Editorial

Pushing the limits in pancreatic cancer therapy

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With an incidence of 338,000 estimated new cases and estimated 330,000 deaths, pancreatic cancer is the 7th most common cause of death worldwide representing one of the most deadly malignancies (1). Because of the locoregional growth pattern with infiltration of the visceral arteries that are adjacent to the pancreas and the early systemic spread, palliative therapy is indicated in almost 80% of cases. Most importantly, complete tumour resection is the most relevant predictor of long-term survival in pancreatic cancer. Just recently, the promising results of the ESPAC 4 trial that applied adjuvant gemcitabine and capecitabine, with a 5-year survival rate of 28.8%, were presented by Neoptolemos at the ASCO Meeting 2016.

Best median survival times of patients with unresectable pancreatic cancer undergoing chemotherapy or radiochemotherapy were between 8.6 and 13 months (2). Palliative FOLFIRINOX combination chemotherapy was found highly effective in metastasized disease, but showed substantial side effects (3). Therefore it is only suitable for patients with good performance status. According to two recent studies in patients with locally advanced pancreatic cancer, the FOLFIRINOX regimen also provides an option in the neoadjuvant setting, resulting in a high secondary resection rate and a favourable overall survival (4,5).

Local invasion of the main visceral arteries, peritoneal metastasis, which lead to intestinal obstruction, ascites and malnutrition, can impair the performance status in patients with pancreatic cancer. In those cases, the applicable intensity of systemic chemotherapy is limited and median survival is even poorer, being reported with less than 6 weeks in patients with peritoneal metastasis (6). Gastric, ovarian or colorectal cancers are among the tumour entities in which intraperitoneal chemotherapy is warranted in the presence of peritoneal metastasis. Due to a high drug concentration in the peritoneal cavity, this treatment seems to be advantageous compared to systemic chemotherapy. The effects of the intrapertioneal use of paclitaxel in patients with peritoneal metastasis derived from gastric cancer have been reported in numerous studies. In combination with S-1, remarkable results have been shown by Ishigami *et al.*, with a 1-year overall survival rate of 78% (7).

In the purpose of offering an alternative treatment than palliative care in patients with pancreatic ductal adenocarcinoma (PDAC) and synchronous peritoneal metastasis, Satoi *et al.* conducted a phase-II study in a multicentre setting evaluating the efficacy and tolerability of paclitaxel with S-1 in the systemic and intraperitoneal use (8). The enrolled 33 patients had histologically proven PDAC with peritoneal metastasis. The presence of cancer cells on peritoneal cytology was proven using staging laparoscopy or laparotomy. Peritoneal dissemination was shown either radiographically or during surgery. All patients were chemotherapy-naive with an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1. Patients with other distant organ metastasis or patients with positive peritoneal washing cytology but resectable or borderline resectable PDAC were excluded, as were patients who had concomitant malignancies or other severe medical conditions. Paclitaxel and S-1 were administered intravenously or orally, respectively. In addition, paclitaxel was administered via an implanted peritoneal access port. This regimen was administered for a median of 8.8 months.

The median survival time in the investigated cohort was 16.3 months, with a 1- and 2-year overall survival rate

of 62% and 23%, respectively. A normalization of CA 19-9 levels was observed in 35% of these patients. After treatment with this regimen 24% of patients underwent surgery. At the time of initiation, 5 of those 8 operated patients appeared with peritoneal dissemination and 3 patients had positive peritoneal washing cytology in addition to locally advanced unresectable cancer. Patients who underwent resection had a median survival time of 27.8 months, which is as good as or better than that of patients who underwent tumour resection and adjuvant chemotherapy in most recent randomized controlled trials (9,10). Severe adverse events were observed in two patients, with a thrombosis of the superior mesenteric artery, which led to death and an anaphylactic reaction in another patient. Complications related to the peritoneal access device occurred in three patients. Adverse events, regarding the toxicity of the substances used, were similar to intravenous chemotherapy alone. In summary, the regimen used in this study showed high response and disease control rates with an increase of median survival time in patients with peritoneal dissemination or positive peritoneal washing cytology. Moreover, conversion surgery in a substantial amount of treated patients extended the survival time to comparable levels of that of patients undergoing surgery in locally advanced and predominantly primarily resected PDACs (11).

As the authors implied, the results of this study are promising, but can only be used for generating a hypothesis. The non-randomized study with a small sample size and the favourable patients' constitution, as only patients with an ECOG 0 to 1 were included, limit the strength of the study. However, since a valid treatment option other than palliative care is still missing for patients with PDAC and peritoneal dissemination, there is an immense need for improving the therapy of these patients. Based on the interindividual biologic differences of pancreatic cancer, one future key issue will be the identification of the proper subset of patients who qualify for this intensive treatment regimen. Along with the development of more effective substances and combinations used for chemotherapy, it's just a matter of time that hepatic as well as peritoneal metastases will be amendable to curative intention therapy, as this has already been established for other tumour entities.

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