Abstract

Median as well as overall survival of pancreatic cancer patients in the advanced stage is extremely low despite advances in cancer therapy regarding tumor cell biology, therapy resistance, and diagnosis. In matters of chemoradiation therapy (CRT) in locally advanced pancreatic cancer, favorable positive effect has been reached with different radiotherapy proceedings such as intraoperative radiation therapy with or without external chemo-/radiation therapy or with CRT alone with regard to local tumor pain, local tumor remission, or local control of disease and overall survival. Primary (chemo-) radiation therapy only rarely leads to local remission. Intraoperative radiation therapy (IORT) merely reaches pain palliation in most cases. By administering up-to-date primary CRT, especially with gemcitabine-associated CRT, local remission in up to 50% of patients can be observed. By applying neoadjuvant CRT, better resectability and the reduction of postoperative positive lymph node metastasis has been seen in patients with resectable or possibly resectable pancreatic cancer. With primary CRT, resectability can also be achieved in patients with primary unresectable pancreatic cancer. It has been shown at the evaluation of patients' progression samples—either treated with neoadjuvant or primarily with radiotherapy (with conventional radiation technique)—that the rate of local recurrence or local progression can be reduced in comparison with historical cohorts. By contrast, the rate on distant metastases was not affected. Whereas concurrent CRT leads to favorable local tumor control, this procedure has a minor effect as to the survival in most of the studies. Because metastases occur mostly out of the irradiation field and because of partly advanced local tumor progression, the concept of combined CRT with continuing chemotherapy was developed.

Median survival of pancreatic patients in the advanced stage is approx. 3–5 months, with a 12-month survival probability of 10% despite advances in cancer therapy. On the other hand, the 5-year survival probability is 0.4%–3.0% (Bramhall et al. 1995, 1998).

The causes of such a dismal prognosis can be understood first of all in the commonly late diagnosis (Haycox et al. 1998), second in the aggressive tumor cell biology with continuing therapy resistance (Magee et al. 2001), and finally because an acceptable resection rate can be achieved only in specialized centers (Birkmeyer et al. 2002; Neoptolemos et al. 1997).

Only 10%–15% of patients can be resected after the diagnosis of pancreatic cancer. Resection is considered a potential curative therapy. However, median survival of these patients amounts to only 13–18 months, with a 5-year survival of 10%–20% (Bramhall et al. 1995; Yeo et al. 1997). The survival rate did not improve with a radical resection and extended lymphadenectomy (Pedrazzoli et al. 1998).

Furthermore, 15%–30% of primary nonmetastatic pancreatic cancer is unresectable due to extended vessel infiltration at time of diagnosis. The prognosis for these patients is very dismal due to lack of specific therapy; moreover, median overall survival is a maximum of 6–8 months (Niederhuber et al. 1995; Shinchi et al. 2002).
10.1 Chemotherapy of Advanced Pancreatic Cancer

Although more chemotherapeutic agents have been examined for the purposes of the therapy of advanced pancreatic cancer, only 5-FU, mitomycin-C (MMC) (Haycox et al. 1998) and, lately, gemcitabine (Burris et al. 1997; Moore et al. 1995; Rothenberg et al. 1996) have shown reproducible outcomes with objective results.

A 5-FU-based combined chemotherapy has shown a clear survival advantage compared to patients without treatment in randomized controlled studies (Glimelius et al. 1996; Mallinson et al. 1980; Palmer et al. 1994). However, compared to monotherapy with 5-FU, a toxicity increase without additional improvement of survival has been reported (Cullinan et al. 1990).

Gemcitabine belongs to a series of new chemotherapeutic agents tested for pancreatic cancer. It has shown superior efficacy both in monotherapy and in combined therapies (Berlin et al. 2002; Burris et al. 1997; Heinemann et al. 1999b, 2000). Nevertheless, the application of fluoropyrimidine continues to be of interest in trials where the efficacy of 5-FU after portal vein infusion (PVI) application and the development of orally applicable chemotherapeutic agents is sought (Neoptolemos et al. 2004). The National Cancer Research Institute in Britain has recently started a Gem-Cap phase III trial where gemcitabine (Gem) will be applied with capecitabine (Cap).

The survival advantage with gemcitabine is minor compared to bolus 5-FU (Burris et al. 1997). Nevertheless, it is being used in advanced pancreatic cancer increasingly as the standard therapy.

However, a significant breakthrough in the therapy of advanced pancreatic cancer with chemotherapy has not been found yet.

10.2 Chemoradiation in Locally Advanced Pancreatic Cancer

A favorable positive effect has been reached with different radiotherapy proceedings such as intraoperative radiation therapy (IORT) with or without external chemo-/radiation therapy or with chemoradiation (CRT) alone with regard to both local tumor symptomatic (local tumor pain), local tumor remission, or local control of disease and overall survival (Fossati et al. 1995; Nishimura et al. 1997; Staley et al. 1996). Therefore, chemoradiation with a total irradiation dose of 45.0–50.0 Gy (eventually up to 60.0 Gy) with conventional fractionation and a concurrent chemotherapy with 5-FU (eventually PVI during the whole therapy with 200–225 mg/m² per day) was recommended as the standard and most effective therapy procedure for patients in good general condition (German Cancer Association 2002).

Randomized trials reporting significant improvement of median survival after chemoradiation are listed in Table 10.1 (Moertel et al. 1981; Li et al. 2003; Shichiti et al. 2002).

For decades, 5-FU has been considered the agent of choice with regard to the chemotherapeutic agents administered concurrently or sequentially to radiation. Combined chemotherapies such as FAM (5-FU, doxorubicin, mitomycin-C) or SMF (streptozotocin, mitomycin-C, 5-FU), or the Mallinson regimen (5-FU, cyclophosphamide, methotrexate and vincristine) resulted in increased toxicity and no improvement as to survival (Bruckner et al. 1993; Cullinan et al. 1990). Even newer agents tested recently for pancreatic cancer such as paclitaxel, docetaxel, irinotecan, topotecan, and oxaliplatin could not be established as treatment (Ashamalla et al. 2003; Kamthan et al. 1997). Only after the introduction of the pyrimidine analog gemcitabine it was possible to reach an improved response rate for unresectable (Epelbaum et al. 2002; Kornek et al. 2001; Okusaka et al. 2004; Safran et al. 2002) or metastatic (Burris et al. 1997; Carmichael et al. 1996; Casper et al. 1994; Heinemann et al. 1999a; Rothenberg et al. 1996) patients in different studies. Gemcitabine has a favorable side effect profile: positive clinical benefit response, practically no hepato- or nephrotoxicity. Only hematotoxicity can be seen as a dose-limiting factor. Because of that, radiation-sensitizing effects have been experimentally proved for gemcitabine (Lawrence et al. 1996; McGinn et al. 1996; Mose et al. 1999; Shewach et al. 1994), which suggests some hope for successful administration of this agent concurrent to radiation.