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Palliative Chemotherapy and Radiotherapy for Pancreatic Cancer: Is It Worthwhile?

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Abstract. The role of palliative chemotherapy or radiotherapy (or both) in pancreatic cancer is discussed. In patients with disseminated pancreatic cancer chemoradiotherapy has so far not been effective in prolonging survival. Recent trials with gemcitabine has shown a modest improvement in clinical benefit and survival. Patients with locally advanced disease should be offered 5-fluorouracil and radiation therapy, as valid data have repeatedly shown better median survival compared to no therapy. The option of a second-look laparotomy to evaluate resectability after palliative chemoradiotherapy in patients with locally advanced disease should be applied liberally because currently available imaging techniques sometimes do not accurately reflect tumor size and tumor progression. New treatment strategies, such as regional perfusion, are being investigated.

At presentation only 10% to 20% of patients with pancreatic cancer have localized disease and can be considered for a resection procedure. Unfortunately, most patients have locally advanced tumors or metastatic disease. Life expectancy in these cases is short, with practically no survival at 1 year. Palliative therapy in these patients ideally encompasses the following objectives: It should alleviate tumor-related symptoms or delay their onset; it should not add new morbidity or mortality and preferably prolong survival. The value of (neo)adjuvant chemotherapy, radiation therapy, or chemoradiotherapy is not discussed in this paper.

Disseminated Disease

In patients with manifest disseminated pancreatic cancer chemotherapy has so far not been effective. A study in 40 patients by Mallinson et al. suggested that chemotherapy could prolong survival of those with disseminated pancreatic cancer compared to supportive care [1]. The combination chemotherapy used was an induction cycle of 5-fluorouracil (5-FU), cyclophosphamide, methotrexate, and vincristine, followed by maintenance with 5-FU and mitomycin C. This trial has been criticized because the nature of the tumor was not confirmed histologically in one-third or more of the patients. Yet only one patient lived longer than 2 years, and the side effects were severe. A much larger phase III trial conducted by the North Central Cancer Treatment Group (NCCTG) using the same regimen could not confirm this survival benefit [2]. Median survival was only 19.5 weeks compared to 15.2 weeks in the 5-FU monotherapy control arm (not statistically significant).

A phase II trial of continuous infusion of 5-FU and cisplatin showed a median survival of 5.8 months and a 1-year survival of 25% [3]. Although 20% of the patients had no known metastases at entry of the study, the results are encouraging. Confirmation by other trials is, however, needed.

Hormonal therapy with tamoxifen, somatostatin analog, cyproterone acetate, and progestational agents have been used to treat patients with metastatic pancreatic cancer, but these studies could not show any survival benefit [4–7]. The same can be said for studies utilizing immunotherapy (interleukin-2, interferon gamma, or monoclonal antibodies) [8, 9]. Most trials considering palliative chemotherapy, radiotherapy, or chemoradiotherapy for pancreatic cancer focus on the response rate and survival benefit. A regimen is considered valuable if it shows an objective response of $\geq$20% or significantly prolongs survival. Recently conducted trials have been using clinical benefit, which incorporates pain intensity, analgesic consumption, performance status, and weight as primary endpoints. In a phase II study gemcitabine therapy in 5-FU-refractory patients resulted in a clinical benefit in 17 of 63 patients (27%) [10]. Another phase III trial of 126 patients with histologically confirmed advanced or metastatic adenocarcinoma of the pancreas were randomized to gemcitabine or to 5-FU therapy. Approximately 75% had metastatic disease. The gemcitabine-treated patients fared significantly better than the 5-FU-treated patients when considering the clinical benefit (23.8% vs. 4.8%), median survival time (24.5 vs. 19.1 weeks), and 1-year survival rate (18% vs. 2%) [11]. Although these results suggest only modest improvement, for the individual patient with end-stage pancreatic cancer they are considered important.

Radiotherapy for disseminated pancreatic cancer is of limited value because by definition it is a regional modality. However, it can give good palliation in terms of the alleviation of pain due to retroperitoneal extension of the tumor.

Locally Advanced Disease

In patients with locally advanced disease the outlook is slightly better. Several trials have shown prolonged survival with chemoradiotherapy. The Gastrointestinal Tumor Study Group random-

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ized 194 patients with locally unresectable pancreatic cancer into three groups: radiotherapy alone (60 Gy), 40 Gy radiotherapy plus 5-FU, and 60 Gy plus 5-FU. Median survival time was 17 weeks in the radiotherapy-alone group compared with 32 weeks for the 40 Gy plus 5-FU group, and 44 weeks for the 60 Gy plus 5-FU group [12]. We also reported our experience with 5-FU and radiotherapy in patients with unresectable pancreatic cancer without distant metastases and found a median survival time of 43 weeks [13].

In a more updated study of these patients, the value of a second-look laparotomy was considered. Thirty-five patients with histologically proven carcinoma of the pancreas, locally unresectable, were treated with a 50 Gy split-course radiotherapy schedule in combination with 5-FU. In four patients leukopenia necessitated discontinuation of the 5-FU infusion before completing the protocol. Other side effects that occurred were nausea, diarrhea, and fever; but they were all mild. Evaluation of the chemoradiotherapy regimen was planned 2 months after the treatment was completed. Ten patients had a second-look laparotomy; eight had shown tumor regression on at computed tomography (CT), and two had stable disease but were strongly motivated and in a good physical condition to undergo a second-look laparotomy. A resection could be performed in 5 of these 10 patients, even in one of the two patients with stable disease on CT scan. This treatment dramatically prolonged survival, with a median survival time of 30.5 months; one patient is still alive after 7 years.

This concept of clinical down-staging has also been described by Pilepich and Miller [14]. They performed a second-look laparotomy in 11 of the 17 patients after preoperative irradiation. The tumor could be resected in six of them, and two of the patients are still alive after 5 years.

Hoffman and colleagues reported the results of treatment with radiotherapy in combination with 5-FU and mitomycin C in 34 patients with localized pancreatic cancer, which resulted in a pancreas resection in 11 patients. The median survival time in these 11 patients was 45 months with a 5-year survival rate of 40% [15]. Jessup et al. treated 16 patients who had locally advanced tumors with external radiation therapy plus continuous infusion of 5-FU. Ten patients underwent a second look laparotomy that resulted in two resections. These patients remained free of disease at the time of their report, 20 and 22 months later [16]. These studies indicate that a small number of patients with unresectable pancreatic cancer without distant metastases may benefit from palliative chemoradiotherapy in such a way that resection becomes possible. This prolongs survival with even a small chance of cure.

The effects of chemoradiotherapy have induced modest reductions in tumor size, as measured by CT scan, but significant histologic responses. The problem is how to identify these patients. Preoperative staging with currently available techniques such as CT scan, (endo)ultrasonography, magnetic resonance imaging (MRI) and endoscopic retrograde cholangiopancreatography (ERCP) have made great progression during the 1990s. It did not, however, solve the specific problem of how to distinguish a desmoplastic reaction, frequently surrounding the tumor, from the tumor itself. Even at laparotomy this desmoplastic reaction makes it difficult to obtain a correct impression of the extent of the tumor.

Ballard et al. studied the correlation between the size of the tumor measured by CT scan and the size measured by the pathologist [17]. They found that of the 29 tumors evaluated 20 of the measurements (69%) were within 1 cm of the diameter found by the pathologist. Of the nine cases in which errors of at least 2 cm were made, six tumors were measured by CT scan to be larger than they actually were.

In our opinion every patient with a localized process in the pancreas seen with imaging techniques, and in a good physical condition, should be explored surgically. The laparoscopic approach is just an elegant way to avoid a laparotomy in patients with small peritoneal or liver metastases and those with positive lymph nodes outside the resection margins. By either way, a thorough search must be undertaken for distant metastases and for unresectability and proved by histology. If localized advanced disease is encountered, we think that chemoradiotherapy (50 Gy + 5-FU) should be offered. If the tumor does not progress, a second-look laparotomy should be done to evaluate for possible resection.

Recurrent Disease after Resection

Recurrent disease after resection is, sadly, a frequent finding (50–65%). If the recurrence is metastatic, the same options as mentioned above in patients with primarily metastatic disease are possible, but the prognosis remains dismal. There are few studies that address the treatment of patients with a locoregional recurrence without distant metastases. We reported a 1-year survival rate of 22% after treatment of recurrent disease in 18 patients. Surgical resection of the tumor recurrence was possible in only two cases, although it was followed by survival of up to 74 months [18].

Other treatment modalities are currently being investigated. A promising new concept is regional perfusion, which has resulted in impressive responses in patients with malignant melanoma and soft tissue sarcoma of the extremities. This strategy has also been applied to pancreatic cancer by Aigner and Gailhofer [19]. They described their technique as aortic stop-flow infusion therapy. A balloon catheter is placed in the aorta above the level of the celiac trunk. A second balloon catheter is placed in the inferior vena cava at the level between the liver and the right atrium. Tourniquets are placed around both thighs to exclude the lower limbs from the circulation. During a 15- to 20-minute period a cytotoxic drug (mitomycin C) is infused into the aorta (hypoxic abdominal perfusion). A balloon catheter is placed in the celiac trunc via Seldinger's technique, through which a combination of chemotherapeutic agents [mitomycin C, CDDP (cisplatin), and 5-FU] is administered during the same period (celiac axis stop-flow infusion). The first results in patients with locally advanced pancreatic cancer showed an impressive response rate of 77%. Pain relief was observed in 70% of the patients [19].

We are currently executing a phase I–II trial of regional hypoxic perfusion chemotherapy (mitomycin C and melphalan) for locally advanced pancreatic cancer. Patients with nonresectable tumors of the pancreas undergo hypoxic abdominal perfusion and, at an interval of 6 weeks, a celiac axis stop-flow infusion, provided toxicity allows such a procedure and there is no evidence of progressive disease. Patients who show an objective response or stable disease on CT/MRI scanning and who are in a good physical condition then undergo a second-look laparotomy to attempt a resection.

Conclusions

To answer the question, "Is palliative chemotherapy or radiotherapy worthwhile in patients with pancreatic cancer?" one should discriminate the following situations. In patients with disseminated pancreatic cancer gemcitabine is the only chemotherapeutic agent that seems to offer effective palliation (but in only about 25% of patients with a short survival benefit of a few weeks). Radiotherapy is a valid alternative for pain management in these patients. Patients with locally advanced but unresectable disease, a combination of radiotherapy and 5-FU has proved effective and prolongs survival; a few patients may even benefit from a second-look laparotomy and subsequent resection. In patients with a locoregional recurrence after an intentional curative resection, there are no valid data to support standard use of chemoradiotherapy.

Currently, new strategies are being investigated where regional perfusion is a promising feature. Meanwhile, patients and the doctors treating these patients should be encouraged to participate in ongoing and future trials to search for an effective therapeutic regimen to change the dismal outlook of the disease.

Résumé

Le rôle de la chimiothérapie et/ou de la radiothérapie palliative dans le cancer du pancréas est discuté. Chez le patient ayant un cancer du pancréas disséminé, la radiochimiothérapie n'a pas encore démontré son efficacité en ce qui concerne la prolongation de survie. Une amélioration modeste en terme de bénéfice clinique et de survie a été obtenue par des essais récents avec la gemcitabine. En cas de maladie avancée, la littérature est en faveur d'une chimiothérapie par le 5 FU combinée à la radiothérapie montrant de façon répétée que la survie est meilleure dans ce cas que quand ces patients ne reçoivent aucune thérapie. L'option qui consiste en une laparotomie de deuxième intention pour évaluer la résecabilité après chimioradiothérapie palliative chez le patient ayant un envahissement local doit être appliquée librement puisque toutes les techniques d'imagerie disponibles ne peuvent toujours bien indiquer ni la taille ni la progression tumorale. De nouvelles stratégies thérapeutiques, telles que la perfusion régionale, sont actuellement sous investigation.

Resumen

El papel paliativo de la quimioterapia y/o radioterapia en el tratamiento del cáncer de páncreas sigue siendo controvertido. En pacientes con cáncer de páncreas diseminado, la quimioterapia hasta ahora, no ha sido capaz de prolongar la vida. Ensayos recientes con gemcitabina han demostrado una modesta mejoría, tanto desde el punto de vista clínico como por lo que a la supervivencia se refiere. A pacientes con enfermedad local avanzada debe ofrecérseles un tratamiento con 5-FU y radioterapia, pues diversos trabajos fiables constataron una supervivencia media mayor, que en enfermos que no fueron tratados. La relaparotomía, tras quimioradioterapia paliativa, está casi siempre indicada en pacientes con enfermedad local avanzada, para evaluar la resecabilidad del tumor, ya que actualmente no existe ningún método diagnóstico por imagen, que permita precisar con exactitud, ni el tamaño, ni el crecimiento del cáncer. Se estan investigando nuevos tratamiento tales como la perfusión regional.

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