PLCRC-PROVENC3: assessing the prognostic value of post-surgery liquid biopsy cell-free circulating tumor DNA in stage III colon cancer patients.

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Background & objectives

Background: Surgery followed by adjuvant chemotherapy (ACT) is standard of care in stage III colon cancer. However, only 15-20% of the patients benefit from ACT. Therefore, there is a need for prognostic biomarkers to better stratify this group of patients. Circulating tumor DNA (CtDNA)-guided minimal residual disease assessment after resection of the primary tumor has shown to have a strong prognostic value in colon cancer, but studies with large well-defined patient cohorts are needed to demonstrate clinical utility and determine optimal usage.

Objective: Determine the prognostic value of ctDNA in stage III colon cancer patients treated with ACT to reduce futile treatment.

Methods

Methods: Stage III colon cancer patients treated with ACT were included in the prospective observational study “PROVENC3” (PROgnostic Value of Early Notification by Ctdna in Colon Cancer stage 3), a substudy of the Prospective Dutch Colorectal Cancer cohort (PLCRC). Using the PLCRC infrastructure, patients with colorectal cancer were accrued in 26 hospitals in the Netherlands. After informed consent, blood was collected pre-surgery, post-surgery, post-ACT and every six months up to three years. Tumor-informed detection of ctDNA was performed through integrated whole genome sequencing analyses of formalin-fixed paraffin-embedded tumor tissue DNA (80x), germline DNA (40x), and plasma cell-free DNA (30x).

Results

Results: 238 patients with a median follow-up of 38 months were included. Analytical studies demonstrated a limit of detection of the test of 0.005% ctDNA levels utilizing contrived reference models derived from six independent cell lines, with a specificity of 99.6% across 119 noncancerous donor plasma specimens. From the PROVENC3 study, ctDNA analyses are ongoing for pre-surgery (n=118), post-surgery (n=238) and post-ACT (n=219) samples. Preliminary results demonstrated a ctDNA detection rate of 93.4% pre-surgery and 17.1% post-surgery, which was associated with disease recurrence. Final analysis will enable determination of: 1) the proportion of ctDNA-positive/negative patients after surgery and the corresponding recurrence rates; 2) the prognostic value of post-surgery ctDNA; and 3) the lead time between post-surgery ctDNA detection and recurrence.

Conclusion

Conclusion: Ultimately, the results of this study will be used to model and design a ctDNA-guided interventional trial in stage III colon cancer patients, to optimize administration of ACT.