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Adjuvant therapy: colorectal cancer chemotherapy study (LIitännäishoito: Paksu- ja PeräsuoliSYövän SYtostaattiTerapiaTutkimus): comparison of 5-fluorouracil (5-FU) and leucovorin as bolus injection or continuous infusion with special emphasis on toxicity, cost-benefit, quality of life, effect of nutrition, changes in bacterial flora and prognostic factors

Submission date
02/07/2012

Recruitment status
No longer recruiting

Registration date
16/07/2012

Overall study status
Completed

Last Edited
09/08/2021

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Colorectal cancer is the third most common cancer worldwide. Surgery is the mainstay for treatment but adjuvant chemotherapy with 5-fluorouracil in combination with leucovorin has improved survival significantly. Adjuvant treatment is linked to considerable toxicity and thus means for alleviation need to be explored. The mode of chemotherapy administration may improve tolerability, as may nutritional factors such as lactose intolerance and the gut bacterial flora.

Who can participate?
Patients aged between 18-75 years with colorectal cancer, fit for chemotherapy with no significant morbidity.

What does the study involve?
Participants will be randomly allocated to receive 5-fluorouracil and leucovorin either as a single large dose (bolus injection) or by continuous infusion. Participants will also be randomly allocated to receive nutritional counselling with or without supplementation with lactobacillus GG or guar gum fiber. Blood and fecal sampling will be taken before, during and after adjuvant chemotherapy. Patients will be followed up for 10 years.

What are the possible benefits and risks of participating?
The possible benefits and risks are not fully known. The assessed chemotherapy treatments have been tested in colorectal cancer and found to be safe. Lactobacillus rhamnosus GG has been found to be non-toxic and possible infection with these bacteria will be carefully followed. Guar gum fiber has been found to be safe but may cause diarrhoea and flatulence. If the nutritional intervention is found to be effective the patients may benefit as toxicity is alleviated. Typical toxicity from 5-fluorouracil includes digestive symptoms and more rarely infections.

Where is the study run from?
Helsinki University Central Hospital (Finland).

When is the study starting and how long is it expected to run for?
The study started in November 1997 and patients were recruited for about 4 years. Patients were followed up for 10 years after participating in the study.

Who is funding the study?
The study is an academic study. Pumps were subventionated by Baxter, lactobacillus rhamnosus was given free of charge from Valio Ltd who also partly funded the bacterial sampling for example methane analysis. Study leave will be funded by educational grants from example from the Finnish Medical Association, the Finnish Cancer Society etc.

Who is the main contact?
Dr Pia Osterlund
pia.osterlund@hus.fi

Contact information

Type(s)
Scientific

Contact name
Dr Pia Österlund

Contact details
Helsinki University Central Hospital
Department of Oncology
PO Box 180
Helsinki
Finland
00029
+35 (0) 850 427 0860
pia.osterlund@hus.fi

Additional identifiers

Protocol serial number
LIPSYT

Study information

Scientific Title
A comparison of 5-FU and leucovorin treatment as bolus injection or continuous infusion in the adjuvant therapy of Dukes' B, C and radically operated D colorectal cancer: a randomized phase III trial studying toxicity, cost-benefit and quality of life in bolus injection and continuous infusion treatment regimens, effects of nutrition and nutritional support, changes in bacterial flora and prognostic factors

Acronym
LIPSYT

Study objectives
In the adjuvant treatment of colorectal cancer, this trial is designed to answer the question of:
1. Differences in toxicity profile, adverse events and quality of life in bolus and infusional treatment regimens. The aim is to develop a new adjuvant treatment standard that enables cytostatics in home care, and to prevent and treat side-effects efficiently. The intention is to interfere with patients´ everyday life as little as possible during 6 months of adjuvant treatment.
2. Cost-benefit differences in bolus and infusional treatment. In preliminary calculations the continuous infusion at home should be 30% cheaper than bolus treatment in the clinics. Though continuous infusion has been considered expensive, no accurate studies verifying these assumptions have been made.
3. The relationship between nutrition, nutritional status, lactose tolerance and adverse events. Is nutrition a prognostic factor in the outcome of colorectal cancer and does the tolerance of chemo- and radiotherapy correlate with nutritional factors?
4. Lactobacillus GG's preventive and curative effect on gastrointestinal side-effects, especially the reduction of diarrhoea incidence that is apparent in 33-42% of the patients.
5. Effect of hydrolyzed guar gum fiber on gastrointestinal side-effects. Benefiber is an essential ingredient of the nutritional support given during periods of gastrointestinal side-effects. Does the fiber reduce and alleviate diarrhoea?
6. The possible synergetic effect of guar gum fiber and lactobacillus GG will also be assessed.
7. Effects of prophylactic additional nutritional support on nutritional status and adverse events. Supplemental oral nutrition with fiber is given prophylactically during 8 days per month in order to maintain a resonable oral intake when side-effects affect eating. Can nutritional disadvantegous changes of chemo- and radiotherapy be prevented?
8. Changes in gastrointestinal bacterial flora during treatment and symptoms. General changes in microbial flora and digestive enzymes will be assessed. More thoroughly analysis of fecal flora and Helicobacter pylori antibodies in sera will be carried out for a selection of the patients.
9. The prognostic value of nutrition and nutritional status and different serum and fecal factors, including angiogenetic factors and methane production.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical Review Board at Helsinki University Hospital, 05/11/1997

Study design
Open randomized phase III trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Radically operated colorectal cancer Stage II-IV

Interventions
Comparison of 5-fluorouracil and leucovorin as bolus injection or continuous infusion.

Secondary randomization to
1. Nutritional counselling 1/3
2. Lactobacillus rhamnosus 1/3 lactobacillus rhamnosus and guar gum fibre 1/3.

Adjuvant chemotherapy consists of 5-fluorouracil (5-FU) and leucovorin as bolus injection (Mayo regimen) or continuous infusion (simplified de Gramont regimen) according to randomization. The Mayo regimen consists of a 3-5 minute intravenous bolus of 5-FU 370-425 mg/m2 and infusion of LV 10-20 mg/m2 on days 1-5 of a 4 weekly cycle repeated 6 times.

In rectal cancer during 5.5-week pelvic chemoradiation (50.4/1.8 Gy), starting on day 56, single 5-FU bolus 500 mg/m2 is given intravenously during days 1-3 on the first and fifth week. After penetration of the preoperative Swedish radiotherapy results patients could receive 25/5 Gy over 5 days preoperatively without concomitant chemotherapy.

Simplfied de Gramont regimen consists of 2-hour infusion of LV 400 mg/m2 followed by 5-FU bolus 400 mg/m2 and continuous 5-FU infusion 3.0-3.6 g/m2 for 48 hours repeated every 14 days 12 cycles. During radiotherapy days 56-96, given as mentioned above, continuous infusion 5-FU 225 mg/m2/day is administered.

The participants were also randomly assigned to receive or not to receive at a 2:1 ratio Lactobacillus rhamnosus GG and at a 1:2 ratio fibre-containing nutritional support (guar gum). The allocation group was concealed until interventions had been assigned. All patients received nutritional counselling.

1. Nutritional counselling
2. Nutritional counselling and Lactobacillus GG
3. Nutritional counselling, Lacobacillus GG and guar gum fibre

Nutritional counselling
In this trial a leaflet about general nutritional guidelines during chemotherapy and radiotherapy has been developed and is to be given to all patients. Patients will also meet with a nutritional therapist for general guiding and for counselling if problems occur.

Lacobacillus GG
Lactobacillus rhamnosus GG (ATCC 53103, Gefilus®, Valio Ltd, Helsinki, Finland) was administered orally as gelatine capsules twice daily at a dose of 1-2 x 10^10 per day during the 24 weeks of adjuvant cancer chemotherapy. Lactobacillus capsules were swallowed as such, or the capsule content was dissolved in cold milk or juice.

Guar gum fibre nutritional supplement
Guar gum containing nutritional supplement (500 mL, Novasource GI control®, Novartis Nutrition, Basel, Switzerland (contains 11 g guar gum and 550 kcal/2,300 kJ), was administered daily, on cycle days 7 to 14, for eight days per month.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
5-fluorouracil (5-FU), leucovorin

Primary outcome(s)
1. Differences in toxicity profile, adverse events and quality of life in bolus and infusional treatment regimens. The aim is to develop a new adjuvant treatment standard that enables cytostatics in home care, and to prevent and treat side-effects efficiently. The intention is to interfere with patients' everyday life as little as possible during the 6 months of adjuvant treatment.
2. Cost-benefit differences in bolus and infusional treatment. In preliminary calculations the continuous infusion at home should be 30% cheaper than bolus treatment in the clinics. Though continuous infusion has been considered expensive, no accurate studies verifying these assumptions have been made.
3. The relationship between nutrition, nutritional status, lactose tolerance and adverse events. Is nutrition a prognostic factor in the outcome of colorectal cancer and does the tolerance of chemo- and radiotherapy correlate with nutritional factors?
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In the study protocol primary and secondary outcome measures have not been specified.

Key secondary outcome(s))
No secondary outcome measures

Completion date
31/12/2012

Eligibility

Key inclusion criteria

1. Aged 18 to 75 years
2. Had histologically confirmed radically operated stage II-IV colorectal cancer (CRC)
3. WHO performance status 0 2 and adequate bone marrow, kidney and liver function

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Presence of other invasive cancer than CRC in history except for adequately treated carcinoma in situ of the cervix or non-melanoma skin cancer
2. Metabolic, neurological or psychiatric illness that was incompatible with chemotherapy
3. Serious thromboembolic event currently under treatment
4. Pregnancy, lactation or absence of adequate contraception in fertile patients

Date of first enrolment
07/11/1997

Date of final enrolment
31/12/2012

Locations

Countries of recruitment
Finland

Study participating centre
Helsinki University Central Hospital
Helsinki
Finland
00029

Sponsor information

Organisation
Helsinki University Central Hospital (Finland)

ROR
https://ror.org/02e8hzf44

Funder(s)

Funder type
Not defined

Funder Name
Baxter (Finland)

Funder Name
Valio Ltd (Finland)

Funder Name
Finnish Medical Association (Finland)

Funder Name
Finnish Cancer Society (Finland)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	22/10/2007		Yes	No
Other publications	post-hoc analysis	01/12/2020	17/08/2020	Yes	No
Other	Lead Time and Prognostic Role of Serum CEA, CA19-9, IL-6, CRP, and YKL-40 after Adjuvant Chemotherapy in Colorectal Cancer	02/08	09/08	Yes	No

publications		/2021	/2021		
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes