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SPARC and treatment in pancreatic ductal adenocarcinoma: evidences and new challenge for the future

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Pancreatic ductal adenocarcinoma (PC) is the fourth most common cause of cancer deaths , and50% of patients (pts) have metastatic disease at diagnosis; another 30% have localized but unresectable primitive. Overall survival ranges between 6 and 12 months in metastatic cases, and about 11 and 16 months for those with locally advanced inoperable cancers (1). In the past three decades, the standard therapies for pancreatic cancer consisted of fluoropyrimidines like 5-fluorouracil (5-FU), and gemcitabine. In 2011, the association of Oxaliplatin, irinotecan and 5FU in FOLFIRINOX schedule, showed to improve survival (OS) to 11 months when compared with gemcitabine alone in a phase III randomized clinical trial in the first line setting (3). After failure of first line therapy, however, the options continue to be even more limited. More recently, the international phase III trial MPACT compared the combined use of *nab*-paclitaxel (Nab-p) with gemcitabine versus gemcitabine alone in pts with metastatic PC, and the study demonstrates a significant difference in median OS, the primary endpoint (8.5 months vs. 6.7 months; *P*<.001)and in median progression free survival (PFS): 5.5 months vs. 3.7 months; *P*<.001 (4) . There are currently no standard treatments beyond first line. In this setting only a randomized trial was positive with an association of oxaliplatin/5-FU/leucovorin (OFF) in pts progressing while on gemcitabine, wich improved overall survival to 4.8 months from 2.3 months versus best supportive care (5).

Pancreatic cancer is characterized by desmoplastic, fibroinflammatory and hypoperfused stroma, often blamed for its overall chemoresistance. Moreover, there is evidence to suggest that the stroma constitutes a dynamic compartment of PC that is involved in tumour formation, progression and metastasis. The development of agents capable of targeting both the tumour and stroma has become an area of intense research, with a lot of agents that are being studied, including SHH inhibitors, agonist CD40 antibodies, PDGF receptor (PDGFR) inhibitors, hyaluronidase and SPARC(secreted protein acidic and rich in cysteine / osteonectin) -mediated cytotoxic agent Multimodal therapies that target both tumor cells and stroma, blocking their interaction and stimulating immunity represent a promising approach in PC (6-10).

SPARC is a member of the family of matricellular glycoproteins that is highly expressed in PC and the tumour/stroma interface, and its role in tumourigenesis remains unclear, but evidences suggest that it plays a role in the regulation of adhesion, proliferation, survival and migration. It has therefore been proposed that SPARC functions as an extracellular scaffolding protein that intervents in propagation of cellular events of some cellular signalling pathways (11). SPARC has been shown to bind ECM proteins such as collagen and influence the activation of metalloproteinases, and interacts with or indirectly regulates several growth factors, including FGF, VEGF, PDGF and TGF-b (12,13).

Clinical data indicate that approximately 80% of PC express SPARC and that expression in the stroma, but not in the tumour, is associated with a poor prognosis (14, 15). SPARC demonstrates an high affinity

for albumin, and co-localization of SPARC and albumin within tumour cells has been demonstrated in the MX1 tumour mouse model (16). Preclinical studies suggest evidence regarding the potential role of SPARC in transporting albumin from the ECM into cancer cells, but this hypothesis is worthy of further exploration(17, 18).

Nab-paclitaxel, a water-soluble albumin-bound formulation of paclitaxel, could disrupt the PC stromal architecture in tumor xenografts and induce reactive angiogenesis, resulting in increased perfusion and delivery of gemcitabine. The mechanism of delivery of Nab-p is mediated by active transport of albumin via gp60-mediated transcytosis, or by SPARC that is highly expressed and secreted by peritumoral fibroblasts and may serve as an albumin-binding protein (11). Given that PDA is a stromal-rich tumor with abundant SPARC expression, in a series of clinical trials investigators are evaluating the combination of Nab-p and gemcitabine in patients with advanced PC. An exploratory analyses of Phase I/II study by Von Hoff et al, that evaluated Nab-p plus gemcitabine in metastatic PC, high SPARC expression was associated with a significantly longer OS vs. low SPARC expression (median 17.8 vs. 8.1 months; p=0.0431 [n=36]). Furthermore, SPARC remained a significant predictor for OS after adjusting for clinical covariates (age, sex, race, baseline CA19-9) (p=0.041), and stromal SPARC, but not SPARC in tumour cells, was significantly correlated with OS (p=0.013 and p=0.15, respectively) (19).

SPARC may have utility as a predictive biomarker in the future. However, further prospectical evaluations are required before SPARC will be considerate a predictive factor of response to Nab-p in PC.

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