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PUSHING BOUNDARIES IN CANCER THERAPY

Tackling liver and pancreatic cancer from many angles is advancing treatment options for these devastating conditions.

Committed researchers at Tianjin Medical University Cancer Institute and Hospital (TMUCIH) are driving varied and innovative studies for liver and pancreatic cancer to improve survival rates and quality of life.

According to cancer statisticians GLOBOCAN 2020, more than 45% of new liver cancer cases and related deaths occur in China. TMUCIH's Wei Lu says that, worryingly, up to 80% of liver cancer cases in China are already in the mid or late stage when diagnosed. "The five-year survival rate of liver cancer in mainland China is only around 14%."

Jihui Hao, president of TMUCIH and director of its Department of Pancreatic Tumour, paints a similar picture for pancreatic cancer: "The incidence of pancreatic cancer is increasing. There is a lack of early diagnosis, a low radical resection rate, and poor prognosis."

In response to this, the hospital has dedicated ever greater efforts and resources towards basic research on these two types of cancer to improve treatment.

A multidisciplinary approach to liver cancer

"TMUCIH's liver department is a multidisciplinary team, including experts in chemotherapy, surgery, and radiotherapy, for example, so that we can devise the best treatment plan," says Lu.

While having a multidisciplinary team provides more holistic treatments for patients, Lu notes that disagreements often arise during the treatment decision-making process, due to a lack of evidence-based studies evaluating different therapies on several parameters.

To provide a guide for clinicians and patients on which treatment benefits different individuals, he led a study that evaluated three therapies for 283 patients in China with hepatocellular carcinoma (HCC), the most common primary liver cancer in adults, that fell within the Milan Criteria, a set of standards to be applied for patients for liver transplantation. The three treatment options were transplantation, liver resection (the surgical removal of a portion of the liver), and local ablation, a series of techniques that destroy liver tumours without removing them.

The retrospective study explored an individualized assessment prediction model, which predicts the survival and recurrence rates of HCC, with respect to the three therapies, by looking at variables such as tumour number, tumour size, and aetiology.

In an article published in *Gut*, the study noted that the prediction model showed feasibility as an individualized assessment of therapeutic alternatives to assist with multidisciplinary team decision-making for HCC patients.

Lu adds that in collaboration with the University of Pittsburgh, the model was also tested and verified with good results in around 300 HCC cases provided by the US university.

"If we can make decisions on treatment for these liver cancer patients in an individualized and tailored way, recurrence rates can go down, while survival rates and quality of life can be improved," he says.

A collaboration between the Liver Cancer Placement Research Center at TMUCIH, and Peking University, published a study in *Gastroenterology* in 2016 that showed the extent of intra-tumour heterogeneity varies considerably among patients with HCC. Increasing numbers of studies show that tumour heterogeneity reflecting complex tumour clonal architecture has profound implications in tumour characterization, therapy management, and drug resistance.

In another paper by this collaboration, published in *Cancer Cell* in 2019, the team performed genomic and transcriptomic sequencing in a rare subtype of liver cancer, called combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma (cHCC-ICC). Integrative comparison of cHCC-ICC with hepatocellular carcinoma and intrahepatic cholangiocarcinoma revealed that combined and mixed type cHCC-ICCs are distinct subtypes with different clinical and molecular features. Using laser microdissection, cancer cell fraction analysis, and single nucleus sequencing, they revealed both mono- and multiclonal origins in the separate types of cHCC-ICC, whereas combined and mixed type cHCC-ICCs were all of monoclonal origin.

Exploring new treatment regimens for pancreatic cancer

TMUCIH has also been making advances in pancreatic cancer research, including its work on pancreatic ductal adenocarcinoma (PDAC), a highly immune-suppressive tumour that is also very aggressive.

Despite anti-PD1 therapy emerging as a promising immunotherapy in recent years, Hao notes several factors resulting in the resistance to this regimen, including the hyper infiltration of regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSC), which are both immune suppressive.

To study how to improve the efficacy of anti-PD1 therapy for PDAC patients, he and his colleagues conducted a trial in mice and published their findings in the *Journal of Experimental Medicine*. "We identified ETS homologous factor (EHF) deficiency as the primary molecular event that triggered the accumulation of regulatory Treg cells and MDSC in PDAC," says Hao. EHF is a human protein that suppresses tumour development in PDAC.

They also found that mice with PDAC tumours that had EHF-overexpressed responded significantly better to anti-PD1 treatment than those with control tumours.

The researchers note that EHF overexpression may improve PDAC checkpoint immunotherapy. "For a tumour with EHF deficiency, a combined regimen of Treg cell plus MDSC depletion and anti-PD1 therapy could be considered," Hao says.

He says one of the challenges of tackling pancreatic cancer is its genetic heterogeneity, which results in significant differences between patients in the disease progression, clinical curative effect, and prognosis.

"Revealing pancreatic cancer's molecular characteristics and its correlation with clinical manifestation, sensitivity to radiation and chemotherapy, corresponding targeted drugs research and development, is the key step to move from histological classification to molecular classification," says Hao.

"In the age of molecular targeting, the treatment of pancreatic cancer will be transformed by comprehensive diagnosis, which will be a breakthrough," he adds.

Such an approach includes studies like the one on EHF. Hao says that TMUCIH remains committed to such a direction and will continue with innovative research on areas including the microenvironment regulation of pancreatic cancer and molecular mechanism of immunotherapy. ■

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