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Work in Progress

PRODIGE 34 – FFCD 1402 – ADAGE
Adjuvant chemotherapy in elderly patients with resected stage III colon cancer: A randomized phase 3 trial

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1. Rationale and aims

Colorectal cancer occurs mainly in elderly patients. Recent estimations have shown that in France more than 50% of the patients diagnosed with a colorectal cancer are 70 years old or more. Adjuvant chemotherapy has demonstrated a benefit on disease-free survival and overall survival after a stage III colon cancer resection [1]. Nevertheless, adjuvant chemotherapy is poorly used in elderly patients [2]. A post-hoc analysis of a prospective randomized trial suggested a prognostic improvement with chemotherapy, based on 5FU. However, in this study, elderly patients were highly selected and patients older than 80 years represented only 0.7% of the total population [3]. Thus, the question about the benefit of 5FU-based adjuvant chemotherapy in very elderly, unselected patients is still an issue.

The recommended adjuvant treatment for stage III is a combination of fluoropyrimidine and oxaliplatin [4]. Nevertheless, oxaliplatin treatment has not demonstrated a survival advantage in elderly patients [5].

Altogether, there are still two concerns: Firstly, is there a benefit of fluoropyrimidine-based adjuvant chemotherapy for unfit elderly patients? Secondly, is there a benefit of oxaliplatin-based adjuvant chemotherapy for fit elderly patients?

The selection of patients that should be treated remains a challenge. Geriatric evaluation [6] and tumour biology [7] are possibly helpful, therefore ancillary studies will be performed to evaluate possible geriatric and biologic prognostic factors.

The aim of this randomized phase III study is to evaluate the disease-free survival (DFS) benefit of adjuvant chemotherapy in elderly patients for the different chemotherapy regimens.

The elderly population will be dichotomized into two groups according to the physician's choice based on a multidisciplinary evaluation involving a geriatrician.

2. Study design

ADAGE is an academic, multi-centre, randomized phase III study comparing 3-year DFS of two therapeutic strategies in two groups of elderly patients with completely resected colon cancer. Patients are selected for one of the two groups by the physician, based on a multidisciplinary evaluation involving a geriatrician:

- The group 1 (arm A and B) is defined as "able" to be treated with bi-chemotherapy
- The group 2 (arm C and D) is defined as "unable" to be treated with bi-chemotherapy

In each group, patients are randomized in a 1:1 ratio and the randomization is stratified according to centre, gender, stage (IIIA *vs* IIIB *vs* IIIC), presence of occlusion and/or perforation (yes *vs* no) and IADL (normal *vs* anormal).

Arm A and D receive LV5FU2 or capecitabine (choice of the mono-chemotherapy by physician), arm B receives FOLFOX4 or XELOX (choice of the bi-chemotherapy by physician) and arm C is an observation arm.

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Patients will receive 12 cycles (1 cycle every 2 weeks) if treatment is LV5FU2 or FOLFOX4 or 8 cycles (1 cycle every 3 weeks) if treatment is capecitabine or XELOX.

The main objective is to compare 3-year disease-free survival between arm A and B (group 1) and arm C and D (group 2).

Eligible patients are over 70 years of age, with stage III colon adenocarcinoma and R0 resection of the primary tumour. Patients are considered able to receive chemotherapy. They should be naïve to chemotherapy for colon cancer. Adjuvant chemotherapy should start within 12 weeks after surgery. Geriatric questionnaires and Lee score [8] must be completed before randomization, as well as written informed consent.

Exclusion criteria include the presence of another progressive disease (cancer uncontrolled for less than 2 years), rectal cancer (located less than 15 cm from the anal verge endoscopy or subperitoneal), neutrophils <2000/mm^3 for group 1 and neutrophils <1500/mm^3 for group 2, platelets <100,000/mm^3, haemoglobin <9 g/dL, neuropathy for patients in group 1, known deficit of dihydropyrimidine dehydrogenase (DPD), severe hepatic insufficiency, any contraindication to the drugs used in the study, inability to submit to medical follow-up for geographical, social or psychological reasons.

Standard clinical and laboratory evaluation are performed within 14 days before randomization.

Radiological assessment (Thoraco-abdominal-pelvic CT scan or thoracic CT scan with MRI or abdominal ultrasound with thoracic radiography) is performed every 6 months for 3 years after randomization and then annually for 2 years. Safety is evaluated based on laboratory and clinical tests in arms A, B and D before each cycle. Geriatric assessments are performed every 3 months for 3 years after randomization and then every 6 months for 2 years.

This protocol, sponsored by the FFCD, is registered on clinicaltrials.gov with the number NCT02355379.

2.1. Trial endpoints

The primary endpoint is 3-year DFS, defined as the time between randomization and the first recurrence (distant or local) or death for any cause.

Secondary endpoints are overall survival defined as the time between randomization and death for any cause, time to recurrence defined as the time between randomization and the first recurrence (distant or local), safety with all observed toxicities graded according to NCI-CTC v4, quality of life and geriatric evaluations.

Geriatric evaluations contain co-morbidities (Charlson score), quality of life (Spitzer), physical activity (RFQ), cognitive functions (mini-COG), nutrition (G8, MNA-SF), activity of daily living and instrumental functions (ADL, IADL), depression (mini-GDS), audition, vision, and mobility (one-leg balance <5 s or falls within 6 months).

A biological ancillary study on formaldehyde fixed tissue is planned to allow prognostic evaluation of mismatch repair status and other molecular signatures.

2.2. Statistical methods

Group 1:

In group 1, hypothesis is to improve 3-year DFS from 65% (arm A) to 72% (arm B) [4]. With a one-sided α risk of 5%, and a power of 80%, 330 events will be necessary. Taking into account an assumption of inclusion duration of 60 months and a 10% loss to follow-up, a sample size of 598 patients is required.

Group 2:

Group 2 hypothesis is to extend 3-year DFS from 40% (arm C) to 55% (arm D) [1,4]. With a one-sided α risk of 5%, and a power of 80%, 134 events will be necessary. Taking into account an assumption of inclusion duration of 60 months and a 10% loss to follow-up, a sample size of 178 patients is required.

In the study, a total of 776 patients is required.

All efficacy analyses will be based on intent-to-treat (ITT), and for the primary endpoint a per-protocol analysis is also planned. The safety analysis will be performed on the ITT patients having received at least one dose of chemotherapy (mITT).

Survival analyses will be done using the Kaplan–Meier method and survival curves comparison done by log-rank test. Survival time will be described using medians and their 95% confidence intervals. Hazards ratios will be estimated by Cox model and all hypotheses linked to this method will be graphically tested.

Toxicities will be described by treatment group based on NCI-CTC grade. Dose intensity will be calculated and reported for each treatment and by treatment group.

Exploratory analysis are planned to determine geriatric prognostic factors for the primary endpoint.

Conflict of interest

None declared.

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