An Assortment of Journal Abstracts to Enhance Oncology Care

PANCREATIC CANCER

BL-8040, a CXCR4 Antagonist, in Combination With Pembrolizumab and Chemotherapy for Pancreatic Cancer: the COMBAT trial

A new study lead by an international team of researchers showed how pancreatic cancer patients can benefit from immunotherapy (*Nat Med* 2020; https://doi.org/10.1038/s41591-020-0880-x). In the COMBAT trial (NCT02826486), a prospective, open-label, phase IIa clinical trial for patients with metastatic pancreatic cancer, patients were given pembrolizumab, an immune therapy drug, in combination with BL-8040, an agent that makes the tumor microenvironment more receptive to immune therapy. The study was conducted in Arizona at the HonorHealth Research Institute and at 30 other locations in the U.S. and across the globe, including Spain, Israel, and South Korea. The two-part clinical trial began in September 2016: Cohort 1, a group of 37 patients whose cancer had already progressed on other therapies, were treated with pembrolizumab and BL-8040. Importantly, it appeared this combination therapy made pancreatic cancer more "hot," meaning it could work in tandem with the body's own immune system. Previous studies have shown pancreatic tumors to be "cold," meaning immune therapies like pembrolizumab were not able to act on the cancer. Preliminary results of Cohort 2 were reported in the manuscript on a group of 22 patients (out of approximately 40 patients in total expected in the cohort), who had previously received one line of chemotherapy. These patients received pembrolizumab and BL-8040, as well as chemotherapy drugs 5-fluorouracil and nanoliposomal irinotecan. This clinical trial is currently in a follow-up phase of the study. Next steps for this research would be to compare this COMBAT combination therapy in future studies to other treatment options, such 5-fluorouracil, leucovorin, and nanoliposomal irinotecan.

MALIGNANT MELANOMA

Fluorescence Biomarkers of Malignant Melanoma Detectable in Urine

Researchers have identified fluorescent molecules in urine that may allow patients with malignant melanoma to provide a urine sample rather than undergo a painful surgical procedure to find out if the cancer is responding to treatment (*Open Chem* 2020; https://doi.org/10.1515/chem-2020-0143). At present, malignant melanoma patients require invasive biopsies to diagnose and track the progression of their cancer. Using this new approach, doctors could ask patients to provide a urine sample instead, and then fluorescent molecules in the sample could reveal disease progression rapidly and inexpensively. The study describes a group of fluorescent molecules—easily detectable in urine—which correlate with melanoma progression, creating new possibilities for monitoring the disease. The researchers focused on specific fluorescent molecules that cancer cells produce during metabolic processes involved in their growth and progression, and which end up in urine. The researchers then analyzed urine samples from patients with malignant melanoma and healthy controls using fluorescence spectroscopy, a simple and inexpensive detection method, to see if there were any differences in levels of the fluorescent markers. They also performed genetic analysis for the same patients to examine genes involved in melanoma progression. The urine samples from the malignant melanoma patients contained different levels of the metabolism-linked fluorescent markers compared with those from healthy controls. Strikingly, the levels of the fluorescent molecules in the urine correlated with the stage of melanoma and the expression of genes that are linked to melanoma progression, suggesting that the molecules have significant potential as biomarkers.

Serine Restriction Alters Sphingolipid Diversity to Constrain Tumour Growth

The enzyme serine palmitoyltransferase can be used as a metabolically responsive "switch" that decreases tumor growth, according to a new study (*Nature* 2020; https://doi.org/10.1038/s41586-020-2609-x). By restricting the dietary amino acids serine and glycine, or pharmacologically targeting the serine synthesis enzyme phosphoglycerate dehydrogenase, the team induced tumor cells to produce a toxic lipid that slows cancer progression in mice. Further research is needed to determine how this approach might be translated to patients. The enzyme serine palmitoyltransferase, or SPT, typically uses serine to make fatty molecules called sphingolipids, which are essential for cell function. But if serine levels are low, the enzyme can act "promiscuously" and use a different amino acid such as alanine, which results in the production of toxic deoxysphingolipids. The team decided on this research direction after examining the affinity that certain enzymes have for serine and comparing them to the concentration of serine in tumors. These levels are known as Km or the Michaelis constant, and the numbers pointed to SPT and sphingolipids. These toxic deoxysphingolipids are most potent at decreasing the growth of cells in "anchorage-independent" conditions—a situation where cells cannot easily adhere to surfaces that better mimics tumor growth in the body. Further studies are necessary to better understand the mechanisms through which deoxysphingolipids are toxic to cancer cells and what effects they have on the nervous system. The research team fed a diet low on serine and glycine to xenograft model mice. They observed that SPT turned to alanine to produce toxic deoxysphingolipids instead of normal sphingolipids. In addition, researchers used the amino acid-based antibiotic myriocin to inhibit SPT and deoxysphingolipid synthesis in mice fed low serine and glycine diets and found that tumor growth was improved.

SOLID TUMORS

HORMONE THERAPY

Factors Associated With Counseling and Postoperative Hormone Therapy Use in Surgically Menopausal Women

Removal of the ovaries before natural menopause often exacerbates menopause symptoms and places women at increased risk for heart disease, osteoporosis, and cognitive decline. A new study identified the frequency of hormone therapy (HT) use and factors that determine who is more likely to use hormones after oophorectomy to manage symptoms (*Menopause* 2020; doi: 10.1097/GME.0000000000001560) Women who carry the high-risk BRCA gene may be likely to develop ovarian cancer. As a result, these women often undergo an oophorectomy to mitigate the risk. However, the preventive removal of the ovaries before a woman reaches natural menopause typically creates added problems, including severe hot flashes, sleep disturbances, mood changes, vaginal dryness, and decreased libido, in addition to potential long-term adverse effects on health. Hormone therapy has proven to be one of the most effective means for managing these symptoms and reducing long-term risks, but its use is somewhat limited because of concerns in this population of an increased risk of breast cancer, which was shown in women with a uterus who used a combination of estrogen plus a progestin in the Women's Health Initiative trials. The new study involved nearly 800 premenopausal women who underwent a preventive oophorectomy as a result of carrying the BRCA gene sought to understand how often women use HT after surgery and what factors most influence their decision to do so. Researchers found that 61 percent of study participants used HT after their oophorectomies. The clinical and demographic factors that most influenced their decision were age, education, and surgical history. In particular, women who were younger at the time of surgery, who had a higher level of education, and who had also undergone a preventive mastectomy were more likely to use HT for the management of their menopause symptoms. The researchers hope that by understanding the factors that influence women's decisions regarding therapy options, health care providers may be better positioned to address barriers to HT use and help improve women's overall quality of life after surgery. OT