Feasibility and efficacy of adjuvant chemotherapy in stage II colon cancer patients with detectable circulating tumor DNA after surgery

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Background & objectives

Patients with stage II colon cancer not classified as high risk (pT4 microsatellite stable) do not receive adjuvant chemotherapy (ACT) according to Dutch guidelines. However, 15-20% of these patients experience recurrence, indicating there is an unmet clinical need to identify patients who need adjuvant treatment. Postoperative cell-free circulating tumor DNA (ctDNA) is indicative of minimal residual disease (MRD) and a strong prognostic biomarker for disease recurrence.

The MEDOCC-CrEATE trial aims to investigate 1) what proportion of stage II colon cancer patients with detectable postoperative ctDNA accept ACT; 2) whether ctDNA-guided ACT reduces 2-year recurrence rate (RR).

Methods

MEDOCC-CrEATE is an interventional 'trial within cohorts', randomizing participants of the Prospective Dutch Colorectal Cancer cohort with stage II colon cancer and no indication for ACT. Patients randomized to the intervention arm are asked informed consent for tissue-informed ctDNA testing of postoperative blood (targeted next-generation sequencing of 33 genes using the PGDx elio™ Platform). If ctDNA is detected, patients are offered 8 cycles of adjuvant capecitabine plus oxaliplatin. Patients in the intervention arm who test ctDNA-negative and patients in the control arm receive standard of care follow-up. For MRD monitoring of all patients, blood is collected every 6 months during 3 years.

The primary endpoint is the proportion of patients with detectable postoperative ctDNA willing to receive ACT. Secondary endpoints include 2-year RR, disease-free and overall survival, quality of life and cost-effectiveness of ctDNA-guided ACT. The study is powered on 2-year

RR, randomizing 660 patients to each study arm in order to treat 30 patients in the intervention arm with postoperative ctDNA (assuming 5% detectable ctDNA and 10% noncompliance).

Results

At present, 78 out of 158 patients have been randomized to the intervention arm, of whom 64 provided consent for ctDNA analysis (82%). Logistics for timely multicenter collection of tumor tissue and blood have been optimized across 24 Dutch hospitals. The average turnaround time from surgery to ctDNA result is 51 days.

Conclusion

Multicenter postoperative tumor-informed ctDNA testing for MRD is technically feasible within the clinically relevant 8-12 week window to start ACT. MEDOCC-CrEATE thereby facilitates clinical implementation of ctDNA-guided ACT, pending demonstration of clinical utility.