Monitoring KRAS mutations from plasma circulating free tumor DNA as non-invasive approach to evaluate pancreatic cancer dynamics

E. Rofi1, C. Vivaldi2, M. Del Re1, L. Fornaro2, E. Vasile2, A. Falcone2, R. Danesi1

1Clinical Pharmacology and Pharmacogenetic Unit, Department of Clinical and Experimental Medicine, University of Pisa
2Medical Oncology Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa

Introduction: Pancreatic cancer is a solid tumor that is still lacking of predictive biomarkers. For this reason, increasing efforts are focused to identify new and more sensitive biomarkers for assessing prognosis and monitoring patients' outcome. Increasing evidences displayed that mutant KRAS is a driving oncogene occurring in over 90% of pancreatic cancer [Eser S, *et al*., 2014]. However, the role of KRAS as predictive biomarker in pancreatic cancer has still to be clarifiyed. The detection of somatic mutations in circulating cell-free tumor DNA (cftDNA) released in plasma could represent a valid non-invasive method for the molecular characterization of the tumor, monitoring of tumor dynamics and evaluation of tumor response to therapy.
Aim: To evaluate if a longitudinal monitoring of KRAS in cftDNA can early predicts thetumorprogression.
Methods: Sixteen patients affected by advanced pancreatic cancer were enrolled in this study. Three ml of plasma were collected at baseline and before each cycle of chemotherapy with gemcitabine plus nab-paclitaxel (G-NP) or FOLFIRINOX. cftDNA was extracted from plasma with the QIAmp Circulating nucleic acid Kit (Qiagen®, Valencia, CA, USA) and analyzed by the Droplet Digital™ PCR (ddPCR, BioRad®, Hercules, CA, USA) for KRAS mutations in codon 12 (G12X) and G13D.
Results: Of 16 patients 7 were treated with FOLFIRINOX and 9 with G-NP. In the FOLFIRINOX group 5 patients progressed (PD) and 2 had a partial response (PR), while in the G-NP group 2 patients had PD, 2 had stabilization of the disease (SD) and 5 had RP. ddPCR analysis of cftDNA at baseline revealed that 14 patients (82,3%) displayed a KRAS p.G12X/G13D mutations, whereas 3 patients (17,6%) were KRAS wild-type. During patients follow-up, 6 patients (35,3%), were characterized by an increasing in KRAS p. G12X/G13D and, accordingly, they displayed a progression of disease. Of those, 4 patients were treated with FOLFIRINOX and 2 with G-NP. By contrast, 7 patients (41,2%) carrier of a KRAS p. G12X/G13D decrease, had a partial response. In the RP group 5 patients received treatment with G-NP and 2 with FOLFIRINOX. Two patients (11,8%), both treated with G-NP, in which no meaningful changes in cftDNA were observed over time showed a clinical stabilization of the disease. Only in one patient we found a decrease in KRAS p. G12X/G13D while the patient was progressing. Moreover, the analysis of KRAS mutations on cftDNA was able to anticipate the clinical response with a median of 2 months earlier compared to the standard CT-scan procedures.
Conclusion: Our preliminary results showed that cftDNA analysis of KRAS mutations could be a suitable non-invasive approach to early predict thetumorprogression and responsiveness to chemotherapy in pancreatic cancer patients.
Reference: Eser S, Schnieke A, Schneider G, Saur D. Oncogenic KRAS signalling in pancreatic cancer. Br J Cancer. 2014 Aug 26;111(5):817-22.