Combination of chemoTherapy aNd chemoradioTherapy for adenocarcinoma of the OESophagus and gastro-oesophageal junction with oligometastatic disease

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23939

Source
NTR

Brief title
TNT-OES-1

Health condition

Adenocarcinoma of the oesophagus or gastro-oesophageal junction

Sponsors and support

Primary sponsor: Erasmus MC
Source(s) of monetary or material Support: None

Intervention

Outcome measures

Primary outcome

Primary endpoint is the tolerability of the combined regimens, defined as the number of patients that complete the administration of 4 x FLOT and the full CROSS CRT regimen.

Secondary outcome

Secondary eindpoints are the number of patients that have progressive disease after four cycles of FLOT CT, disease control rate (DCR) and objective response rate (ORR), both according to RECIST 1.1, serious adverse events and adverse events according to Common Terminology Criteria for Adverse Events (CTCae) v4.0, cumulative administered dose of FLOT and number of cycles of carboplatin/paclitaxel administered as part of CROSS CRT, progression free survival [PFS], overall survival [OS], number of patients with a clinically complete response, QoL, the number of patients proceeding to local therapy of distant metastases and/or oesophagectomy.

Study description

Background summary

Rationale: Metastatic adenocarcinoma of the oesophagus or gastro-oesophageal junction (GOJ) has a dismal prognosis and is associated with a poor quality of life (QoL), mainly due to locoregional complaints such as dysphagia and odynophagia. The recently published FLOT3-study showed that in selected patients with limited metastatic disease, induction chemotherapy followed by surgery may prolong survival. Furthermore, in the (potentially) curatively treated patients, chemotherapy (CT), consisting of a combination of Fluorouracil, Leucovorin, Oxaliplatin and doceTaxel (FLOT) is currently a standard of care as peri-operative treatment for adenocarcinomas of the stomach and GOJ. On the other hand, neoadjuvant chemoradiation (CRT) according to the CROSS regimen improves locoregional control, QoL and survival in patients with resectable oesophageal and GOJ tumours. After CRT, 23% of patients have a pathologically complete response (pCR). The combination of systemic CT (FLOT) with mainly locoregional acting CRT (CROSS) is an attractive treatment option for patients with limited metastatic disease, aiming for better survival, but also better locoregional control and thus improved QoL. It is currently unknown however whether FLOT CT can be safely combined with CROSS CRT. This phase II study investigates the safety and feasibility of the combined, sequenced regimen.

Objective: To assess the safety and feasibility of a multimodal combination of FLOT CT with CROSS CRT.

Study design: Phase II, prospective single-centre intervention study

Study population: Patients aged 18-75 years old with resectable adenocarcinoma of the oesophagus or GOJ with limited distant metastatic disease (e.g. retroperitoneal or supraclavicular lymph node metastases, limited visceral metastases).

Intervention: In total 20 patients will be included. All patients will start with four courses of FLOT in 2-week cycles. Patients with progressive disease will be excluded from further study and treated according to the decision of the multidisciplinary tumour board. Patients with stable or regressive disease will continue with CROSS CRT (weekly administration of five cycles of carboplatin and paclitaxel with concurrent radiotherapy). After this time-point in the study, further treatment, if any, is determined in our multidisciplinary tumour board according to guidelines and institutional practice and not by the study protocol. The options include best supportive care, continuation of chemotherapy and treatment of the primary tumour and/or metastases (by local ablative therapies and/or surgery).

Main study parameters/endpoints: Primary endpoint is the tolerability of the combined regimens (defined as the number of patients that complete the administration of four cycles of FLOT CT and the full CROSS CRT regimen). Secondary outcomes are the number of patients that have progressive disease after four cycles of FLOT CT, disease control rate (DCR) and objective response rate (ORR), both according to RECIST 1.1, serious adverse events and adverse events according to Common Terminology Criteria for Adverse Events (CTCae) v4.0, cumulative administered dose of FLOT and number of cycles of carboplatin/paclitaxel administered as part of CROSS CRT, progression free survival [PFS], overall survival [OS], number of patients with a clinically complete response, QoL, the number of patients proceeding to local therapy of distant metastases and/or oesophagectomy.

Study objective

We hypothesize that it is feasible and safe to test the proposed FLOT-CROSS in a planned future phase III trial, defined as a success rate or at least 40% (success defined as completion of all four FLOT chemotherapy cycles and all CROSS CRT sessions).

Study design

In the first stage, 11 patients will be accrued. If there are 3 or fewer successes in these 11 patients, the study will be stopped (success defined as completion of all four FLOT cycles and all CROSS CRT sessions). Otherwise, 9 additional patients will be accrued for a total of 20.

Intervention

The combination of two standard-used regimens consisting of CRT (CROSS) with CT (FLOT) is studied. A first clinical response evaluation (CRE-1) will take place 4-6 weeks after the last CT cycle using CTneck/chest/abdomen. Only patients who have stable disease or regression of disease according to RECIST criteria, will be eligible for continuation in the study. A second clinical response evaluation (CRE-2) will take place 4-6 weeks after the last CRT session using a combination of endoscopy with bite-on-bite biopsies, EUS-FNA of suspected lymph nodes and CTneck/chest/abdomen. The on-study treatment stops for all patients after CRE-2. After this timepoint in the study, further treatment decisions are made in our multidisciplinary tumour board.

Chemotherapy:

Patients receive chemotherapy according to the FLOT4 regimen, starting with 4 courses according to the standard schedule:
1.Docetaxel (50 mg/m2) in 250 ml NaCl 0.9% i.v. for 1 h, d1
2.Oxaliplatin (85 mg/m2) in 500 ml G5% i.v. for 2 h, d1
3. Leucovorin (200 mg/m2) in 250 ml NaCl 0.9% for 1 h, d1
4. 5-FU (2600 mg/m2) continuous infusion for 24 h, d
Repeated every two weeks (q2w), following the treatment schedule.

Chemoradiotherapy:

Patients receive chemoradiation according to the CROSS regimen, which consists of weekly administration of five cycles of CT (intravenous carboplatin [AUC 2 mg/mL per min] and intravenous paclitaxel [50 mg/m2] for 23 days) with concurrent radiotherapy (41·4 Gy, given in 23 fractions of 1·8 Gy on 5 days per week). Chemoradiation will start no earlier than 4 weeks but within 8 weeks after the last FLOT cycle.

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Histologically-proven, resectable adenocarcinoma of the oesophagus or GOJ according to the UICC TNM7 definition (appendix 2). Tumours of the oesophagus and tumours of which the epicentre is within 5 cm of the GOJ are eligible for inclusion in the trial in the case of adenocarcinomatous histology (Type 1 and Type 2 according to Siewert classification of oesophagogastric adenocarcinoma)

2. Pre-treatment stage cT1N+ M1 or cT2-4a N0/N+, M1 (In case of stage cT4a, curative resectability has to be explicitly verified by the multidisciplinary tumour board.

3. Oligometastatic disease, which for this study is defined as a maximum of four resectable/treatable metastatic lesions. These four lesions can be present in a maximum of two organs (liver, lung, bones, or adrenal gland). Lymph nodes are not counted as an organ. If metastatic retroperitoneal or supraclavicular lymph nodes are present, this lymph node site counts as one metastatic lesion, and together with the possible metastases in organs cannot exceed the four lesions.

4. Age ≥ 18 years, <75 years

5. No prior abdominal, thoracic or cervical radiotherapy overlapping with the CROSS irradiation fields

6. No prior cytotoxic chemotherapy

7. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix 1)

8. Adequate cardiac function (cardiac function tests such as echocardiography only necessary in symptomatic patients).

9. Adequate respiratory function (pulmonary function tests only necessary in symptomatic patients)

10. Adequate bone marrow function (White Blood Cells >3x10^9/l; Haemoglobin mmol/L; platelets >100x10^9/l). In the event of transfusions, the last red blood cell transfusion should be more than 2 weeks before
inclusion.

11. Adequate renal function (Glomerular Filtration Rate >50 ml/min) or Serum creatinine <=1.5 x upper limit of normal (ULN) and adequate liver function (Total bilirubin <1.5x Upper Level of Normal (ULN); Aspartate transaminase (AST) <2.5x ULN and Alanine transaminase (ALT) <3x ULN

12. Written informed consent and ability to understand the nature of the study and the study-related procedures and to comply with them .

13. Women of child-bearing potential must have a negative serum pregnancy test during screening period.

14. Patients must be willing to use adequate contraception during the study and for 3 months after the end of the study.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation

in this study:
1. Patients with tumours of squamous, adenosquamous or other non-adenocarcinoma histology

2. Patients with advanced irresectable or extensive metastatic oesophageal adenocarcinoma (involving 3 or more organs or more than 4 metastatic lesions)

3. Patients with overt peritoneal dissemination, as detected on PET-CT or regular CT-scan. In patients in whom a diagnostic laparoscopy is indicated, tumour-positive cytology peritoneal fluid is also an exclusion criterion

4. Oesophageal adenocarcinoma evaluated as not curatively-resectable by the multidisciplinary tumour board , for instance because ingrowth in the trachea

5. Gastric carcinoma (according to UICC TNM7)

6. Clinically significant (active) cardiac disease (e.g. symptomatic coronary artery disease or myocardial infarction within last 12 months)

7. Clinically significant lung disease (Forced Expiratory Volume in one second (FEV1) <1.5 l)

8. Peripheral neuropathy grade >1 according to CTCae v4.0

9. Pregnant and lactating women, or patients of reproductive potential who are not using effective birth control methods. If barrier contraceptives are used, they must be continued by both sexes throughout the study.

10. Participation, current or during the last 30 days prior to informed consent, in another intervention trial with interference to the chemotherapeutic or chemoradiotherapeutic intervention of this study

11. Expected lack of compliance with the protocol

12. Secondary primary cancer with the exclusion of basal cell carcinoma of the skin

13. Language difficulty, dementia or altered mental status prohibiting the understanding and giving of informed consent and to complete quality of life questionnaires;

Study design

Design

Study type:	Interventional
Intervention model:	Other

Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-01-2021
Enrollment:	20
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	08-02-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9269
Other	METC Erasmus MC : MEC-2020-0747

Study results