Modified-FOLFIRINOX combined with deep regional hyperthermia in pancreatic cancer: a retrospective study in Chinese patients

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ABSTRACT

Background: FOLFIRINOX chemotherapy displays significant survival improvements in patients with pancreatic cancer. However, toxicities have hampered enthusiasm for the use of FOLFIRINOX in full dose. In order to increase the tolerability, many researchers focused on the modification of FOLFIRINOX. On the other hand, hyperthermia (HT) has been considered as an effective ancillary treatment for cancer therapy. Up to now, there is no report evaluating combining deep regional hyperthermia (DRHT) with modified-FOLFIRINOX for pancreatic cancer patients.

Methods: In this study, we conducted a retrospective review of pancreatic cancer patients treated with the combination of new form modified-FOLFIRINOX and DRHT. Patients underwent chemotherapy that included low-dose irinotecan (70–130 mg/m²), oxaliplatin (65–70 mg/m²) on day 1 and 5-FU (2400 mg/m² as a 46 h continuous infusion, no bolus) or capcitabine (CAP) (1000 mg/m² twice daily on days 1–10) or tegafur, gimeracil and oteracil potassium (TS-1) (80–120 mg/d twice daily on days 1–10), 2-week schedule. Generally, DRHT treatment was performed weekly, 45 min for each time during chemotherapy.

Results: The patients receiving mFOLFIRINOX as the first line chemotherapy combining with DRHT, obtained an improvement in OS and PFS, 17 months (95% CI 1.97–32.03 months) and 4 months (95% CI 0–8.29 months) respectively. Overall, this combination regimen was safe; 17.6% patients suffered from grade 3/4 toxicities.

Conclusions: In conclusion, we conducted a retrospective study combining mFOLFIRINOX and DRHT, which was well tolerated. The efficacy in the treatment of pancreatic cancer was encouraging, but further studies would be required to prove its merit, compared with conventional treatment.

Introduction

Pancreatic cancer remains the fourth leading cause of cancer-related death over the world in 2015 [1], with a 5-year survival rate of 1–5% [2]. In 2015, there are approximately 90,100 new pancreatic cancer patients in China, with an estimated 79,400 deaths [3,4]. Of all cancers, pancreatic cancer is ranked 10th in incidence and mortality is ranked 7th [3]. Because of lateness in diagnosis, and the biology of pancreas cancer, only 10–20% pancreatic cancer patients present with resectable disease [5]. For most pancreatic cancer patients, especially for those with locally advanced or metastatic pancreatic cancer, systemic chemotherapy is the main choice of treatment [6,7].

The standard treatment for pancreatic cancer has evolved over the last few decades, moving away from 5-fluorouracil (5-FU) or 5-FU combination chemotherapy [8,9] to gemcitabine (Gem) or Gem combination chemotherapy [10]. 5-FU has been studied extensively by altering different doses and schedules. However, its response rate rarely exceeds 20% [11]. 5-FU in combination with other drugs offers little improvement, in fact, more toxicities over single-agent 5-FU [11–13]. In 1997, a randomize controlled trial (RCT) demonstrated that Gem was more effective than 5-FU in treating pancreatic cancer, with better median survival (5.6 vs. 4.4 months; \( p = .0025 \)) [11]. Subsequently, a series of studies focused on Gem combination treatment to prolong the survival time of pancreatic cancer patients [14–25]. Gem and Gem combination regimens have been the standard treatment of locally advanced or metastatic pancreatic cancer for over a decade [14–25]. Despite the improvements, overall survival (OS) time has not been satisfactory; median OS ranges from 5.0 to 10.1 months [18,25–27]. Recently, attention has been focused onto the more complex regimen, FOLFIRINOX. The synergism between irinotecan, oxaliplatin and 5-FU has formed the FOLFIRINOX regimen, which was initially prescribed in metastatic colorectal cancer, displaying significant improvements in OS (11.1 vs. 6.8 months), progression-free survival (PFS) (6.4 vs. 3.3 months) and response rate (31.6% vs. 9.4%) comparing to Gem [28] in treating pancreatic cancer.
The survival gain came at a cost, however. Toxicities have hampered enthusiasm for the use of FOLFIRINOX in full dose. Many studies tried to reduce this regimen toxicity without compromising efficacy [29–33]. Stein et al. reduced the dose of FOLFIRINOX with irinotecan (85%) and bolus 5-FU (85%). This attempt decreased the neutropenia, vomiting and fatigue to a great extent, meanwhile maintained the efficacy [31]. Gunturu et al. also tried to decrease the dose of the FOLFIRINOX and indeed obtained a satisfactory result [30]. Mahaseth et al. published their research that during modified-FOLFIRINOX (no 5-FU bolus) regimen, providing growth factors to all patients could improve the safety and guarantee the efficacy [29]. There are few reports about modified-FOLFIRINOX treating Chinese patients. One institution in China evaluated modified-FOLFIRINOX (75% irinotecan, 85% oxaliplatin and no 5-FU bolus) in Chinese metastatic pancreatic cancer patients [4], which indeed provided a better tolerance with similar efficacy to FOLFIRINOX.

On the other hand, regional therapeutic hyperthermia (HT) has been considered as an effective ancillary treatment for cancer therapy, especially in the treatment of head and neck tumors, cervix cancer, breast cancer, melanoma and glioblastoma [34–39]. HT uses high-frequency electromagnetic waves to heat tumor cells to 41–45°C, which can alter the metabolism and the surrounding microenvironment of the tumor cells. Besides that, HT can facilitate the delivery and diffusion of chemotherapeutics by improving blood flow and at the same time strengthen the drug cytotoxicity to tumor cells [40,41]. Thus, HT combining with chemotherapy would enhance the efficacy of chemotherapy.

In this study, we conducted a retrospective review of pancreatic cancer patients treated with the combination of new form modified-FOLFIRINOX (mFOLFIRINOX) (irinotecan, oxaliplatin, 5-FU/5-FU analog) and deep regional hyperthermia (DRHT) in the Second Affiliated Hospital of Dalian Medical University, in order to assess the efficacy and the toxicity of this combination treatment. As far as we know, this is the first report evaluating combining DRHT with new form modified-FOLFIRINOX for pancreatic cancer patients [42]. We hope this report can benefit more pancreatic cancer patients.

Materials and methods

Patients

This report is a retrospective study involving locally advanced, metastatic and postoperative pancreatic cancer patients receiving modified-FOLFIRINOX (irinotecan, oxaliplatin and 5-FU/5-FU analog) and DRHT from January 2014 to February 2018 at the Department of Oncology, the Second Affiliated Hospital, Dalian Medical University. Patients who were histologically or cytologically diagnosed with pancreatic cancer prescribing modified-FOLFIRINOX (mFOLFIRINOX), with or without prior treatments, were eligible for inclusion. Written informed consent was obtained from each patient’s family for the publication of this study. Before each cycle of mFOLIRINOX regimen, patients were evaluated regularly to make sure they were able to tolerate the treatment (Eastern Cooperative Oncology Group Performance Status Scale ≤1, granulocyte count ≥1500 per cubic millimeter, hemoglobin count ≥80 g/L, platelet count ≥80,000 per cubic millimeter, bilirubin ≤1.5 times the upper limit of the normal range, and creatinine ≤the upper limit of the normal range).

Chemotherapy

Full dose FOLFIRINOX consists of oxaliplatin (85 mg/m²), followed by irinotecan (180 mg/m²) and leucovorin (400 mg/m²), followed by 5-FU (400 mg/m²) as a bolus and a 46 h continuous infusion (2400 mg/m²), 2-week schedule. In view of racial differences, Western people’s experience may be not suitable for Chinese patients. The FOLFIRINOX regimen needs to be modified to get a better outcome while attracting more Chinese pancreatic cancer patients to receive this therapy. In our study, the FOLFIRINOX regimen was modified in all patients starting with the first cycle. Dose modifications were made at the treating physician’s discretion, mainly based on patients’ performance status. During the treatment process, we modulated the dose according to the status of patients as well. Patients underwent chemotherapy that included low-dose irinotecan (70–130 mg/m²), oxaliplatin (65–70 mg/m²) on day 1 and 5-FU (2400 mg/m² as a 46 h continuous infusion, no bolus) or capecitabine (CAP) (1000 mg/m² twice daily on days 1–10) or tegafur, gimeracil and otacil potassium (TS-1) (80–120 mg/d twice daily on days 1–10), 2-week schedule. The treatment period could be prolonged depending on patient tolerance.

Patients routinely received palonosetron and dexamethasone for antiemetic prophylaxis. Before initiation of chemotherapy, patients were provided with anti diarrheal medications and were asked to administrate these medications at the first sign of diarrhea. When patients suffered from jaundice, biliary stenting or drainage procedures were performed. Chemotherapy would continue until disease progression, unacceptable toxicity or patients’ refusal.

Deep regional hyperthermia (DRHT)

DRHT integrated in multimodal approaches is recommended for patients with unresectable deep-seated tumors. DRHT was carried out according to European Society for Hyperthermic Oncology (ESHO) quality and safety assurance guidelines [43,44] using the annular phased-array system BSD-2000 (BSD Medical Corporation, Pyrexar Medical, Salt Lake City, UT) [45]. The target area of HT was focused on the pancreas or metastatic lesion. The frequency and average output power were 75–120 MHz and 450–550 W, respectively. Based on ESHO protocols quality assurance guidelines, in terms of electromagnetic heating techniques, CT and/or MRI were applied to locate the target area. The amplitude and phase of each channel were adjusted to form a thermal field suitable for the specific tumor shape, which can enable a positioning of the tumor with an accuracy of 1 cm. This approach can reduce the damage to the surrounding normal tissue [46].

The temperature control is a key element influencing the efficacy and security of HT. As the interior temperature of
tumor cannot be obtained directly and noninvasively, BSD2000 establishes a simulation system, giving the thermal mapping according to the parameters of physical characteristic, location and size of tumor, heating frequency, and output power. A typical thermal mapping is shown in Figure 1. The energy densities of different areas are indicated by colors, which can reflect the temperature change of different zones under HT treatment. With the help of unique technique and based on great amount of experiments, BSD2000 achieves that the temperature changes on the projection point (I) and in the tumor area (II) are approximately the same. On the other hand, the temperature of point (I) is measured directly by a noninvasive thermometry subsystem through a probe attached on the skin. Through this measured temperature, we could get the temperature change in area II. The temperature feedback is collected by a computer and can be modulated by the output power so that the tumor temperature is kept at 41–43 °C.

A water bag is used to protect the skin from overheating. Generally, the HT treatment was performed weekly, on the second and ninth day of the chemotherapy regimen, 45 min for each time during the treatment of mFOLFIRINOX regimen. The temperature profile for each HT treatment was collected, based on which an average maximum temperature and the temperatures achieved in 20, 50 and 90% (T20, T50 and T90, respectively) time of all treatments were calculated. Patients were carefully instructed to report any discomfort during treatment. HT treatment was stopped when patients suffered from unacceptable adverse events, or patients refused to receive any more treatment.

**Assessment**

Imaging studies (CT and/or MRI) were checked at baseline and every 8 weeks to assess the tumor burden variation. All scans were systematically reviewed by the investigators for response by RECIST (complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)). Two physicians reviewed the results of imaging studies independently and compared the results with official radiology reports. Images were included in response analysis if patients had received at least two cycles of mFOLFIRINOX regimen prior to image acquisition. Adverse events were graded using National Cancer Institute Common Toxicity Criteria version 4.0 (Rockville, MD). PFS was defined from the start of therapy until the date of first documented progression. OS was calculated from initial time of therapy until date of death or loss to follow-up. Data collection was stopped in February 2018.

**Statistical analysis**

Survival was calculated by the Kaplan–Meier method. All calculations and survival displays were conducted using the SPSS version 21.0 statistical software package (SPSS, Chicago, IL) [29].

**Results**

**Patient characteristics**

From January 2014 to February 2018, 17 patients, with locally advanced, metastatic and postoperative pancreatic cancer were treated with at least one period of mFOLFIRINOX. The baseline patient characteristics are shown in Table 1. The range of age was 46–74, with a mean age of 56. All the patients had an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. The primary tumor of pancreatic cancer located in the head, body, and tail of the pancreas in 7 (41.1%), 5 (29.4%) and 5 (29.4%) patients, respectively. The past treatments that these patients had are shown in CONSORT diagram (Figure 2). Twelve patients received...
mFOLFIRINOX combined with DRHT, while the other five patients received only mFOLFIRINOX. Fourteen patients (82.3%) had metastatic disease and two patients had locally advanced pancreatic cancer at the beginning of mFOLFIRINOX regimen. Only one patient received mFOLFIRINOX as adjuvant chemotherapy. Of the 14 metastatic pancreatic cancer patients, 6 (42.8%) were first line of chemotherapy, 8 (57.1%) had two more further lines of chemotherapy. Seven (41.1%) patients received CAP and six (35.2%) patients prescribed TS-1, while four (23.5%) patients received 5-FU during the treatment. Two patients received the percutaneous transhepatic cholangial drainage (PTCD) because of obstructive jaundice. The baseline laboratory testing outcomes, such as tumor biomarkers, hematological index and hepatorenal function are also listed in Table 1. Elevated CA19-9 levels were found in 15 patients (88.2%) before chemotherapy. Average maximum temperature was 41.8 °C (95% CI 40–43.2 °C), T20, T50 and T90 were 40.8 °C (95% CI 39–43 °C), 40.3 °C (95% CI 38.5–42.5 °C) and 39.2 °C (95% CI 37.5–40 °C) respectively.

Table 1. Patient characteristics at baseline.

| Patients characteristics | N = 17 |
|--------------------------|--------|
| Age-mean (range)         | 56     |
| Gender-no. (%)           |        |
| Male                     | 12 (70.5) |
| Female                   | 5 (29.5) |
| No. of the patients received mFOLFIRINOX and DRHT | 12 |
| No. of the patients received only mFOLFIRINOX | 5 |
| No. of metastatic PC patients | 14 |
| No. of local advanced PC patients | 2 |
| No. of adjuvant chemotherapy | 1 |
| Smoke-no. (%)            |        |
| No                       | 12 (70.5) |
| Yes                      | 5 (29.5) |
| Alcohol-no. (%)          |        |
| No                       | 12 (70.5) |
| Yes                      | 5 (29.5) |
| Presenting               |        |
| Jaundice                 | 2      |
| Pain                     | 2      |
| Weight loss              | 2      |
| Co-morbidities-no. (%)   |        |
| Hypertension             | 5 (29.5) |
| Diabetes mellitus        | 9 (52.9) |
| Coronary heart disease   | 0      |
| Chronic obstructive pulmonary disease | 0 |
| Other malignancy         | 0      |
| History of pancreatitis  | 0      |
| Hashimoto thyroiditis    | 15.8   |
| Hepatitis                | 15.8   |
| Atrial fibrillation      | 15.8   |
| Family history           | 4(23.5)|
| ECOG performance score-no. (%) |       |
| 0                        | 13 (76.4) |
| 1                        | 4 (23.5) |
| 2                        | 0       |
| Pancreatic tumor location-no. (%) |    |
| Head                     | 7 (41.1%) |
| Body                     | 5 (29.5%) |
| Tail                     | 5 (29.5%) |
| Metastatic sites-no. (%) |        |
| Liver                    | 13 (92.8) |
| Lung                     | 3 (21.4) |
| Lab tests—mean           |        |
| CA19-9 (U/mL)            | 11,299 (3–140,000) |
| Carcino-embryonic antigen (U/mL) | 163 (1–159) |
| Albumin (g/L)            | 42 (33–50) |
| Serum creatinine (umol/L) | 57.3 (36–72) |
| Total bilirubin (umol/L) | 18.9 (6–74) |
| Blood platelet (10^9/L)  | 230 (91–368) |
| Hemoglobin               | 126 (107–146) |
| White blood cell (10^9/L) | 5.81 (3–13) |

*The initial lab test results after admission.

**One patient demand to receive FOLFIRINOX when bilirubin was much higher than normal. After two cycles of mFOLFIRINOX regimen, the bilirubin gradually decreases to normal.

Toxicity

Modified-FOLFIRINOX

The adverse events reported in this study are shown in Table 2. We observed three patients (17.6%) with grade 3/4 toxicities. Two patients who received combination treatment of chemotherapy and regional HT developed grade 3 neutropenia. One patient treated with chemotherapy alone developed grade 4 diarrhea. Three patients (17.6%) treated with the combination treatment stopped treatment after the first cycle when suffering grade 2/3 adverse events. For hematologic toxicities, 11 patients (8 with combination treatment and 3 with chemotherapy) required granulocyte-colony stimulating factor (G-CSF) treatment during chemotherapy. Moreover, 8 patients (6 with combination treatment and 2 with chemotherapy alone) received interleukin 11 therapy. No patients were treated with provided with hemopoietin. No other unexpected or severe toxicities, such as neutropenia or thromboembolism were observed in our study. Overall mFOLFIRINOX was safe.

Hyperthermia (HT)

Overall, grade 1/2 (mild) position-related pain during HT treatment was the main side effect. No patient gave up HT as a result of adverse events and there was no treatment-related death.

Efficacy

The median number of mFOLFIRINOX treatment cycles was 5 (range, 1–12 cycles). Fourteen patients received mFOLFIRINOX for at least two cycles, among which, 10 patients had SD, 3 patients got PD, and one was lost to follow up. The disease control rate (CR + PR + SD) was 76.9%.

Seventeen patients, with locally advanced, metastatic and postoperative pancreatic cancer were treated with at least one cycle of mFOLFIRINOX. The past treatments that these patients received are shown in CONSORT diagram (Figure 2). The corresponding relationship between these patients and the OS & PFS results (Kaplan–Meier plots in Figures 3–5) is also indicated in the CONSORT diagram (Figure 2). Fourteen patients had metastatic pancreatic cancer. Six patients received mFOLFIRINOX as first line chemotherapy. Their median OS and PFS were 10 months (95% CI 0.00–22.00 months) and 2 months (95% CI 0.0–5.60 months), respectively (Figure 3). Eight patients underwent mFOLFIRINOX as the second line or further line chemotherapy. Their median OS and PFS were 6 months (95% CI 1.08–10.92 months) and 1 month (95% CI not estimable), respectively (Figure 4). Twelve metastatic patients underwent
mFOLFIRINOX combined with DRHT. Five received mFOLFIRINOX as first line chemotherapy. Their OS and PFS were 17 months (95% CI 1.97–32.03 months) and 4 months (95% CI 0–8.29 months), respectively (Figure 5). Two of the five patients were able to undergo resection after mFOLFIRINOX regimen. Actually, only one of the two patients chose to receive the surgery and indeed benefit from the excision.

For the two locally advanced pancreatic cancer patients, they were both alive in February 2018. Their survivals were 9 and 3 months, respectively. For the one patient receiving mFOLFIRINOX as adjuvant chemotherapy, tumor recurrence had not happened. As of the time of writing of this article, the survival of this patient was >4 years.

Table 2. Adverse events.

| Events                        | Pancreatic cancer patients with mFOLFIRINOX and DRHT | Pancreatic cancer patients with mFOLFIRINOX only |
|-------------------------------|-----------------------------------------------------|--------------------------------------------------|
|                               | N = 12      | 3/4 grade | N = 5      | 3/4 grade |
| Hematologic—no. (%)           |            |           |            |           |
| Neutropenia                   | 12 (100)   | 2         | 5 (100)    | 0         |
| Febrile neutropenia           | 0 (0)       | 0         | 0 (0)       | 0         |
| Thrombocytopenia              | 1 (8.3)     | 0         | 1 (20)     | 0         |
| Anemia                        | 0 (0)       | 0         | 0 (0)       | 0         |
| Non-hematologic—no. (%)       |            |           |            |           |
| Infection                     | 0 (0)       | 0         | 0 (0)       | 0         |
| Fatigue                       | 3 (25)      | 0         | 2 (40)     | 0         |
| Vomiting                      | 3 (25)      | 0         | 2 (40)     | 0         |
| Diarrhea                      | 2 (16.6)    | 0         | 1 (20)     | 1         |
| Sensory neuropathy            | 0 (0)       | 0         | 0 (0)       | 0         |
| Elevated level of ALT         | 4 (33.3)    | 0         | 1 (20)     | 0         |
| Thromboembolism               | 0 (0)       | 0         | 0 (0)       | 0         |
| Hematopoietin                 | 0 (0)       | 0         | 0 (0)       | 0         |
| G-CSF                         | 8 (66.6)    | 0         | 3 (60)     | 0         |
| IL-11                         | 6 (50)      | 0         | 2 (40)     | 0         |
| TPO                           | 0 (0)       | 0         | 0 (0)       | 0         |
| EPO                           | 0 (0)       | 0         | 0 (0)       | 0         |

Notes: G-CSF: granulocyte-colony stimulating factor; IL-11: interleukin 11; TPO: thrombopoietin; EPO: erythropoietin.

Figure 2. A CONSORT diagram of the study.

Figure 3. Survival analysis of metastatic pancreatic cancer patients receiving mFOLFIRINOX as the first line chemotherapy.
Pancreatic cancer's prognosis is extremely dismal. Therefore, multi-disciplinary therapy and selection of optimal treatment means are crucial for achieving prolonged survival. FOLFIRINOX chemotherapy can provide dramatically efficacy in locally advanced and metastatic pancreatic cancer patients with observably increased survival, compared to Gem mono-therapy or combined treatment [4,25,26].

The different mechanisms of the three drugs (irinotecan, oxaliplatin and 5-FU) and their nonoverlapping toxicities provided the rationale for regimen of FOLFIRINOX [47], which has initially been used in several gastrointestinal malignancies. Irinotecan, a camptothecin analog, has been shown to have a higher growth inhibitory effect than cisplatin, mitomycin and 5-FU in pancreatic adenocarcinoma cells in vitro [48]. SN-38, the main active metabolite of irinotecan, and oxaliplatin showed synergistic activity in vitro, delaying the reversion of oxaliplatin inducing DNA inter-strand cross-links [49]. Preclinical studies have indicated SN-38 sequentially diminishes DNA synthesis, inhibiting dUMP synthesis and enhancing efficacy of 5-FU when irinotecan precedes 5-FU/leucovorin [50–52]. On the basis of these encouraging results, FOLFIRINOX has been used in pancreatic cancer treatment with promising results. However, many physicians hesitate to prescribe FOLFIRINOX for pancreatic cancer patients because of its considerable toxicity. The association of three drugs is reported with a higher rate of grade 3/4 adverse toxicities, compared with Gem, including hematologic toxicity, sensory neuropathy and digestive system toxicity, which may limit its applicability [26]. Many investigators have tried to improve patients’ tolerance to this chemotherapy through decreasing the dose of the regimen and they indeed get some satisfactory outcomes [29–33].

In this article, we applied a novel combination regimen, which united mFOLFIRINOX with DRHT. The dose of irinotecan was as low as 70–130 mg/m², meanwhile, CAP or TS-1 were applied as alternatives of 5-FU. The pancreatic cancer patients receiving this regimen indeed benefited in both tolerability and efficacy. The metastatic pancreatic cancer patients who received mFOLFIRINOX as the first line chemotherapy obtained an OS of 17 months, which was longer than that reported by Corney’s (11.1 months) [26]. Eight patients underwent mFOLFIRINOX as the second line or further line chemotherapy with median OS of 6 months. It was quite a remarkable result which can be compared with other studies’ outcomes of second line FOLFIRINOX chemotherapy [53,54].

Overall our modified regimen was well tolerated. Only 17.6% patients suffered grade 3/4 neutropenia and diarrhea. What is more, we observed no grade 3/4 fatigue, sensory neuropathy or vomiting. Compared with former studies [29–33], our modification suggested a good tolerability. Combinations of DRHT with mFOLFIRINOX did not yield any additional toxicities over those yielded by FOLFIRINOX or mFOLFIRINOX regimen.

Low dose irinotecan and replacing 5-FU with oral drugs can significantly decrease adverse events. It is a recommended way to reduce the adverse events by decreasing the dose of regimen. By reducing the dose of irinotecan, diarrhea has been reduced, which was caused by SN-38, active form of irinotecan, accumulating on the intestinal epithelium. What is more, hematologic toxicities, hepatotoxicity and many other kinds of toxicities were also decreased, compared with low dose irinotecan. As a result, in our study, we observed good tolerability.

CAP and TS-1 are orally-administered chemotherapeutic agents [55,56], which can be well absorbed after oral ingestion and gradually converted to 5-FU in the body. Thus, they have widely been applied in multiple kinds of tumors treatment as alternatives of 5-FU. Meanwhile, the convenience of
oral administration makes CAP and TS-1 attractive treatment options in various kinds of cancers [18,57]. Experiments have demonstrated that CAP and TS-1 can provide improved tolerability and similar efficacy of 5-FU in the treatment of pancreatic cancer [17,18,27,58–60]. Thus in this study, we replaced 5-FU with CAP or TS-1 in the regimen of FOLFIRINOX, increasing the convenience and tolerance to the chemotherapy, at the same time, maintaining efficacy.

Combining DRHT with mFOLFIRINOX can help to kill tumor cells and at the same time enhance the efficacy of chemotherapeutics. The regimen of mFOLFIRINOX consists of three different kinds of chemotherapy agents, oxaliplatin, irinotecan and 5-FU. Rietbroek et al. [61] demonstrated that the efficacy of oxaliplatin was increased by 180% at 43 °C, in vitro. This occurred because of enhancement of platinum-DNA adduct formation in human lung cancer cells. Urano et al. [62] showed that the thermal enhancement ratio of oxaliplatin increased with the rise in the temperature in mouse fibrosarcoma cells, in vitro. Kondo et al. [63] showed that HT increased irinotecan induced DNA strand breaks in mouse mammary carcinoma FM3A cells. Katschinski et al. [64] confirmed that HT can enhance the cytotoxicity of SN-38, the main active metabolite of irinotecan, through increased Topo I activity in human lung cancer cells.

A number of investigators have indicating that exposure time of 5-FU before the administration of HT is critical determinants of its cytotoxicity. Urano et al. [65] and Monge [66] demonstrated a weak relationship between 5-FU and HT when graded doses of 5-FU were given within 5 or 15 min before HT in mouse tumors. Takemoto et al. [67] also reported that 5-FU has the smallest thermal enhancement ratio (1.1) in mice mammary carcinoma when the agents were given by intraperitoneal injection immediately before HT. Oppositely, when 5-FU was administered before HT for over 2 h, some positive results were observed. In vitro, Kido et al. [68] showed that 48 h exposure to 5-FU caused Chinese hamster lung fibroblasts to accumulate in S-phase. Cells in this part of the cell cycle were shown to be more sensitive to HT. Mini et al. [69] showed that cytotoxic effects would be enhanced when a longer exposure (4 and 8 h) to 5-FU followed heat (42 °C for 1 and 2 h). Heat exposure (42 °C for 1 and 2 h) induced a rapid decrease in the synthesis of DNA of human leukemia cells. In our study, 5-FU was either orally taken or intravenously injected over 2 h before HT. According to the above references, we presumed that HT could help to increase the cytotoxicity of 5-FU.

The above research results basically indicated the enhanced cytotoxicities of oxaliplatin, irinotecan and 5-FU by HT. This positive effect could be explained by two aspects. On one hand, HT can alter the pathophysiology of tumor cells by many modalities, such as DNA adduct formation [61], DNA strand breaking [63], Topo I activity [64], synthesis of DNA [69] and cell cycle [68].

On the other hand, HT is also believed to be able to affect the microenvironmental factors of tumor cells, such as perfusion and oxygenation, improving its sensitivity to chemotherapeutics [70–73]. Song et al. [74] summarized in a review that an improvement in tumor oxygenation caused by HT resulted from a heat-induced increase in blood perfusion in human breast, head and neck cancers. They confirmed that 39–42 °C was the temperature range which can improve oxygenation for up to 1–2 days. Jones et al. [75] also found that HT was able to improve the tumor oxygenation which led to consequent treatment response in locally advanced human breast cancer. In normal conditions, pancreatic cancer is quite resistant to conventional therapies. This resistance can be explained by abundant and compact accumulation of nontumor cells and extracellular matrix, known as the stroma, which can hamper vascularization and the delivery of chemotherapeutics, at the same time, obstruct the transportation of oxygen, causing hypoxia [76]. Sensitivity to chemotherapeutics could be decreased by hypoxic microenvironment, leading to negative prognosis [77,78]. Although no direct experimental evidence has revealed that HT would lead to improved perfusion/oxygenation in pancreatic cancer. Considering its effects on breast, head and neck cancers listed above, we suppose there may also exist an enhancement effect in blood flow in pancreatic cancer. Interstitial pressure can be reduced and vessel permeability can be promoted slightly by HT in the region of interest. Thus hypoxia is decreased and PH value around tumor cells can be modulated. All these effects may facilitate a better inflow of the chemotherapy drugs into the region of tumor [79–81], in addition to increasing tumor sensitivity to chemotherapies [82].

In this combination regimen, low dose irinotecan can significantly decrease the adverse events. Replacing 5-FU with oral drugs can provide patients more flexibility and convenience. What is more, HT is an appropriate method to enhance the effect of chemotherapy and help killing tumor cells. These three aspects produce synergy effect which enable this combination treatment to achieve a satisfactory outcome, reducing the adverse events and maintaining the efficacy. This combination regimen provides a promising choice for pancreatic cancer treatment.

Conclusion

In conclusion, we conducted a retrospective study about combination mFOLFIRINOX and DRHT, which demonstrated well tolerability and efficacy in pancreatic cancer patients. Limitation of this study is small sample size. Based on the results of this study, a randomized trial focusing on first line or further line treatment of locally advanced or metastatic pancreatic cancer will be necessary in the near future to further clarify the factors and mechanism influencing the efficacy of this combination therapy.

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Disclosure statement

No potential conflict of interest was reported by the authors.
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