Neoadjuvant and Adjuvant Strategies for Chemoradiation

A. Kaiser, V. Budach

Recent Results in Cancer Research, Vol. 177
© Springer-Verlag Berlin Heidelberg 2008

Abstract

There is an increasing body of evidence showing that patients with resectable pancreatic cancer might benefit from adjuvant therapy. Based on phase III trials, potential options for adjuvant treatment are chemotherapy alone or a multimodal approach involving radiotherapy. Available data are heterogeneous and have been discussed controversially. Hitherto, a worldwide standard of care has not yet been established. Adequate patient selection might be the key element for a tailored adjuvant treatment. Clinical research currently focuses on gemcitabine alone or in combination, and some molecular biologic approaches with epidermal growth factor receptor monoclonal antibodies (EGFR-MoABs) and anti-angiogenic drugs. Recent advances in radiooncology offer better dose conformality and reduced morbidities. Currently, the co-operative Radiotherapy and Gastrointestinal Groups have launched a multicentric European Organization for Research and Treatment of Cancer (EORTC) trial investigating the impact of radiotherapy in combination with gemcitabine in R0-resected pancreatic head cancer.

9.1 Introduction

Only about 10%–20% of pancreatic cancer patients are deemed to be resectable and could be ideal candidates for adjuvant or neoadjuvant treatment strategies (Evans 2005; Kelly and Benjamin 1995; Sener et al. 1999). Surgery is the only possibly curative treatment option. Remarkable progress has been made in terms of clear resection margins, which could be increased from 26% to 43%. From the 1970s through the 1990s, perioperative mortality improved from 30% to 0.9%, respectively. Five-year survival rates increased from 14% in the 1970s to more than 30% in the 1990s (Yeo et al. 1995; Yeo and Cameron 1999). In the 1990s more than 65% of patients received some form of adjuvant therapy compared to less than 25% in the 1980s. This reflects a major change in the treatment paradigms from therapeutic nihilism to intensified adjuvant therapy.

Prognostic factors after surgery are performance status, extent of tumour spread and tumour size, nodal status, grading and status of resection margins (Kalser et al. 1985; Kalser and Ellenberg 1985; Neoptolemos et al. 2001, 2004; Sohn et al. 2000). Additional and well-known factors are blood loss during pancreaticoduodenectomy and time to recovery. Less common ampullary carcinoma and intrapancreatic bile duct carcinoma have a more favourable prognosis than pancreatic ductal adenocarcinoma (Magee et al. 2002). For pancreatic cancer, a prolonged median survival of about 15–20 months can be expected after R0 surgery compared to 8 to 12 months after R1 surgery (Evans et al. 1998). Even after R0 surgery, however, relapses occur regularly. Local recurrences account for the majority (80%), recurrence in the peritoneal cavity for 25%, and liver metastasis for about 50% of all cases (Wayne et al. 2002). Metastases to other regions such as lung are rare and usually occur at a late stage.

Though there is remarkable progress of pancreatic cancer treatment, survival data are still dismal. Therefore, adjuvant therapy is of major importance.
9.2 Adjuvant Chemoradiation

The Gastrointestinal Tumor Study Group (GITSG) GI-9173 data published in 1985 has proved that post-operative chemoradiation (CRT) is highly effective (Kaiser and Ellenberg 1985). This randomized trial investigated surgery followed by a 40-Gy split-course radiotherapy (RT) combined with 5-fluorouracil (5-FU) versus surgery alone. The treatment arm \(n=21\) was superior to surgery alone \(n=22\), resulting in median survival of 20 months versus 12 months. These results were confirmed by the GITSG in a non-randomized controlled phase II study in 1987 (Gastrointestinal Tumor Study Group 1987). Both studies had great impact on adjuvant treatment of pancreatic cancer in the USA. This treatment regimen has become the new standard of care, and until recently it was in widespread use in the United States. A number of additional studies confirmed these results (Foo et al. 1993; Foo and Gunderson 1998; Mehta et al. 2000; Paulino 1999; Yeo et al. 1995, 1997). The combination of 5-FU with leucovorin seemed to be only marginally effective (Abrams et al. 1999). A recent study from Johns Hopkins University compared two schemes of chemoradiation with surveillance. Chemoradiation was either intensified 50–57 Gy to the pancreas and a prophylactic dose of 23–27 Gy to the liver combined with 5-FU or a standard dose of 40–45 Gy to the pancreas combined with 5-FU/leucovorin. Patients receiving adjuvant therapy had a median survival of 19.5 months compared with only 13.5 months after resection alone. More intense treatment schemes did not appear to further improve survival (Sohn et al. 2000; Yeo et al. 1997). A European Organization for Research and Treatment of Cancer (EORTC) multi-centre trial including 207 evaluable patients combined split-course RT with 5-FU and also found a statistically insignificant improved survival trend of 24.5 versus 19 months (Klinkenbijl et al. 1999). Subgroup analysis indicated a benefit for pancreatic head cancer patients with survival of 17.1 versus 12.6 months.

Some of these studies have methodological limitations. Patient accrual was either slow or the numbers of patients were statistically insufficient. Patient selection was non-uniform, thereby including patients with pancreatic cancer and those with peripancreatic cancer, who have a better prognosis. Mono-institutional studies suffered from selection bias. Up to 25% of the patients did not receive the planned radiochemotherapy because of withdrawal of consent, lack of post-operative recovery or rapid tumour progression. There was no stratification for tumour sites, nor was there a detailed analysis of resection margins. From the current point of view, treatment was often suboptimal, with split-course RT and a heterogeneous dose distribution, and 5-FU given as bolus instead of as continuous infusion.

A rather modern treatment scheme was applied to 52 patients by Mehta et al. (2000). RT was intensified from 45 Gy (R0) to 54–60 Gy (R1) and in a few cases intraoperative RT was added. This was combined with a continuous infusion of 5-FU. The resulting median survival was a promising 32 months and morbidities were only moderate.

9.3 Adjuvant Chemotherapy

The first randomized trial to demonstrate a positive effect of adjuvant chemotherapy without RT was published in 1993 (Bakkevold et al. 1993). Sixty-one radically resected patients were randomized either for post-operative adjuvant combination chemotherapy using 5-FU, doxorubicin and mitomycin C (AMF), or as controls (no adjuvant chemotherapy). The median survival in the treatment group was 23 months compared to 11 months in the control group. The authors concluded that adjuvant chemotherapy prolongs the incidence of recurrence during the first 2 years following radical surgery; however, an increased cure rate was not observed.

The benefits of chemoradiation have been questioned since the publication of the European Study Group for Pancreatic Cancer (ESPAC) trial (Neoptolemos et al. 2001, 2004). This was the most ambitious and largest adjuvant trial in pancreatic cancer with 548 patients involved. It had a 2×2 factorial design: of 541 eligible patients, 289 were assigned to chemotherapy versus radiochemotherapy, 68 to chemoradiotherapy...