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Editorial

Genetic Therapy for Pancreatic Cancer: Is it the Future?

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Although surgery is still the only curative therapy for pancreatic cancer, oncological therapies have started to be more and more promising.

We firstly have to consider two important points. The first one is that surgery for pancreatic cancer is complex and risky: perioperative mortality is 4-18% and major complications occur in more than 40% of cases.[1] Moreover, only 15-20% of patients have a resectable tumour at the first diagnosis.[2] Furthermore, disease's recurrence following operation is very high because of local invasion and micrometastases at the time of surgery.[3] The second point is that the first chemotherapies for pancreatic cancer (5-fluoro-uracile, and the actually used, gemcitabine) are not specific for pancreatic tumours and have been provided only a little impact on overall survive.[4]

The actually used chemotherapies are gemcitabine, the association of gemcitabine and nab-paclitaxel (that improved overall survival, progression free survival and response rate compared to gemcitabine alone) and the recent FOLFIRINOX (oxaliplatin, irinotecan, leucovorin) that have been shown to be more efficient than gemcitabine.[5]

To obtain more efficient chemotherapies, we have to comprehend the molecular biology of pancreatic cancer.

Recent articles have shown the principal gene mutations in pancreatic tumoural cells. The earlier events involve telomere shortening, KRAS (Kirsten rat sarcoma viral oncogene homolog) mutation and p16 loss; the later ones are mainly P53 loss, SMAD4 (SMAD family member 4) loss and BRCA2 (breast cancer 2) mutations.[3]

Pancreatic cancer also overexpress multiple mitogenetic growth factors and their ligands i.e. epidermal growth factor receptor (EGFR).[6]

Other studies have underlined the importance of the developmental program of epithelial to mesenchymal transition (EMT) especially for metastatisation. This process is regulated by inducing transcription factors as TGF-beta, Wnt/beta-catenin, Notch signaling, Snail transcription factors, zinc-finger-enhancer binding (Zeb) protein family and basic helix loop helix (bHLH) transcription factors.[7]

Recently, the role of cancer stem cells has been found to be responsible for tumour recurrence and metastases. Notch, Hedgehog and Wnt/beta-catenin signaling pathways have a role in maintaining stem cells' line in pancreatic cancer.[8,9]

All these new knowledges have extended the scientific research about therapies that can specifically interrupt the tumoural development.

Thus, K-ras has been choosen as an important target trying to block K-ras membrane localization (i.e. Deltarisin) or SOS/K-ras interaction or K-ras downstream effector targets (i.e. sulfinyl cytidine).[10]

Another considered target is HDAC (histone deacetylase). It is involved in Snail mediated epidermal to mesenchymal process. Many histone deacetylase inhibitors have been tested in preclinical and early clinical studies.[11]

Targeting cancer stem cells is being considered and this is the recent therapeutical concept.[12] Hedgehog inhibitors are under preclinical and clinical development. Notch inhibitors seem to be more effective than gemcitabine and monoclonal antibodies that has been studied.[12]

In conclusion, pancreatic cancer biology is better understood than 10 years ago. This is the first step to develop a specific genetic therapy. Surgery is still the only curative therapy but it has many important limitations. Therefore, it cannot be considered the

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future definitive therapy. However, there are no effective therapies available because the multifactoral nature of the tumour i.e. we will have to consider the different types of pancreatic cancer on the base of different gene mutations and we may finally find a curative therapy.

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