicity will be scored according to the Common Terminology Criteria for Adverse Events (CTCAE) guidelines, v5.0. Questionnaires The following questionnaires will be used to measure quality of life: EORTC QLQ-C30, EORTC-QLQH& N35 and EQ-5D-5L. Global quality of life is assessed with the EORTC-QLQ-C30 global measure. The EORTC-QLQ-H&N35 is designed

to be head and neck cancer-specific, multidimensional in structure, appropriate for self-administration and applicable across a range of cultural settings. The EQ-5D-5L is a standardized instrument can be used as a quantitative measure of health outcome that can be used in a wide range of health conditions and treatments, and reflects the patient*s own judgement. Questionnaires are asked to fill out before and 3, 6, 12 and 24 months after CRT. Standard scoring methods are applied to quality-of-life questionnaires. All scores are normalized, ranging from 0 to 100, and transformed to unweighted summated scales in which higher scores indicates better health. Separate comparisons are made at each time point. Unadjusted p values are used. On the EORTC questionnaires a 10-point difference in scores was considered to be clinically relevant. Cost analysis Substitution of weekly low dose cisplatin for three-weekly high dose cisplatin in patients treated with concurrent CRT is expected to result in cost-savings and an increase in quality of life due to reducing the number of complications. A detailed analyses of cost differences for low SMM patients with weekly low dose cisplatin and standard of care (three-weekly high dose cisplatin) demands a detailed collection of all health care consumed by these patients in relation to the intervention and complications. In the prospective cohort we will collect all health care consumed by patients in each of the three different groups with a follow-up of 12 months. All data will be collected from the electronic patient files in each different hospital and will be collected using respective units for each sort of health care consumption (hospital stay per day, cost per dose, etc). As indicated, quality of life will be measured before and 3, 6, 12 and 24 months

after CRT using the EQ-5D-5L. Productivity loss of low SMM patients will be collected during the study at baseline and at 12 months after CRT using the productivity cost questionnaire (PCQ). This will only be done for the low SMM group, since our main interest is the difference between the two chemotherapy schemes in the low SMM group. All different units of care consumed will be linked to their respective unit costs. Reimbursement prices issued by the Dutch Healthcare Authority (NZA) and national reference prices will be used for this assessment as outlined in current Dutch pharmaco-economic guidance. In addition to total health care consumption of these patients it is essential to perform micro-costing of CRT treatment to have detailed insight in the additional costs. We therefore aim to perform a micro-costing study using the activity based costing (ABC) method. To link both costs and effects we aim to develop a decision-tree completely outlining all probabilities of having complications (CDLT resulting in non-compliance) and their respective costs and effects (quality of life) in each of the three different groups. Outcome measure will be incremental costs per quality adjusted life year. Moreover, complete sensitivity analysis (both deterministic as well as probabilistic) will be carried out to have detailed insights into the impact of uncertainty on our outcome measures. In addition to a cost-effectiveness analyses we aim to perform a budget impact analysis (BIA) as well. The BIA adheres to the Zorginstituut guidelines and applies the perspectives: societal, health insurance/third party payer and health care (Budgetair Kader Zorg (BKZ)). The BIA Prices will be linked to perspectives: societal-CEA based prices, BKZ-average rates according to NZa, for health insurance perspective also NZa

average rates and, for example, for a local health care provider perspective specific passenger rates (*passanten tarieven*). The BIA will be assessed through (decision analytical) modelling and analyzed in a probabilistic way.
Other parameters: To allow for comparison with the recent nation-wide Dutch Head and Neck Society audit, the same characteristics and potential predictive factors will be scored. Collected patient characteristics are gender, age, weight, stature (length), smoking history, use of alcohol, loss of weight, Eastern Cooperative Oncology Group (ECOG performance status), medical history regarding heart, lung, diabetes mellitus, oncology and nefrology, grip strength (if available), comorbidity (ACE-27 and Charlson Comorbidity Index), Tumor Node Metastasis (TNM) classification, tumor localisation, estimated Glomerular Filtration Rate (eGFR), serum creatinine, neutrophil count, platelet count, leukocyte count, lymphocyte count, monocyt count and hemaglobin level, baseline audiometry results and treatment plan (including use of co-medication). SMM will be estimated using a validated technique based on measurement of the cross-sectional area of the sternocleidomastoid muscle and paravertebral muscles on the level of C3 on routinely performed CT or MRI. In patients who underwent fluorodeoxyglucose-positron emission tomography(FDG-PET)/CT as part of the diagnostic work-up, as a control of SMM measurement at the level of C3, SMM will also be measured at the level of L3, which is the most commonly used method in medical literature as a control of SMM measurement at the level of C3. Based on the cut-off value calculated by Wendrich et al., low SMM is defined as skeletal muscle mass <43,3 cm2/m2. Patients with low SMM will be randomised between weekly low dose cisplatin and three-weekly high dose

cisplatin with concurrent RT. The rate of compliance to proposed cisplatin scheme will be compared between three groups: patients with low SMM with weekly low dose cisplatin, patients with low SMM and three-weekly high dose cisplatin and the rest group of normal SMM receiving standard three-weekly high dose cisplatin.

Study description

Background summary

In the Netherlands, 3160 patients were diagnosed with HNSCC in 2018. Two-thirds of HNSCC patients present with locally advanced disease (LA-HNSCC). The standard of care consists of intravenous cisplatin concurrently given with conventional external beam radiotherapy (chemoradiotherapy, CRT). High cumulative cisplatin dose is associated with better outcome. The most commonly used scheme is three-weekly high dose cisplatin of 100mg/m2. Though effective in terms of overall survival (OS) and loco-regional control (LRC), high rates of severe acute events lead to cisplatin dose limiting toxicity (CDLT) in up to 40% of patients and cause decrease in local control and survival. Furthermore in 13% of the patients late toxicity is reported, which leads to permanent comorbidity. This is a high rate of adverse events in comparison to other anticancer treatments. Decresed compliance to treatment because of CDLT can lead to a cumulative dosage less than the adviced >200 mg/m2, which leads to worsened local control of disease and survival. Therefore another commonly used scheme is weekly low dose cisplatin of 40 mg/m2 during 7 weeks concurrently given with radiotherapy (RT). This scheme is considered as standard in daily clinical care. However, the most scientific evidence is available for the three-weekly scheme and for the whole patient population the weekly scheme does not lead to improved survival. Currently, patients at risk for CDLT cannot be accurately identified upfront and thus it is not possible yet to decide which patients possibly benefit from the weekly scheme. However, it is known for patients with low skeletal muscle mass (SMM), assessed on routinely performed CT and/or MRI scans, are three times more likely to develop CDLT than patients with normal SMM. Cisplatin possibly distributes mainly to the fat-free mass, of which SMM is the largest component, and thereby a higher and more toxic peak dosage might be reached in patients with low SMM receiving high dose cisplatin. Since early discontinuation of therapy automatically leads to a reduced cumulative cisplatin dose, which is associated with lower overall survival, it can be anticipated that particularly patients with low SMM might benefit from weekly low dose cisplatin based concurrent CRT to achieve a adequate cumulative

dose comparable to patients with normal SMM.

Study objective

This study has been transitioned to CTIS with ID 2024-514919-10-00 check the CTIS register for the current data.

To investigate if the use of weekly low dose cisplatin increases compliance to the planned chemotherapy scheme in LA-HNSCC patients with low SMM to a level of compliance to three-weekly high dose cisplatin of patients without low SMM. We hypothesize that in LA-HNSCC patients with low SMM, receiving weekly low dose cisplatin concurrent RT have a higher compliance rate to planned chemotherapy scheme compared to patients receiving the three-weekly scheme, resulting in a higher cumulative dosage and possibly improved outcomes.

Study design

In this multicenter prospective low-intervention clinical trial the compliance of weekly low dose compared to three-weekly high dose cisplatin with concurrent RT in seventy LA-HNSCC patients with low SMM will be investigated. To assure the inclusion of seventy low SMM patients, a total of 160 LA-HNSCC patients should be included according to the incidence rate of low SMM in this population. The goal of this study is to treat patients more effective and safer. Patients with low SMM will be randomised between two schemes, weekly low dose cisplatin versus three-weekly high dose cisplatin. Both schemes are considered as standard of care in which the goal is to obtain a equivalent cumulative dosage.

Cumulative cisplatin dose, time to recurrence, 2-year overall survival, costs, quality of life and patient*s preference will be assessed. Toxicities will be recorderd using the Common Terminology Criteria for Adverse Events (CTCAE) criteria. Quality of life will be measured using European Organisation for Research and Treatment of Cancer (EORTC) questionnaires and will be send by e-mail. When the patient or treating physician ask for a non-digital questionnaire, the questionnaires will be send via post and answers will be put into Castor by the investigator. A cost-effectiveness analysis will be performed. Semi-structured interviews will be done, to assess patients' preferences.

Intervention

Randomisation between high- (100 mg/m2 cisplatin three-weekly) and low dose (40 mg/m2 cisplatin weekly) treatment in patients with low SMM. Cisplatin treatment itself and concomitant radiotherapy are not part of the intervention, but part of standard treatment. The intervention is not cisplatin or radiotherapy because those are both part of standard of care, but the intervention is the

randomisation between schemes. Patients with a normal SMM receive the scheme that is the local standard of care.

Study burden and risks

Burden to patients is limited to completion of four (or three when the patient has normal SMM) questionnaires for five times, which will take about 30 minutes and a 10-minute interview over the phone with the investigator 3 months after therapy. Therefore it is likely that most patients will agree to participate.
There will be no need for extra diagnostic procedures, because MRI and/or CT at cervical level is standard pre-treatment procedure in LA-HNSCC.

Moreover each patient receives RT daily, so no additional hospital visit is necessary: Radiotherapy will be given daily during 7 weeks. Chemotherapy will be given three or seven times, depending on the randomisation group, on a day radiotherapy is planned as well. For low SMM patients, this study may serve as a basis for increase in compliance to therapy and might increase survival and LRC, since early discontinuation of CRT increases risks at recurrence of disease.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3508GA
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3508GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- considered eligible and planned for primary cisplatin CRT by treating physician;
- eighteen years of age or older;
- sufficient understanding of Dutch and medical consequences to give informed consent.

Exclusion criteria

- mentally disabled or patients with significantly altered mental status that would prohibit understanding and giving informed consent; - a history of bilateral lymph node dissection in the neck and no available (PET-)CT scan of the third lumbal vertebra; - an absolute contraindication for cisplatin as defined by the treating physician, including relevant pre-existing kidney insufficiency, clinically apparent vascular disease (for example claudicatio intermittens), clinically relevant perceptive deafness, serious neuropathy and poor performance score. - an absolute contraindication for high dose three-weekly cisplatin 100 mg/m2 as defined by the treating physician; - interval between diagnostic scan and planned CRT >2 months; - cisplatin CRT planned as non-primary or induction treatment.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-01-2022
Enrollment:	160
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Generic cisplatin will be used, specialité differs in standard of care
Generic name:	Cisplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-07-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-08-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-06-2023
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-10-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-10-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 25064
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-514919-10-00
EudraCT	EUCTR2021-002634-16-NL
CCMO	NL76533.041.21
Other	NL9217
OMON	NL-OMON25064