Promoter hypermethylation of SFRP1 as a prognostic and potentially predictive blood-based biomarker in patients with localized pancreatic ductal adenocarcinoma

Benjamin Emil Stubbe[1]
Anders Christian Larsen[1], Poul Henning Madsen[2], Henrik Bygum Krarup[2], Inge Søkilde Pedersen[2], Søren Lundbye-Christensen[3], Carsten Palnæs Hansen[4], Jane Preuss Hasselby[5], Astrid Zedlitz Johansen[6], Ole Thorlacius-Ussing[7], Julia Sidenius Johansen[6] and Stine Dam Henriksen[7]
[1] Department of Gastrointestinal Surgery, Aalborg University Hospital, Denmark
[2] Department of Molecular Diagnostics, Aalborg University Hospital, Denmark
[3] Unit of Clinical Biostatistics, Aalborg University Hospital, Aalborg, Denmark
[4] Department of Surgery, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[5] Department of Pathology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
[6] Department of Oncology, Copenhagen University Hospital – Herlev and Gentofte, Herlev, Denmark
[7] Department of Gastrointestinal Surgery, Aalborg University Hospital, Denmark

Background & objectives

Currently no reliable predictive blood-based biomarkers are available for determining survival from pancreatic adenocarcinoma (PDAC), a cancer type with very poor prognosis. Recently a study has linked a promoter hypermethylation of SFRP1 (phSFRP1) to poor prognosis in gemcitabine treated patients with stage IV PDAC. This study further explores the effects of phSFRP1 lower stage PDAC, eligible for curative treatment.

Methods

Based on a bisulfite treatment process, the promoter region of the SFRP1 gene was analyzed with methylation-specific polymerase chain reaction analysis. Kaplan-Meier curves, log-rank tests and generalized linear regression analysis were used to assess Restricted Mean Survival Time at 12 and 24 months. Adjusted regression models included SFRP1 promoter hypermethylation status, Resection status, Stage of disease, type of chemotherapy, age above 65, CA 19-9 > the median, ECOG performance status and sex.

Results

The study included 211 patients with stage I-II PDAC, of which 155 patients were R0 resected, 27 R1-resected and 29 deemed inoperable. The median overall survival (mOS) of patients with phSFRP1 (n=43) was 13.1 months, compared to 19.6 months in patients with unmethylated SFRP1 (umSFRP1). In adjusted analysis phSFRP1 was significantly associated with a loss of 1.15 months (95%CI -2.11, -0.20) and 2.71 (95%CI -2.71, -0.45) months of life at the 12- and 24-month landmark, respectively. There was no significant effect of phSFRP1 on neither disease-free nor progression-free survival.

Conclusion

Patients with stage I-II PDAC and phSFRP1 have poorer prognosis compared to patients with umSFRP1. The poor prognosis witnessed in these patients despite intensive adjuvant chemotherapy may at least partly be explained by phSFRP1. Results could indicate that patients with phSFRP1 may not benefit from adjuvant chemotherapy. SFRP1 may be a possible target for epigenetically modifying drugs and could help guide the clinician towards the optimal treatment choice.