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HIGHLIGHT ARTICLE

Pharmacogenetics and Other Molecular Targets in the Management of Pancreatic Adenocarcinoma

Highlights from the "2010 ASCO Annual Meeting". Chicago, IL, USA. *June 4-8, 2010*

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Summary

Among various abstracts presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO) held in Chicago, June 2010, four interesting abstracts focusing on pancreatic cancer merit further discussion in this post-ASCO commentary as they potentially provide insight to clinicians and hope to patients. These abstracts point to the future of pancreatic cancer management through identification of molecular targets and prognostic factors to overcome the limits of efficacious chemotherapy delivery.

What We Knew before ASCO 2010

Pancreatic cancer remains the most lethal, aggressive abdominal malignancy, frequently presenting at the metastatic stage. This renders treatment extremely difficult, leading to poor prognosis and five-year survival of 15% for early stage disease and life expectancy of 6-11 months for locally advanced disease [1]. The main challenges in the treatment of locally advanced pancreatic adenocarcinoma are understanding pancreatic tumour behaviour and microenvironment, overcoming the limits of delivery and efficacy of chemotherapy and identifying biomarkers for prediction of outcome success.

What We Learnt at ASC0 2010

Pancreatic Microenvironment

It is well recognised that the pervasive growth of dense, collagen-rich, fibrous tissue around pancreatic tumours, known as the desmoplastic reaction, forms a barrier to chemotherapy penetration and hence efficacy.

Key words BRAF protein, human; epidermal growth factor receptor-neu receptor; KRAS protein, human; Pancreatic Neoplasms; Pharmacogenetics; Polymorphism, Single Nucleotide

Abbreviations ASCO: American Society of Clinical Oncology; MMP: matrix metalloproteinase; MT1-MMP: membrane type 1-matrix metalloproteinase

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Many matrix metalloproteinases (MMPs) have been associated with the extent of the desmoplastic reaction as well as enhanced adhesion and invasion of pancreatic tumours [2, 3]. Protein membrane type 1-matrix metalloproteinase (MT1-MMP) is over-expressed in colorectal [4] and lung tumour cells [5] and serves as a key protein for tumour growth and invasiveness. MT1-MMP appears to activate MMP-2, which has a catalytic function in the basement membrane degradation (Figure 1), leading to increased pancreatic cancer cell inva-

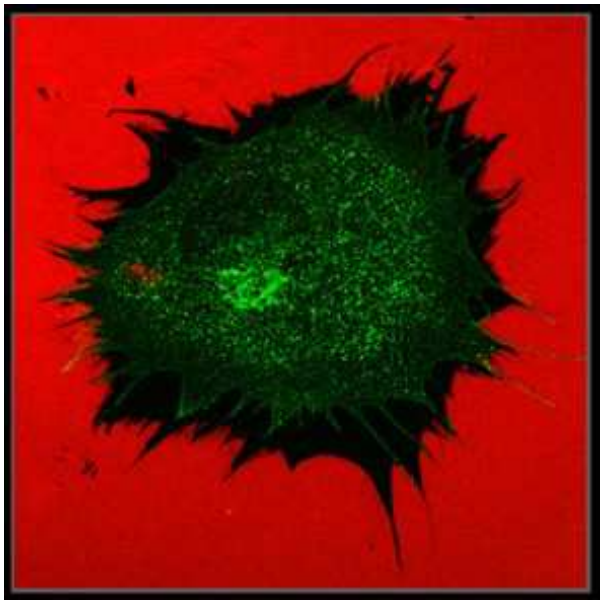

Figure 1. Matrix degradation by MT1-MMP (with permission of Yoshifumi Itoh Lab Imperial College. London, UK).

siveness but their expression is also directly linked with the extent of the desmoplastic reaction in pancreatic cancer tissue [6].
New evidence in the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting shows that these MMPs may also be implicated in the tumour microenvironment and pose an obstacle to treatment penetration to the tumour. Krantz *et al* (Abstract #4158) demonstrated that MT1-MMP over-expression in transgenic mice led to an increase not only of precancerous lesions and metaplasia but also in tumour invasiveness [7]. They also showed that MT1-MMP is linked to more peripancreatic tumour fibrosis.
This study comes to support our knowledge of the role of MMPs in tumour progression and the desmoplastic reaction. MMPs seem to play multiple roles in tumour progression and further investigation has the potential of serving as a molecular target for treatment delivery.

Molecular Targets and Pancreatic Cancer

One of the most interesting studies presented at ASCO Annual Meeting in relation to pancreatic cancer, showed an association between certain *KRAS* mutations and reduction in overall survival in pancreatic cancer patients after surgery. Recent research, as seen in the CRYSTAL [8], OPUS [9] and CAIRO 2 [10] trials, suggests that genetic polymorphisms can be used to predict treatment outcome, such as *KRAS* and *BRAF* mutations in colorectal cancer and response to monoclonal antibodies against EGFR, such as cetuximab or panitumumab. Certain mutations in particular serve as negative predictive factors for therapy success, as expressed in the provisional clinical opinion in the ASCO 2009 Gastrointestinal Meeting [11]. The *KRAS*/*BRAF* pathway has also been shown to play a key role in the development of pancreatic ductal adenocarcinoma [12]. The investigators from Denmark looked at the presence of *KRAS*, *BRAF* and *HER2* mutations in patients operated for pancreatic adenocarcinoma and their link to overall survival (Abstract #4043 [13]). Certain variations in the *KRAS* genotype could be correlated with a poorer overall survival (hazard ratio, HR: 1.48; 95% CI: 1.07-2.05; P=0.02). In fact the HR for overall survival was 1.79 in patients who had certain *KRAS* mutations compared to patients with normal variations of *KRAS*. The majority of mutations occurred in codons 12 and 13, as in colorectal cancer patients.
Whether this gene analysis will lead to better future treatment outcomes by targeting EGFR in the subgroup of patients with these mutations remains to be seen. Analysis of a single gene is unlikely to be fully informative of the exact pharmacogenetic mechanism. However, the results suggest it is worth pursuing the route of analysis and genotyping of specific oncogenes present in pancreatic cancer patients, which can subsequently serve as molecular targets for successful treatment. Needless to say this will be true for other cancers, such as breast and gastric. The *KRAS*/*BRAF* pathway has potential to serve as predictive factor for anti-EGFR therapy in various gastrointestinal tumours.

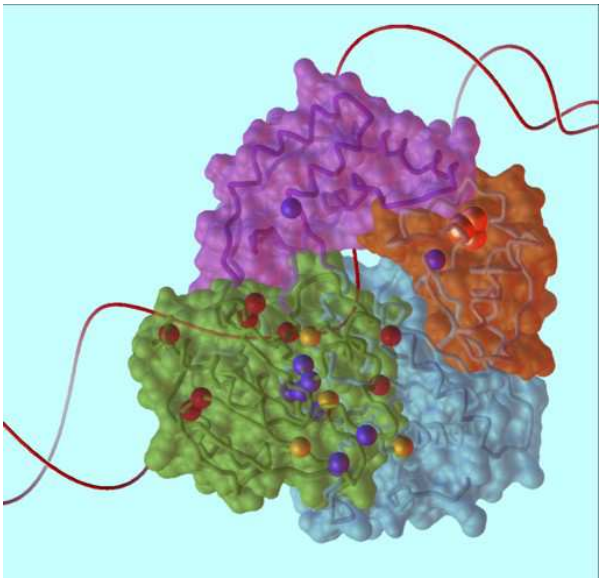

Figure 2. XPD protein (with permission of Department of Energy Lawrence Berkeley National Laboratory, CA, USA).

Pharmacogenetics

Two papers look into the prognostic significance between gene polymorphisms and treatment success. One of the main challenges in the treatment of pancreatic cancer patients is overcoming resistance to chemotherapeutic agents. Traditional and even newer pharmaceutical therapeutic regimens are limited in terms of tolerance, efficacy and cross-resistance. Resistance is multifaceted and stems from both tumour immunosuppressive mechanisms as well as genetic polymorphisms.
Various genes have been characterised that contribute to tumour cell protection against immune defence mechanisms, such as the *xCT* gene, which codes for part of the plasma membrane cysteine/glutamate transporter [14]. This balance is critical for protection of tumour cells against the immune system [15].
In the first paper Huang *et al*. (Abstract #4065 [16]), looked at the prognostic significance of single nucleotide polymorphisms in the *xCT* gene in patients with advance pancreatic cancer treated with gemcitabine and platinum. They identified specific polymorphisms that correlated with better overall survival in patients receiving treatment, with maximum median survival time of 13.6 months for specific genotypes alone and even higher at 14.1 months in patients receiving the combination treatment.
In the second paper Pacetti *et al* (Abstract #4098 [17]) exploited polymorphisms in genes involved in activity and resistance to drugs, mainly DNA repair gene polymorphisms, in an effort to link them to treatment response. The substitution of Gln for Lys in position 751 of the *XPD* gene (Figure 2) led to increased overall survival from 262 days (95% CI: 202-423 days) to 446 (95% CI: 346-446 days).
Both papers suggest that genetic variants in genes like *xCT* have the potential to serve as predictors of treat-

ment outcome and to the development of personalised chemotherapeutic therapy.

Conclusion

The 2010 ASCO Annual Meeting in relation to pancreatic cancer focuses towards the emerging field of identification of molecular biomarkers and molecular profiling in treatment selection and highlights the challenges this emerging field presents. These advances in genomic, transcriptomic and proteomic technologies have led to a step towards materialisation of the concept of personalised medicine. There is still a significant gap between literature and routine clinical practice, which needs to start bridging.

Conflict of interest The authors have no potential conflicts of interest

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