Protocol synopsis

EU trial number and Full trial title

2023-504144-33; PERI-OPERATIVE Selective Decontamination of the Digestive tract to prevent severe infectious complications after Esophagectomy a Randomized multicenter clinical trial in patients with primary resectable esophageal carcinoma (cT1-4, N0-3, Mo).

Rationale

Esophagectomy is a complex surgical procedure, associated with significant morbidity and mortality rates. Most postoperative complications are caused by infections (10–30%). These are thought to arise from (micro-)aspiration of bacteria residing in the oropharyngeal and gastrointestinal (GI) tract, leading to (respiratory) infections. Selective decontamination of the digestive tract (SDD) is a prophylactic antibiotic strategy that aims to prevent postoperative infections. Pathogenic aerobic gram-negative rods and yeasts are reduced, while anaerobic, protective microbiota are preserved. SDD has been shown to lower the risk for respiratory infections in an intensive care setting. Establishing SDD as effective addition to the standard care of esophagectomy patients is expected to increase their chance of survival.

Objective

The primary aim of PERSuaDER-trial is to evaluate the effect of SDD on infectious complications after esophagectomy, focussed on the prevention of pneumonia. We hypothesize that the intervention will decrease the rate of postoperative pneumonia by one third.

Main trial endpoints

The cumulative incidence of postoperative pneumonia within 30 days after surgery. Pneumonia will be defined by the following criteria: Positive sputum culture OR presence of a new progressive radiographic infiltrate plus at least 2 of the following clinical features: Fever > 38.5°C, Leukocytosis (>11.0) or leukopenia (<4.0) or Purulent secretions.

Secondary trial endpoints

The cumulative incidence of all postoperative infectious complications as registered in DUCA within 30 days after esophagectomy, the cumulative incidence of anastomotic leakage within 30 days after esophagectomy for which re-intervention is needed, mortality within 90 days after surgery, rate of re-operation within 30 days after surgery, postoperative length of stay in hospital and ICU specific (including re-admissions within 6 months after surgery), Quality of Life (QoL) preoperative, after 30 days, 3 months and 6 months and the direct and indirect costs.

Trial design

Randomized controlled pragmatic, open-label, multicentre, binational trial in 854 patients with primary resectable esophageal carcinoma (cT1-4a, N0-3, M0) with a follow-up of 6 months.

Trial population

Patients with primary resectable esophageal carcinoma planned to undergo transthoracic esophagectomy in participating centres in Belgium and The Netherlands, age $\geq$ 18 years, able to give written informed consent. Exclusion criteria are: rescue surgery, patients planned for colonic interposition, pregnant woman, patient who have undergone upper GI surgery within 30 days before randomization, patients enrolled in a trial that would interact with the intervention, patients with known allergy, sensitivity or interaction to one of the SDD components, patients with the inability to swallow the SDD, patients undergoing CVVH, patients with documented chronic renal failure (GFR < 15 mls/min) or who are on chronic intermittent hemo- or peritoneal dialysis, patients with myasthenia gravis, patients with parkinson disease, patients with known/documented colonization of Enterobacteriaceae and or Pseudomonas Aeruginosa that are resistant to both tobramycin/gentamicin and to carbapenem antibiotics.

Interventions

The intervention group receives SDD treatment additional to standard care. The SDD treatment consists of two oral solutions. The first suspension to be taken is 5 ml amphotericin B (100 mg/ml) or 5 ml Nystatine, followed by 5 ml of colistin sulphate (20 mg/ml)/tobramycin sulphate (16 mg/ml) solution. Patients take both drinks four times daily for one week, starting three days prior to the surgery. On the day of surgery, intake is limited to early morning and late evening doses. All other facets of care are equal to the control group (standard care without SDD). All participants will be asked to keep a diary and to fill in quality of life questionnaires, prior to surgery and 30 days, 3 months and 6 months after surgery.

Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks

The study will be conducted according to the declaration of Helsinki, the ICH Guidelines for Good Clinical Practice and in accordance with all applicable national legislation.

Possible benefits for patients receiving SDD: les infectious complications, less anastomotic leakage, shorter hospitalisation and/or ICU stays, less re-operations, lower mortality, better quality of life, better long-term survival. Possible risks for patients receiving SDD: standard risks associated with esophagectomy, risk of mild, but common side effects related to the intake of the SDD treatment such as: vomiting, nausea, diarrhoea, bloating and indigestion, abdominal pain, loss of appetite. Possible risks for patients of the control cohort; standard risks associated with esophagectomy.

If patients are enrolled, there will be no need for additional visits compared with the standard of care.