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Could Gemcitabine Change the Suffering of Pancreatic Cancer Patients?:- Varidation of this Decade and Expectation of Next Decade

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The prognosis for pancreatic cancer remains poor [1], with surgery being considered the only curative therapy. However, the 5-year survival rate after resection of pancreatic cancer is still very low, even when radical surgery is performed [2,3]. The cause of death in patients with advanced pancreatic cancer is primarily the local progression of cancer and distant metastasis. Pancreatic cancer is most commonly found at a locally advanced state at diagnosis, and often accompanied by distant metastases to the liver and peritoneum [2]. In fact, liver metastasis is one of the major causes of cancer death after resection of pancreatic cancer. Foster reported that 73% of the patients who died of pancreatic cancer were found to have liver metastases at autopsy [3]. Most advanced cases are unresectable, and even among the resectable cases, the rate of early recurrence is high [1]. In patients with distant metastases, median survival is about 2 months. To resolve the issues of unresectability and postoperative recurrence in pancreatic cancer, and to improve its prognosis, multidisciplinary treatments such as chemotherapy, intra-arterial injection therapy, and radiation therapy must be adopted.

Gemcitabine [Gemzar: Eli Lilly Co Ltd., Tokyo, Japan] is a promising new agent that has been studied for palliation of advanced [stage IV] unresectable pancreatic cancer. Treatment of pancreatic cancer with Gemcitabine showed a response rate comparable to 5-FU, but with an improved clinical benefit [4]. As reported by Burris et al. [5], chemotherapy for advanced pancreatic cancer now involves gemcitabine instead of 5-fluorouracil [5-FU]. So, comparing 5-fluorauracil [5-FU] and gemcitabine, the standard treatment in the chemotherapy of advanced pancreatic cancer has changed from 5-FU to gemcitabine.

Gemcitabine is a promising agent that improves the survival of patients with unresectable pancreas cancer, and now is a standard first-line agent for such patients [4,6]. It is a nucleoside analogue with broad-spectrum of antitumor activity. The major mechanism of action of gemcitabine is the inhibition of DNA synthesis.

The primary endpoint of trial was the improvement in the clinical benefit response [CBR] score defined by performance status, weight gain, and pain control. However, the response rates have been highly variable, and are often irreproducible. To improve this low response rate, various treatments have been applied; however, no major solution currently exists.

Moreover, the action of gemcitabine seems to be synergetic with 5-FU. Both gemcitabine and 5-FU have shown well-recognized antitumor activity against pancreatic cancer, and in *in vitro* assays showed synergistic activity [7].

Gemcitabine is clinically more beneficial in more patients than other chemotherapeutic agents such as 5-FU, but its efficacy are still insufficient even when combined with other agents.

Since then various dosages, administration periods, and routes of administration have been devised in order to improve the prognosis of pancreatic cancer.

Intra-arterial injection chemotherapy is thought to provide a high antitumor effect by delivering anticancer drugs at high concentrations, directly into the blood vessels feeding the cancer. Compared to the various data hitherto reported for pancreatic cancer, our intra-arterial injection chemotherapy has proven beneficial for extending patient survival time and improving quality of life [8]. For this reason, intra-arterial injection chemotherapy seems promising in the treatment of pancreatic cancer [9]. Furthermore, systemic chemotherapy may not be effective because the sparse vascularity of pancreatic cancer may not allow for adequate drug accumulation in tumor tissues. The ineffectiveness of systemic chemotherapy is probably due to the failure of drug to reach the necessary concentration within the tumor, because of the dose-limited toxicity due to enzymes/proteins produced in bone marrow and epithelial tissue.

In addition, intratumoral blood vessels are immature, lacking both smooth muscle cells and immunoreactive nerves [10]. Therefore, tumor vessels are unable to react to vasoconstricting agents [11,12].

Angiotensin-II [AT-II] causes arteriolar constriction in normal blood vessels. It is a powerful vasoconstrictor which has been shown to alter the distribution of blood flow in favor of intrahepatic tumor perfusion during short [3-4 min] intra-arterial infusions of the compound [13].

We have hypothesized that it is important for the treatment strategy of pancreas cancer to comprehend the hemodynamics of pancreas cancer.

Reports indicate that intra-arterial regional chemotherapy has improved the response rates and quality of life in patients with liver metastases from colorectal cancer [14].

Pancreas cancer is considered a chemoresistant tumor and up to now an single agent drug with a high level of activity has been lacking. The most important reasons for the tumor drug resistance are the presence of both a biological and a mechanical barrier; the multidrug resistance gene [MDR1] product, and a very dense, poorly vasculized, fibrotic envelope that is almost impenetrable by drugs [15].

Furthermore, the chemotherapy drugs are often quickly eliminated by a high multidrug resistance mechanism in pancreas cancer [16]. Pancreas cancer is profoundly resistant not only due to MDR1 product, but also because it expresses moderate to high levels of P-170 glycoprotein.

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P-glycoprotein is a part of a drug or toxin efflux enzyme system that rapidly clears chemotherapeutic agents from the tumor cell [17].

However, the regional chemotherapy is expected that drug dose delivered must be increased at least five-fold to overcome the tumor cell resistance derived from the P-170 drug efflux enzyme system.

The dose-dependent sensitivity of pancreatic cancer to locoregional chemotherapy has been shown in previous studies [16]. Intra-arterial chemotherapy for pancreatic cancer is still in its infancy and the ideal schedule is under study. To improve the effect of chemotherapeutic agents against pancreatic cancers, effective methods for drug delivery into tumor tissues needs to be developed. Intra-arterial infusion allows higher drug concentrations to reach the tumor, overcoming the problem of poor blood flow to the tumor mass in comparison with healthy tissue.

With application to various treatments and administration methods, gemicitabine may be the golden standard chemotherapeutic agents for pancreatic cancer in this decade.

The challenge to provide better treatment against advanced pancreatic cancer is by gemcitabine is just the beginning for next decade.

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