REVIEW

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INTRA-ARTERIAL CHEMOTHERAPY IN ADVANCED PANCREATIC CANCER: A LITERATURE REVIEW

Pancreatic cancer is an extremely aggressive malignancy with a 5-year survival rate among all stages of about 7%. Treatment options for unresectable forms are limited to fluoropyrimidine- and gemcitabine-containing regimens, and starting from the 3rd line, international guidelines do not provide clear recommendations because of the poor clinical condition of patients and the low efficacy of the consecutive lines. The arterial infusion is a promising method of treatment for locally advanced or liver-only metastatic disease, providing a higher local concentration with the same or lower systemic toxicity. The most often used intra-arterial regimens are those based on 5-fluorouracil and gemcitabine. This method was found to be superior in overall survival, response rate, and control of local symptoms compared to control groups treated with systemic chemotherapy. The approach has a good safety profile and is well tolerated. The method is promising for patients with an adequate performance status, who have run out of other potential regimens, in cases without distant metastases or liver-only metastatic disease, and for upcoming clinical trials or studies.

Keywords: intra-arterial chemotherapy, regional chemotherapy, hepatic arterial infusion, pancreatic arterial infusion, advanced pancreatic cancer.

Pancreatic cancer is an extremely aggressive malignancy with a poor prognosis even in its early stages. The five-year survival rate for all stages is only 7%. Only 1 in 5 cases are diagnosed in the early stages, and 4 in 5 are diagnosed in stages III and IV, where the 5-year survival rate ranges from 1% to 3% [1—3]. The median overall survival for advanced pancreatic cancer requiring systemic therapy is reported to be only 5 to 11 months [4]. As per GLOBOCAN 2020, pancreatic cancer ranked 12th in incidence and 7th in mortality among all types of cancer and both sexes [5].

In Ukraine, in 2021/2022, pancreatic cancer ranked 9th in incidence among men and was not present in the top-10 oncological diseases among women, and ranked 6th in mortality among men and 8th among women. The share of the locally advanced and metastatic forms significantly exceeds localized ones: for example, among newly diagnosed cases, 6.6% had stage I, 19.4% — stage II, 12.8% — stage III, and 43.5% — stage IV. 64%

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of patients diagnosed with pancreatic cancer in 2021 did not survive the first year [6].

The therapeutic options for inoperable and recurrent pancreatic cancer remain very limited. Preferred first line for ECOG 0—1 is FOLFIRINOX regimen and for ECOG 2 — gemcitabine-based regimen or monotherapy [7, 8]. Preferred variants for the second line are: gemcitabine-based or irinotecan-based regimen (oxaliplatin-based regimen as alternative with less strong evidence) depending on previous regimens of the first line [7, 8]. As for the third line, by the moment of making a decision about it, the patients are often unsuitable for systemic therapy due to a poor nutritional status and ECOG, and in case of suitability, existing regimens have not shown long-term control of the disease, so even such authoritative guidelines as NCCN and ESMO do not offer clear recommendations [7, 8]. The search for new therapeutic options for this aggressive disease continues in clinical trials.

For recurrent but still not metastatic pancreatic cancer, local methods were tested, such as brachytherapy with iodine-125, physical ablation techniques, irreversible electroporation, and transarterial chemoembolization, and some positive results have been achieved [9]. A separate area of scientific interest is the administration of cytotoxic agents in the supplying artery of pancreatic tumor — pancreatic arterial infusion (PAI). The potential of the technique is that it may be more effective and better tolerated compared to systemic chemotherapy due to a higher local drug concentration and lower systemic concentration [10—12]. Depending on the location of the tumor (head, body, or tail of pancreas), chemotherapy drugs are administered into different arteries: the gastroduodenal artery, proper or common hepatic artery, pancreatic branches of the splenic artery, superior mesenteric artery, pancreaticoduodenal arteries, etc. [13, 14].

In the case of distant metastases, PAI no longer has such a potential advantage. However, if metastatic disease is limited to the liver, which is the most common site of metastasis in pancreatic cancer [15], another variation of the technique can be considered. The healthy liver tissue is perfused by the portal vein system, while the liver metastases are perfused by the branches of the hepatic artery [16], the hepatic arterial infusion (HAI) can be used. Just as in PAI, the local concentration of chemotherapy drugs is higher while the systemic toxicity is the same or lower, being delivered to metastatic lesions through a catheter, port, or pump [17, 18]. This approach has been included in NCCN and ESMO recommendations as a possible option for the treatment of colorectal cancer [19, 20]. Moreover, intrahepatic infusion in metastatic colorectal cancer has demonstrated the ability to overcome chemoresistance and to obtain a response after many previous lines and even to those drugs on which progression occurred when administered intravenously [21]. The success of the technique determined further research on other histological types of malignant neoplasms.

If there are both a primary tumor in the pancreas and liver-only metastases are present, infusion of cytotoxic drugs into the celiac artery, or celiac trunk, is described in some publications. This approach can provide drug supply to both tumor sites because of the arterial anatomy [22, 23].

To date, there is not much research of arterial chemotherapy of pancreatic cancer, but a review of the available publications and highlighting potential opportunities may be interesting for oncologists in the search for additional therapeutic options for this difficult-to-manage disease.

Technical aspects of intra-arterial chemotherapy in pancreatic cancer

For pancreatic intra-arterial chemotherapy, vascular access is provided first. Most often, it is done by the catheterization of the femoral artery. Under an angiographic guidance, the catheter is being moved to the proximal end of the supplying artery of the pancreatic tumor. In particular, the use of digital subtraction angiography (DSA) is described in literature. After the infusion is complete, the catheter is removed. The following catheters are mentioned in publications: 5-Fr (Rösch hepatic, Cobra 2; Goodtec); microcatheters 2.5-Fr, 2.7-Fr (MiraFlex, Progreat), 2.8-Fr, 3-Fr (TARGET) [13, 14, 24], and Sidewinder (Simmons, Sim or SS) [23].

In regard to the vessels through which the cytotoxic drug should be administered, there is no single standard. The methods differ depending on the anatomical features of the blood supply to tumors located in different parts of the pancreas and the clinicians' preferences. Wang et al. [13] performed the infusion through the gastroduodenal artery, the

hepatic artery itself, the pancreatic branches of the splenic artery, and the superior mesenteric artery. Han et al. [25] infused drugs through the celiac trunk for access to the head of the pancreas and through the hepatic artery for the access to the body and tail. Liu et al. [26] administered a ⅓ dose of drugs into the superior mesenteric artery and the ⅔ dose into the gastroduodenal artery, if the tumor was situated in the head of the pancreas. If the tumor was located in the body or tail, the drugs were administered into the great pancreatic artery, caudal pancreatic artery, and dorsal pancreatic artery, depending on the dominant blood flow, which had been determined via angiography before the start of treatment. Qiu et al. [14], at the beginning of their research, introduced a ⅔ dose into the common hepatic artery or gastroduodenal artery and ⅓ dose into the superior mesenteric artery, if the tumor was situated in the head of the pancreas, and the ⅔ dose into the splenic artery or celiac trunk and a ⅓ dose into the superior mesenteric artery, if the tumor was located in the body or tail. Later, the authors used an alternative regimen: a ⅓ dose into the anterior superior pancreaticoduodenal artery, a ⅓ dose into the posterior superior pancreaticoduodenal artery, and the ⅓ dose into the inferior pancreaticoduodenal artery for tumors of head of the pancreas; and a ⅓ dose into the dorsal pancreatic artery, a ⅓ dose into the great pancreatic artery, and the ⅓ dose to the caudal pancreatic artery for the body and tail tumors.

In particular cases, the administration via the celiac artery can be considered, if, in addition to the primary tumor in the pancreas, there are distant metastases in the liver and/or organs supplied by the vessels branching from it. Cantore et al. [23] and Aigner et al. [22] described the placement of an angiocatheter in the celiac trunk (via femoral access) and its removal upon completion of infusion.

If the primary tumor of the pancreas has been removed and the metastatic process is limited to the liver, intrahepatic infusion can be used according to principles similar to this technique for colorectal cancer or cholangiocarcinoma. The most commonly used vessel is the common hepatic artery. Access can be made temporarily, with the separate catheterization for each infusion cycle under angiography control and the removal of the catheter after the infusion is completed, or permanently by installing a port-catheter system or a pump. It is preceded by ligation of the distal gastroduodenal artery, the right gastric artery, and small collateral branches that supply the stomach, small intestine, and pancreas. Cholecystectomy is also performed to prevent chemo-induced cholecystitis [27—29].

Pharmacokinetics

One of the fundamental rationales for intra-arterial chemotherapy is the ability to achieve higher local concentrations than in classical intravenous infusion. Data on the technique in pancreatic cancer are quite limited and described mostly in animal models with descriptions of phase I clinical trials only.

Fluoropyrimidines are more classically used in arterial administration due to their short half-life (8—20 min) and high level of hepatic excretion: in hepatic infusion, it reaches 80% [30]. Tao et al. [31] performed the study on laboratory albino rats and reported a significantly higher maximum local concentration of 5-fluorouracil in pancreatic tissues after intra-arterial administration, namely 20.0 μg/g vs 8.42 μg/g in the venous infusion group, as well as a pancreatic clearance time of 90 min vs 50 min in the venous group. Mitsutsuji et al. [32], in their study on dogs, described higher portal and tissue concentrations of 5-fluorouracil and lower systemic concentration when the drug was administered into the gastroduodenal and splenic arteries compared to the venous administration route. This was also confirmed by Tanaka et al. [33], based on a study on pigs: the AUC of 5-fluorouracil in the head of the pancreas and liver was significantly higher when administered into the celiac trunk than into the venous system.

One of the main active agents in the treatment of pancreatic cancer — gemcitabine — has also been studied using the arterial schemes of administration. Fu et al. [34] tested the distribution of gemcitabine at a dose of 45 mg/kg administered intra-arterially and intravenously to beagle dogs with locally advanced pancreatic cancer. The celiac trunk and superior mesenteric artery were used as arterial accesses, and the peripheral veins were used as venous accesses. The drug concentration was measured at 2, 4, and 8 h after infusion in the blood and tissues (pancreas and surrounding tissues, heart, liver, lungs, and kidneys). In the intra-arterial group, the drug concentration was signifi-

cantly higher in the blood and tissues, and the drug retention time in the body was also prolonged. Van Riel et al. [35], in their phase I study of the pharmacokinetics of gemcitabine during 24-h hepatic arterial infusion, found that the drug had a relatively low plasma concentration in patients, due to a high level of hepatic extraction. The elimination half-life of this drug after intravenous infusion was 42—92 min, becoming significantly shorter after hepatic arterial infusion.

Among platinum drugs, only oxaliplatin showed the advantage of local tissue concentration after hepatic arterial administration compared to venous administration, while for cisplatin there was no difference between the routes of administration — based on the data from a study on the VX2 rabbit tumor model [36]. Oxaliplatin also has an acceptable safety profile, as only half of the dose reaches a systemic circulation after intrahepatic administration, as it was discovered for colorectal cancer metastases [37]. Some advantages of cisplatin administration via pancreatic arterial infusion have been described: according to Kakizaki et al. [38], drug concentrations were 1.3 times higher in pancreatic tissue than in adjacent tissues in patients after PAI and following pancreatic resection.

Toxicity profile

The results of meta-analyses demonstrate that the arterial route of administration of chemotherapy drugs has a significantly lower rate of complications and myelosuppression compared to intravenous administration. Thus, Liu et al. [11] reported on the rate of the adverse events 49.03% vs 71.33% in patients receiving chemotherapy intra-arterially and intravenously, respectively. At the same time, gastrointestinal adverse events (nausea, vomiting, and diarrhea) were observed with mostly the same frequency, but hematological complications and the level of myelosuppression were recorded less often with the intra-arterial route than with the intravenous route (60.87% vs 85.71%, respectively).

Cao et al. [39] in their meta-analysis also reported gastrointestinal, hematological, renal, and hepatic toxicity in the intra-arterial cohort, but without severe grades, in contrast to the intravenous cohort. There were also no treatment-related deaths in the intra-arterial cohort.

Catheter-related complications have historically been associated with intra-arterial chemotherapy regimens. However, several major meta-analyses report no embolization or thrombophlebitis at all [11] or only isolated cases [39] and mention isolated cases of catheter displacement [11, 39].

Intra-arterial chemotherapy in pancreatic cancer

The publications from PubMed, the National Center for Biotechnology Information (NCBI), the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), ASCOPubs, Google Scholar, Web of Science, and the data from ClinicalTrials.gov registry were used; the search criteria included the keywords "intra-arterial chemotherapy", "regional chemotherapy", "pancreatic cancer", "pancreatic arterial infusion", "hepatic arterial infusion".

The review included 17 sources: 15 articles with a total number of 1641 patients and 2 meta-analyses with a total number of 298 and 627 patients.

Cantore et al. [23] were among the first to publish the results for the use of cytotoxic drugs via the arterial route in patients with pancreatic cancer. Within a trial, patients with unresectable disease received 5-fluorouracil 1000 mg/m^2, folic acid 100 mg/m^2, epirubicin 60 mg/m^2, and carboplatin 300 mg/m^2; infusions for 10 min each. Drugs were administered on the 1st day of 21-day cycles. As a result, 21% of patients achieved a partial response, 49% — a stable disease. The overall survival median was 6.2 months for all stages, 13.4 months for stage III and 4.9 months for stage IV. Progression-free survival was 4 months (within the range of 2—11 months).

Homma et al. [24] performed arterial chemotherapy after superselective arterial embolization with the aim of a more targeted distribution of chemotherapy drugs. Both PAI and HAI were used depending on whether the tumor process was locally advanced or liver-only metastatic. In case of the locally advanced disease in the head of the pancreas, the researchers embolized the gastroduodenal artery, anterior and posterior superior pancreaticoduodenal arteries, inferior pancreaticoduodenal artery, and dorsal pancreatic artery, leaving intact only the great pancreatic artery, and caudal pancreatic artery. A catheter for arterial infusion was in-

serted into the splenic artery. If liver metastases were present, another catheter was inserted into the common hepatic artery. The chemotherapy drugs were administered on weeks 1 and 3 of 4-week cycles. For PAI only, they used 5-fluorouracil 250 mg/m^2 per day, for 7 days, and cisplatin 10 mg/m^2 for 1 h on days 1, 3, 5 of each "active" week. For PAI + HAI, 5-fluorouracil was used in the same way, but cisplatin at a dose of 10 mg/m^2 on days 1 and 3 only of each "active" week. In parallel, intravenous hydration with potassium and magnesium supplementation was performed. In the common group (both locally advanced and metastatic pancreatic cancer) response rate was 73.9%, the median overall survival was 18.26 ± 10.06 months ($p < 0.01$), the 1-year survival rate was 90.9%, the 2-year survival rate — 42.8%, and the 3-year survival rate — 18.3%. In the subgroup analysis, patients with liver metastases had a response rate of 68.8% and median overall survival of 16.25 ± 8.35 months, while patients with locally advanced disease had a response rate of 87.5% and median overall survival of 22.86 ± 12.69 months.

Ji et al. [40] described a comparison of different administration routes for chemotherapy after palliative surgery — bilio-enterostomy and/or gastroenterostomy. The patients had advanced pancreatic cancer and liver metastases. After surgery, they received intra-arterial chemotherapy combined with peripancreatic artery ligation, or systemic chemotherapy only. The following drugs were used: 5-fluorouracil 750 mg on days 1, 3, 5 and mitomycin-C 2 mg on days 2, 4, 6 for both cohorts, with the difference only in administration route. In the intra-arterial cohort, the median overall survival was higher (12.5 months vs 4.8 months, $p < 0.01$) and the response rate was higher as well (66.7% vs 18.2%, $p < 0.01$). At the same time, after treatment, the level of CEA did not differ significantly between the groups.

Han et al. [25] presented the results of a randomized, double-cohort study of FAM regimen intra-arterially and intravenously for inoperable pancreatic cancer with involvement of 140 patients. The treatment regimen consisted of adriamycin 40 mg/m^2 and mitomycin-C 6 mg/m^2 on day 1 and 5-fluorouracil 375 mg/m^2 daily on days 2 to 6, repeated each month, regionally or systemically. A higher median overall survival was observed in the intra-arterial group (13.5 months vs 6.2 months, $p < 0.005$); an objective response rate was also higher (77.1% vs 35.7%, $p < 0.005$), and pain control per Visual Analogue Scale was better (2.3 vs 4.6). There were 5 cases of complete response in the intra-arterial cohort, and none in the intravenous cohort.

Liu et al. [42] described the experience of comparing the intra-arterial and intravenous administrations of gemcitabine and 5-fluorouracil. Both cohorts used the schedule and dosing of the drugs as follows: gemcitabine 1000 mg/m^2 on day 1 and 5-fluorouracil 600 mg/m^2 daily from day 1 to day 5. Median overall survival was 11 months in the arterial cohort and 8 months in the systemic cohort [41]. Somewhat updated data using the same regimen are provided by Jia et al. [42] with a median OS of 13.5 months in the arterial cohort and 6.2 in the systemic cohort.

In a study provided by Liu et al. [43], gemcitabine 1000 mg/m^2 and cisplatin 50 mg/m^2 administered intra-arterially and intravenously were compared. Survival rates were significantly higher in the intra-arterial group: 21 months vs 14 months in the systemic group. A similar regimen was used by Qi et al. [44], who also compared the effectiveness of intra-arterial and intravenous routes of administration. According to the results, the median survival was longer in the intra-arterial group (12 months vs 8 months).

Hong et al. [45] assessed the arterial infusion of gemcitabine and 5-fluorouracil combination compared to intravenous administration. Patients with pancreatic cancer of stages III—IV were included and divided into two groups. The arterial group received gemcitabine 1000 mg/m^2 on day 1 and 5-fluorouracil 600 mg/m^2 daily from day 1 to day 5, 28 days each cycle, and systemic (control) group received gemcitabine 1000 mg/m^2 on days 1 and 8, and 5-fluorouracil 600 mg/m^2 daily from day 1 to day 5, 28 days each cycle. The efficacy was assessed after 2 cycles of treatment. The objective response rate in the intra-arterial group was higher than in the systemic group (33.3% vs. 25.0%), but the difference was not statistically significant ($p = 0.626$). The investigators also assessed the clinical benefit response rate (CBR), an indicator that includes pain control, improvement in the Karnoff performance status, and weight gain. In the arterial group, the CBR was 83.3% vs. 58.3% in the control group ($p = 0.014$). The median overall survival was 12.0 months in the arterial

group and 7.3 months in the control group. The toxicity profile did not differ.

Liu et al. [11], presented the results of a meta-analysis of clinical trials of intra-arterial treatment of pancreatic cancer compared with systemic chemotherapy (492 articles were identified and 6 of them were included into the final review). Survival data favored regional intra-arterial chemotherapy: median OS ranged from 5 to 21 months in the arterial cohort and from 2.7 to 14 months in the systemic cohort; 1-year survival rates were 28.6%—41.2% and 0—12.9%, respectively. Also, among patients receiving drugs intra-arterially, 8 patients achieved a complete response and 1 patient was able to undergo R0 resection, while no complete response was achieved in the systemic chemotherapy group. Described regimens of intra-arterial chemotherapy included gemcitabine monotherapy, gemcitabine with cisplatin, gemcitabine with 5-fluorouracil, adriamycin + mitomycin-C + 5-fluorouracil, mitomycin-C with 5-fluorouracil, and mitomycin-C + mitoxantrone + cisplatin. Among the arterial routes of drug delivery, the celiac trunk, splenic artery, gastroduodenal artery, common hepatic artery, superior mesenteric artery, and smaller supplying arteries were mentioned.

Liu et al. [26] provided the results of intra-arterial chemotherapy in 354 patients with advanced pancreatic cancer. Patients received gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2 intra-arterially as a first-line systemic therapy. The median overall survival was 7.0 months. The investigators also noted the following predictive factors for a better response to regional chemotherapy: young age, initial CA 19-9 level <1000 IU/mL, and tumor location in the head of the pancreas.

Aigner et al. [22] published the results of a retrospective study comparing intra-arterial chemotherapy via the celiac trunk and isolated upper abdominal perfusion in advanced pancreatic cancer. One group of patients received cisplatin 30 mg + + adriamycin 2 × 15 mg + mitomycin-C 10 mg administered sequentially into the celiac trunk, 5 min each, daily for 4 days within 3-week cycles. The second group of patients underwent upper abdominal hypoxic perfusion with chemofiltration according to the regimen of cisplatin 50 mg + adriamycin 30 mg + mitomycin-C 15 mg (5 min of high-dose perfusion of chemotherapy and 5 min of perfusion with additional chemofiltration). In stage III patients, the median survival was 7.6 months in the arterial infusion group and 12.1 months in the isolated upper abdominal perfusion group ($p < 0.05$), and in patients with stage IV, it was 6.6 months in the arterial infusion group and 8.7 months in the isolated upper abdominal perfusion group ($p < 0.01$). In all cases of ascites in patients of the abdominal perfusion group, it resolved with treatment.

Qiu et al. [14] published the results of a 10-year experience of arterial chemotherapy of unresectable pancreatic cancer cases with chemoresistance or impossibility to provide systemic therapy. The analysis included data from 115 patients who underwent a total of 224 arterial infusions. Two regimens were used: single-component (gemcitabine 1000 mg/m^2) and double-component (gemcitabine 1000 mg/m^2 + lobaplatin 50 mg/m^2 or cisplatin 75 mg/m^2, by investigator's choice). The drugs were diluted in 20-30 ml of saline and administered by slow injection (over 15 min). The study also included PAI 5-fluorouracil 500 mg/m^2 as a monotherapy or with lobaplatin 50 mg/m^2 or cisplatin 75 mg/m^2 for some patients who had progressed on prior arterial therapy. Infusions were given every 4 weeks with CT follow-up after each. Disease control was achieved in 62.6%. Median progression-free survival was 56 days, and median overall survival was 147 days. The chosen regimen and type of catheter (conventional or microcatheter) did not significantly affect the results.

Endo et al. [46] described a clinical case of hepatic arterial infusion in metastatic pancreatic cancer after resection of the primary tumor. The patient with stage IIB underwent neoadjuvant chemoradiotherapy and distal pancreatectomy with portal vein resection, and was diagnosed with liver metastases one month after surgery. The patient received 2 lines of systemic therapy for metastatic disease: nab-paclitaxel + gemcitabine and mFOLFIRINOX, after which another progression took place. Since the metastatic foci were confined to the liver, it was decided to start an arterial infusion into the hepatic artery with gemcitabine 800 mg/SLV (standard liver volume = (706.2 × BSA+2.4)/1,000) for 30 min on day 1, 5-fluorouracil 250 mg daily on days 1—6 continuously, every 14 days. The patient received a total of 14 cycles (7 months) until progression.

Wang et al. [13] investigated intra-arterial pancreatic nab-paclitaxel in combination with oral S-1 in patients with hepatic metastases of pancreatic

cancer. 15 patients received intra-arterial nab-paclitaxel 180 mg/m^2 (3-hour infusion into the pancreatic tumor-feeding artery) on day 1 and oral tegafur/gimeracil/oteracil (S-1) 60 mg once daily from days 1 to 14 of 28-day cycles. Patients experienced significant and rapid relief of pain and local symptoms within 24 h of arterial infusion. The clinical benefit rate (CBR) was 86.67%, the overall response rate was 26.67%, and the disease control rate was 93.33%. The median progression-free survival was 5.22 months, and the median overall survival was 8.97 months (the maximum recorded in the study was 22 months). The regimen was well tolerated and did not cause procedure-related complications; all adverse reactions were typical for the chemotherapeutic agents used.

Pishvaian et al. [47], presented the first interim results of phase III TIGeR-PaC trial (NCT03257033) of intra-arterial gemcitabine versus intravenous gemcitabine + nab-paclitaxel in patients with non-metastatic pancreatic cancer. Gemcitabine was administered by trans-arterial microperfusion. The detailed treatment regimen was as follows: gemcitabine + nab-paclitaxel intravenously for 2 months, stereotactic radiotherapy, gemcitabine + nab-paclitaxel intravenously for another 1 month, after which patients were randomly assigned to the intra-arterial gemcitabine treatment group (8 infusions over 4 months) and the control group receiving gemcitabine + nab-paclitaxel intravenously for a total of 12 infusions. Interim data, obtained after 30% of deaths, showed a median progression-free survival of 14.8 months in the study group vs 6.7 months in the control group and a median overall survival of 15.7 months in the study group vs 10.1 months in the control group ($p < 0.08$). The intra-arterial chemotherapy group had 65% fewer adverse events than the intravenous group.

A meta-analysis made by Cao et al. [39] reported the results of 11 studies on intra-arterial chemotherapy for pancreatic cancer. The results showed better survival outcomes of patients receiving intra-arterial chemotherapy compared to systemic therapy, as well as a higher partial response rate and lower complication rates. The regimens described in the context of intra-arterial administration included: gemcitabine monotherapy, gemcitabine with cisplatin, gemcitabine with 5-fluorouracil, adriamycin + mitomycin-C + 5-fluorouracil, mitomycin-C with 5-fluorouracil, and mitomycin-C + mitoxantrone + cisplatin. Arterial routes of drug delivery included the celiac trunk, splenic artery, gastroduodenal artery, common hepatic artery, superior mesenteric artery, and smaller tumor-feeding arteries.

The brief comparison of the trials with the main outcomes is presented in the Table.

Clinical trials with active recruitment

The global clinical trials database ClinicalTrials.gov was used with the search criteria: arterial infusion, arterial chemotherapy, pancreatic cancer. The filtering was made by active recruitment or the opening of the recruitment in the near future.

A phase II clinical trial PTCA199-9 (ClinicalTrials.gov ID NCT06196788), initiated by the Fudan University, China, investigates the efficacy of gemcitabine + nab-paclitaxel administered both intravenously and intra-arterially via a combined regimen. According to the study design, nab-paclitaxel 120 mg/m^2 and gemcitabine 1000 mg/m^2 are administered intravenously on days 1 and 8 and intra-arterially on day 15 of 28-day cycles. The study enrolls patients with localized, locally advanced, and metastatic pancreatic cancer. There are no interim results or any other publications regarding the study to date [48].

A phase II clinical trial (ClinicalTrials.gov ID NCT03856658), initiated by the Spectrum Health Hospitals in Michigan, USA, investigates the efficacy of intrahepatic floxuridine (FUDR) in pancreatic cancer with liver-only metastases. One of the main inclusion criteria is stable disease confirmed by radiology and tumor marker levels, after a minimum of 2 months of systemic chemotherapy. Patients will receive 6 courses of intra-arterial infusion of FUDR using a hepatic infusion pump with subsequent observation. There are no interim results or any other publications regarding the study to date [49].

A phase II clinical trial (ClinicalTrials.gov ID NCT06538623), initiated by Ruijin Hospital in Shanghai, China, investigates intra-arterial chemotherapy as a second line for pancreatic cancer. The trial includes two cohorts: an experimental intra-arterial cohort (liposomal irinotecan 60 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-fluorouracil 2400 mg/m^2 every 3 weeks), and a control oral cohort (S-1 40 mg twice daily for 7 days, every

Summary of the results of intra-arterial chemotherapy in pancreatic cancer

Reference	Phase	Arterial chemotherapy regimen	Control group (intravenous)	Artery of infusion	Disease control rate, %	Response rate, %	Median progression-free survival, months (or artery vs control)	Median overall survival, months (or artery vs control)
Cantore et al, 1997 [23]	II	FLEC	No	Celiac trunk	59	15	N/A	9.9
Homma et al, 2000 [24]	II	5-fluorouracil + + cisplatin	No	Splenic artery, common hepatic artery	N/A	73.9	N/A	18.26
Ji et al, 2003 [40]	II	5-fluorouracil + +mitomycin-C	5-fluorouracil + + mitomycin-C	Head of the pancreas: superior pancreaticoduodenal artery; in case of liver metastases: additional catheter into the common hepatic artery	N/A	66.7 vs 18.2	N/A	12.5 vs 4.8
Han et al, 2006 [25]	III	FAM	FAM	Head of the pancreas: celiac trunk; body or tail — hepatic artery	N/A	77.1 vs 35.7	N/A	13.5 vs 6.2
Liu et al, 2007 [41]	II	Gemcitabine + + 5-fluorouracil	Gemcitabine + + 5-fluorouracil	Tumor-feeding artery	N/A	N/A	N/A	11 vs 8
Liu et al, 2008 [43]	II	Gemcitabine + + cisplatin	Gemcitabine + + cisplatin	Tumor-feeding artery	N/A	N/A	N/A	21 vs 14
Jia et al, 2009 [42]	II	Gemcitabine + + 5-fluorouracil	Gemcitabine + + 5-fluorouracil	Tumor-feeding artery	N/A	N/A	N/A	13.5 vs 6.2
Qi et al, 2011 [44]	II	Gemcitabine + + cisplatin	Gemcitabine + + cisplatin	Tumor-feeding artery	N/A	N/A	N/A	12 vs 8
Hong et al, 2012 [45]	II	Gemcitabine + + 5-fluorouracil	Gemcitabine + + 5-fluorouracil	Tumor-feeding artery	N/A	33.3 vs 25	N/A	12.0 vs 7.3
Liu et al, 2012 [11]	Meta-analysis	Various	Various	Celiac trunk, splenic artery, gastroduodenal artery, common hepatic artery, superior mesenteric artery, smaller tumor-feeding arteries	N/A	58.06 vs. 29.37	N/A	5-21 vs 2.7-14

Liu et al, 2016 [26]	Retro-spective	Gemcitabine + + oxaliplatin	No	Head of the pancreas: ⅓ dose of drugs into superior mesenteric artery and ⅔ dose into gastroduodenal artery; body or tail: great pancreatic artery, caudal pancreatic artery, dorsal pancreatic artery	N/A	N/A	N/A	7.0
Qiu et al, 2019 [14]	Retro-spective	Various	No	Head of the pancreas: ⅔ dose into common hepatic artery or gastroduodenal artery and ⅓ dose into superior mesenteric artery; body or tail: ⅔ dose into splenic artery or celiac trunk and ⅓ dose into superior mesenteric artery. Alternative regimen: head: ⅓ dose into anterior superior pancreaticoduodenal artery, ⅓ dose into posterior superior pancreaticoduodenal artery and ⅓ dose into inferior pancreaticoduodenal artery; body of tail: ⅓ dose into dorsal pancreatic artery, ⅓ dose into great pancreatic artery and ⅓ dose to caudal pancreatic artery	62.6	N/A	56 days	147 days
Aigner et al, 2019 [22]	II	Cisplatin + + adriamycin + + mitomycin-C	Isolated upper abdominal perfusion	Celiac trunk	N/A	N/A	N/A	st. III: 8 vs 12, st. IV: 7 vs 8.5
Endo et al, 2021 [46]	Case report	Gemcitabine	No	Hepatic artery	N/A	N/A	7	N/A
Wang et al, 2022 [13]	II	Nab-paclitaxel (+ S1 per os)	No	Tumor-feeding artery	93.33	26.67	5.22	8.97
Pishvaian et al, 2023 [47]	III	Gemcitabine	Gemcitabine + +nab-paclitaxel	Tumor-feeding artery	N/A	N/A	14.8 vs 6.7	15.7 vs 10.1
Cao et al, 2024 [39]	Meta-analysis	Various	Various	Celiac trunk, splenic artery, gastroduodenal artery, common hepatic artery, superior mesenteric artery, smaller tumor-feeding arteries	N/A	N/A	N/A	10–21 vs 4.8–14

3 weeks). No interim results or any other publications regarding the trial have been published to date [50].

A phase II—III clinical trial (ClinicalTrials.gov ID NCT03755739), initiated by the Second Affiliated Hospital of Guangzhou Medical University, China, investigates intra-arterial or intratumoral administration of checkpoint inhibitors combined with chemotherapy in advanced solid tumors, including pancreatic cancer. The study design has an experimental group with two subgroups and a control group. The first experimental subgroup uses pembrolizumab ± ipilimumab, administered at a dose of 1—2 mg/kg by 10-minute infusion into the artery via a micropump + chemotherapy every 3 weeks. The second experimental subgroup uses pembrolizumab ± ipilimumab, administered at a total dose of 150 mg intratumorally by fine-needle injection over 5 min, + doxorubicin every 3 weeks. The control group receives pembrolizumab 2 mg/kg intravenously over 30 min + chemotherapy every 3 weeks. There are no interim results or any other publications regarding the study to date [51].

A phase I—II clinical trial (ClinicalTrials.gov ID NCT05187338), also conducted at the Second Affiliated Hospital of Guangzhou Medical University by the same group of scientists, investigates transarterial or intratumoral administration of a triplet of checkpoint inhibitors in advanced solid tumors, including pancreatic cancer. It has only an experimental group, divided into 3 subgroups: ipilimumab + pembrolizumab + durvalumab at a total dose of 1—2 mg/kg intravenously every 3 weeks; ipilimumab + pembrolizumab + durvalumab at a total dose of 1—2 mg/kg intra-arterially via a micropump every 3 weeks, and ipilimumab + pembrolizumab + durvalumab at a total dose of 50—150 mg intratumorally by fine-needle injection every 3 weeks. There are no interim results or any other publications related to the study to date [52].

Active recruitment is also ongoing for the TIGeR-PaC phase III clinical trial, interim results of which have already been reported in review [47].

To sum up, intra-arterial chemotherapy for pancreatic cancer has an acceptable safety profile and is well tolerated. The technique is promising for patients with adequate performance status, who had run out of other potential regimens, in cases of no distant metastases or liver-only metastatic disease, as well as in further clinical trials.

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ВНУТРІШНЬОАРТЕРІАЛЬНА ХІМІОТЕРАПІЯ ПРИ ПОШИРЕНОМУ РАКУ ПІДШЛУНКОВОЇ ЗАЛОЗИ: ОГЛЯД ЛІТЕРАТУРИ

Рак підшлункової залози — надзвичайно агресивна злоякісна патологія, 5-річна виживаність серед усіх стадій якої становить близько 7%. Лікувальні опції нерезектабельних форм обмежені схемами на основі фторпіримідинів та гемцитабіну, а починаючи з 3 лінії терапії, міжнародні настанови не дають однозначних рекомендацій через здебільшого поганий клінічний стан пацієнтів та низьку ефективність подальших ліній. Артеріальна інфузія є багатообіцяючим методом лікування місцево поширеного та метастатичного раку підшлункової залози, обмеженого печінкою, оскільки забезпечує вищу місцеву концентрацію з незмінною чи нижчою системною токсичністю. Найчастіше внутрішньоартеріально використовуються схеми на основі 5-фторурацилу або гемцитабіну. Методика показала переваги в загальній виживаності, частоті відповіді та контролі локальних симптомів у порівнянні з контрольними групами, що включали системну хіміотерапію. Підхід має задовільний профіль безпеки та добре переносився. Метод є перспективним для пацієнтів із задовільним загальним станом, які вичерпали інші потенційні опції лікування, у випадку відсутності віддалених метастазів або обмеженості їх печінкою, а також для подальшого вивчення у клінічних дослідженнях.

Ключові слова: внутрішньоартеріальна хіміотерапія, регіонарна хіміотерапія, внутрішньопечінкова інфузія, внутрішньопідшлункова інфузія, поширений рак підшлункової залози