Cancer of the pancreas is the fourth leading cause of cancer death in the United States. Of the 28,000 patients diagnosed each year, more than 95% will die of pancreatic cancer. Therefore, the focus of therapy for most patients is palliative care. In fact, the most active single-agent therapy for advanced disease—gemcitabine (Gemzar)—was first compared to fluorouracil (5-FU) with relief of disease symptoms as a primary end point. However, the survival with gemcitabine remains approximately 6 months for advanced disease, and no new agent, either alone or in combination, has exceeded this time frame in phase III study.

Octreotide (Sandostatin) is a synthetic analog of the hormone somatostatin. In vitro, it appears to inhibit cellular proliferation, largely mediated through somatostatin receptors (types 2 and 5).[1] Data with MIA PaCa-2 and other pancreatic cancer cell lines or human tumors suggest that there is an antiproliferative effect mediated by octreotide in tumors that express the type 2 receptor.[2,3] The exact mechanism for this antiproliferative effect is not known, but octreotide has been shown to decrease lipid peroxidation, and inhibition of tumor growth by octreotide is accompanied by increased glutathione reductase and superoxide dismutase activity.[4] Octreotide has been shown in the laboratory to inhibit insulin-like growth factor I, epidermal growth factor, and transforming growth factor-beta. In addition, administration of octreotide appears to decrease vascular endothelial growth factor (VEGF) levels, which may lead to inhibition of angiogenesis.

The above in vitro studies provided the rationale for assessing the efficacy of octreotide in clinical trials. One of the most pivotal trials of octreotide in pancreatic cancer was a randomized trial of low-dose short-acting octreotide vs best supportive care. In that trial, although no responses were seen, there were some patients with stable disease, and survival was improved for the octreotide arm. Unfortunately, a subsequent trial comparing 5-FU vs 5-FU plus leucovorin vs octreotide was closed early due to a lack of efficacy in the octreotide arm. Patients were treated with reasonable doses of short-acting octreotide at 200 to 500 mg tid. Other phase II trials adminstering doses of octreotide as high as 2,000 mg have shown limited activity in pancreatic cancer with median survival times of 4 to 6 months.[5-7] Thus, the single-agent trials suggest that octreotide may have some limited efficacy against pancreatic cancer, but this is inferior to 5-FU-based chemotherapy.

Octreotide may have additive or synergistic effects when given with chemotherapeutic agents. In AR24] pancreatic cancer cell lines, octreotide appears to have synergy with paclitaxel, doxorubicin, and mitomycin (Mutamycin), and additive effects when combined with 5-FU.[8] Gemcitabine, the standard agent for treatment of pancreatic cancer, was not assessed. However, a clinical trial combining gemcitabine with octreotide LAR depot is under way.

Finally, several other hormonal agents have also been tested in pancreatic cancer. Preclinical models suggest that luteinizing hormone-releasing hormone (LHRH) agonists may inhibit growth of pancreatic cancers. In the Syrian golden hamster (BOP-induced) model for pancreatic cancer, the combination of octreotide and RC-160 (an LHRH agonist) resulted in at least additive growth inhibition.[9] Phase II trials with a variety of agents have resulted in median survival times of 4 to 6 months.[10,11]
Thus far, octreotide has shown limited efficacy in patients with pancreatic cancer. While results of the phase II trial of gemcitabine plus octreotide are still pending, none of the prior regimens produced results warranting further investigation. Unless octreotide has relevant interactions with newer biologic agents, further investigation of this agent in pancreatic cancer patients should probably focus on symptom management.

References:

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[1] http://www.diagnosticimaging.com/review-article