Chemoprevention and Treatment of Pancreatic Cancer

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Editorial

Pancreatic cancer (PC) is the fourth leading cause of cancer death, with a median survival of 6 months and a dismal 5-year survival rate of 3-5%, and this figure has remained relatively unchanged over the past 25 years. Even for those patients diagnosed with local disease, the 5-year survival rate is only 15%. Thus, PC is one of the most difficult diseases to treat due to late initial diagnosis and to resistance to the usual treatments [1]. The presence of occult or clinical metastases at the time of diagnosis, together with the lack of effective chemotherapies, contributes to the high mortality in patients with PC. Its lethal nature stems from its propensity to disseminate rapidly to the lymphatic system and distant organs. Moreover, PC is one of the most intrinsically drug-resistant tumors and the cancer cell resistance to chemotherapeutic agents is a major cause of its treatment failure. Gemcitabine (a nucleoside-based compound) is the standard chemotherapeutic drug for patients with an advanced illness state after a phase III trial in 1997. This trial demonstrated a modest survival advantage of this agent over 5-fluorouracil (median survival 5.65 vs. 4.41 months, respectively), but surprisingly this treatment improved alleviation of disease-related effects. Known risk factors for the disease include cigarette smoking, chronic and hereditary pancreatitis, late onset diabetes mellitus, and familial cancer syndromes. However, it has been estimated that more than two-thirds of human cancers, and among them PC, could be prevented by modi c

are linked to meat, red meat in particular and large intakes of high-energy food. Protection is mainly provided by fruit, vegetables, and vitamins. In recent years, more dietary compounds have been recognized as cancer chemopreventive agents because of their anticarcinogenic activity; therefore, early invasion and metastasis of PC could be preventable by these dietary compounds. For instance, the ingest of curcumin, found in a plant widely cultivated in tropical regions of Asia and Central America, and known by its pronounced anti-inflammatory, antioxidative, immunomodulating, antiatherogenic, and anticarcinogenic activities, modulates, among other proteins, the activity of NF-κB through inhibition of IKK activity in PC cells, and it further alters the expression of miRNAs in PC cells. Moreover, the dietary addition of genistein, a soy isoflavone found in soybeans and in most soy-protein products, inhibited NF-κB DNA-binding activity, the Akt activity, and significantly down-regulated Notch signaling, leading to the inhibition of NF-κB and induction of apoptosis in PC cells [3]. The intake of indole-3-carbinol, green tea catechins, lycopenes, and resveratrol (all of them present in several plants) has also been shown to be valuable in the prevention of PC. It is interesting to note that the experimental results with soy isoflavones, indole-3-carbinol, curcumin, and resveratrol appear to target similar signaling pathways, all of which are known to be involved in the development and progression of PC and, therefore, they are important targets for its prevention and/or treatment. However, it is important to keep in mind that primary prevention of PC is not feasible due to lack of identifiable risk factors. Notwithstanding this fact, existing knowledge provides sufficient information as to the novel application of several dietary or

carried out not only by small molecules, able to bind to selected regions of the target protein, but also by using large molecules as ABs.

is is the topic described by Chames and coworkers [5]. e VEGF (vascular endothelial growth factor) protein, which is involved in angiogenesis during tumor growth and dissemination, is one of the rst examples where an AB (called bevacizumab) has been designed to hamper binding to its receptor (VEGFR). EGFR is the other example described by Chames and colleagues. Cetuximab, a monoclonal AB that targets EGFR, binds to EGFR competitively with high a nity, preventing activation of EGFR by its ligands. By binding to EGFR, cetuximab inhibits cell proliferation, enhances apoptosis, and reduces angiogenesis and invasion. Cetuximab is currently under investigation in PC; the combination of cetuximab and gemcitabine showed promising activity against an advanced illness and improved survival in animal study, but it was ine ective in a phase III trial in patients with locally advanced and metastatic PC. No objective responses were seen in phase II trials of cetuximab in combination with gemcitabine and intensity-modulated radiotherapy. Trastuzumab, an anti-HER-2/neu