Original Article

Combination of Recombinant Adenovirus-p53 with Radiochemotherapy in Unresectable Pancreatic Carcinoma

Jin-luan Li[1*], Yong Cai[1*], Shan-wen Zhang[1**], Shao-wen Xiao[1], Xiao-fan Li[1], You-jia Duan[1], Yong-heng Li[1], Bo Xu[1], Kun Yan[2]

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), [1]Department of Radiotherapy, [2]Department of Ultrasonography, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Beijing 100142, China.

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ABSTRACT

Objective: To assess the safety and efficacy of the combination of recombinant adenovirus-p53 (rAd-p53) with radiochemotherapy for treating unresectable pancreatic carcinoma.

Methods: The eligible patients received concurrent rAd-p53 intratumoral injection and radiochemotherapy. Intratumoral injection of rAd-p53 was guided by B ultrasound. Radiochemotherapy consisted of intensity-modulated radiotherapy (IMRT) at two dose levels and intravenous gemcitabine (Gem). For radiotherapy, gross target volume (GTV) and clinical target volume (CTV) were 55-60 Gy and 45-55 Gy in 25-30 fractions, respectively. Concurrent intravenous gemcitabine was administered at 350 mg/m^2, weekly, for 6 weeks. The primary end points included toxicity, clinical benefit response (CBR) and disease control rate (DCR). The secondary end points included progression-free survival (PFS) and overall survival (OS).

Results: Fifteen eligible patients were enrolled. Eight patients (53.3%) were evaluated as CBR and 12 (80%) achieved DCR. The median PFS and OS were 6.7 and 13.8 months, respectively. One-year PFS and OS were 40.0% and 51.1%, respectively. There were 8 (53.3%) patients reported grade 3 toxicities including neutropenia (6 patients, 40%), fever (1 patient, 6.7%) and fatigue (1 patient, 6.7%). There was no grade 4 toxicity reported.

Conclusion: Combination of rAd-p53 in unresectable pancreatic carcinoma showed encouraging efficacious benefit and was well tolerated. Long-term follow-up is needed to confirm the improvement of PFS and OS.

Key words: Recombinant adenovirus-p53; Radiochemotherapy; Pancreatic carcinoma

INTRODUCTION

Pancreatic cancer is responsible for approximately 5% of cancer-related deaths and is the eighth most common cause of cancer-related death for both genders worldwide[1]. Its prognosis remains very poor. Combined all stages, the 1- and 5-year survival rates are only 23% and <5%, respectively[2]. Surgery is only one of possible curative treatment, but unfortunately only 15%-20% of patients present resectable disease at the time of diagnosis[3]. Advanced pancreatic cancer has an even poorer prognosis: a median survival of 2-6 months for metastatic disease and 6-11 months for locally advanced disease[4].

Treatment options for advanced pancreatic cancer include systemic chemotherapy, radiotherapy and combination of radio- and chemo-therapy. Previous randomized trials had shown that radiochemotherapy was superior to radiotherapy alone in treatment of locally advanced patients[5, 6]. The treatment for patients with systemically advanced disease remains palliative and these patients should be offered an opportunity to take new available treatments[7]. For more than a decade, gemcitabine (Gem) has been one choice for these patients based on the results of a randomized trial of Gem versus fluorouracil[8]. The Radiation Therapy Oncology Group trial showed that continuous infusion of Gem and fluorouracil combined with radiation therapy increased overall survival although not statistically significant[7].

p53 gene mutation (tumor suppresser gene) is found up to 50% to 75% of tumors, permitting tumor cells to bypass DNA damage control checkpoints and contributing to genomic instability[8]. Recent studies in genetically engineered mouse models had shown that targeted activation of Kras2 with concomitant inactivation of p53 or Cdkn2A/Ink4A results in development of pancreatic cancer[9-11]. It had been demonstrated that p53 plays a key role in cell cycle arrest and apoptosis, and in cellular response to DNA damage induced by irradiation, hyperthermia, and cytotoxic agents and that rAd-p53 transfection results in suppression and reversal of the malignant phenotype and induces sensitization to conventional treatment. The long-term follow-up of a randomized study of our department had shown that combination of radiotherapy and rAd-p53 improved the

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* Contributed equally to this study.
** Corresponding author.
E-mail: zhangshw4641@sina.com

tumor control rate and survival rate in patients with nasopharyngeal carcinoma (NPC)[12]. Another trial suggested that intraperitoneal treatment with AxCAp53 (recombinant adenovirus carrying a wild-type p53 gene) and cisplatin was beneficial for peritonitis carcinomatosa of ovarian cancer[13]. rAd-p53 was also able to inhibit the growths of pancreatic cancer cell lines and subcutaneous human pancreatic cancerous xenografts in nude mice[14-17]. These findings support rAd-p53 for treatment of pancreatic cancers in clinic.

Here, we report the preliminary results of radiochemotherapy combined with rAd-p53 in treatment of unresectable pancreatic carcinoma.

MATERIALS AND METHODS

rAd-p53

rAd-p53 (Gendicine®; China Shenzhen SiBiono GeneTech Co., Ltd, Shenzhen, China) is a recombinant replication-incompetent human serotype 5 adenovirus, in which the E1 region is replaced by a human wild-type P53 expression cassette. rAd-p53 was stored at -20℃ in concentrations of 1×10^{12} virus particles/ml, and was thawed before injection and diluted in 2-4 ml, or 1500 ml of normal saline for intratumoral injection or intraperitoneal perfusion, respectively.

Trial Design

This trial was a single-arm, nonrandomized clinical trial of combined radiochemotherapy with rAd-p53 in treatment of unresectable pancreatic carcinoma. The primary end points included toxicity, clinical benefit response (CBR) and disease control rate (DCR). The secondary end points included progression-free survival (PFS) and overall survival (OS). This trial was approved by the Ethical Committee for Clinical Research of Beijing Cancer Hospital. It is in accordance with the Helsinki Declaration. And all patients had signed the informed consents before being recruited into the trial.

Patients

Eligibility criteria were as follows: histologically diagnosed as pancreatic adenocarcinoma; age between 18 and 80 years; unresectable disease assessed by surgeons and radiologists; life expectancy longer than 3 months; Karnofsky performance status (KPS) ≥60; adequate liver and kidney function (AST, ALT, blood urea nitrogen, and creatinine <1.5 times the upper limit of normal) and adequate bone marrow reserve (WBC count $\geq3.0\times10^9$/L; hemoglobin ≥90 g/L; platelet count $\geq100\times10^9$/L).

Exclusion criteria included: non-adenocarcinoma; pregnant or nursing women; previous malignancies within 5 years; active infection; and prior history of abdominal radiation therapy.

The 6th edition of TNM staging standard of American Joint Committee on Cancer (AJCC) was used for staging. Stage III was defined as T4NxM0 (Tumor extends directly into the celiac trunk and/or the superior mesenteric artery without distant metastasis). Stage IV was defined as TxNxM1 (distant metastasis includes liver, abdominal cavity, peritoneum, etc.).

Treatment

The intratumoral injection of rAd-p53 was given at a dose of 1×10^{12} virus particles weekly for 6 weeks guided by B ultrasound.

Radiochemotherapy was started the 2nd day after the first injection of rAd-p53. It consisted of intensity-modulated radiotherapy (IMRT) and intravenous infusion of Gem (Gemzar; Eli Lilly & Co, Indianapolis, IN, USA) at a dose of 350 mg/m^2 weekly for 6 weeks. IMRT consisted of gross target volume (GTV) 55-60 Gy and clinical target volume (CTV) 45-55 Gy (10-MV photons) in 25-30 fractions, 1.8-2 Gy for each fraction and five times per week. GTV was defined as primary tumor and metastatic lymph node. CTV included GTV and a margin of 1-2 cm. Planning target volume (PTV) included CTV and a margin of 0.5 cm. If the tumor spread in the peritoneal cavity, intraperitoneal perfusion of 1×10^{12} virus particles diluted in 1500 ml normal saline was performed once a week for 6 weeks through abdominal indwelling catheter. The intraperitoneal perfusion of rAd-p53 was performed weekly 3 days before abdominal hyperthermia at 41-42℃ using a 41 MHz radiofrequency machine for 1 h with cisplatin 50 mg perfusion conducted with 1500 ml normal saline concurrently. Abdominal temperature was maintained at 41-42℃ which was confirmed by a thermo-sensor during hyperthermia (Figure 1).

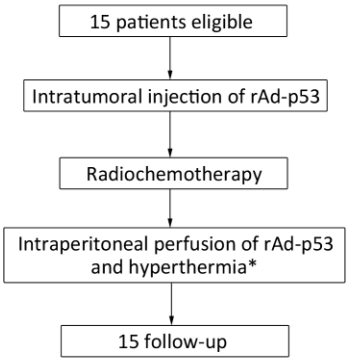

Figure 1. The treatment schema. *The patients with abdominal cavity metastasis.

Assessments

Pretreatment baseline evaluation included complete medical history, physical examination, vital signs (including weight, pain, pulse, and blood pressure), ECG, chest radiography, abdominal ultrasound, abdominal computed tomography (CT), documentation of KPS, and complete laboratory tests (blood routine, urine routine, stool routine, liver and kidney function and CA19-9).

Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST)[18]. Objective responses (complete or partial) were evaluated at least 4 weeks after treatment. Disease control rate (DCR) included complete response (CR) plus partial response (PR) and plus

stable disease (SD).

CBR was defined as improvement from baseline for ≥4 consecutive weeks in pain (pain intensity or analgesic consumption), KPS and weight, at least one of them improved and others kept stable[19] (Figure 2).

Toxicities were analyzed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0.

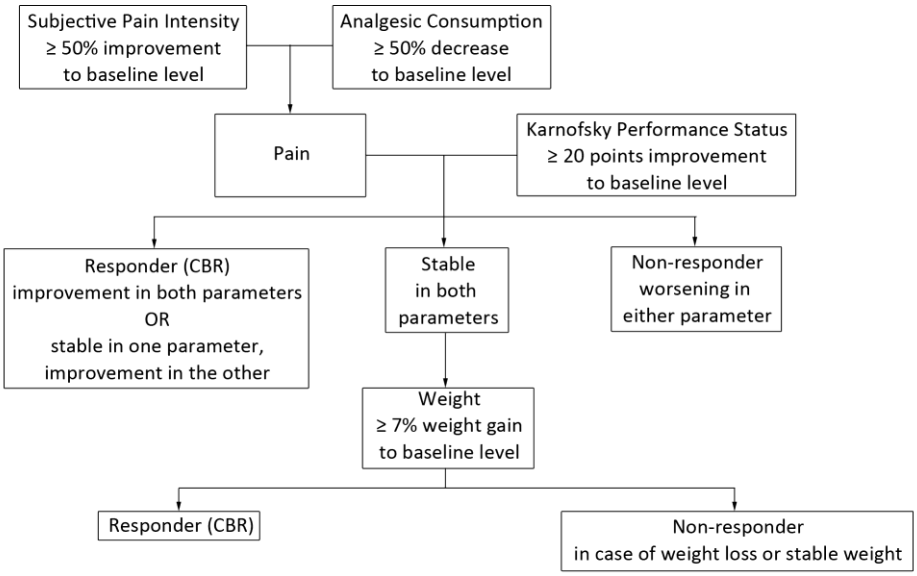

Figure 2. Definition of CBR.

Statistical Analysis

A 45% one-year overall survival rate was considered promising, while a 25% one-year overall survival rate was not considered promising. According to Chen's optimal three-stage designs for phase II oncology clinical trials[20], we planned to enroll 15 patients for the first stage (α=0.005; β=0.1). If a minimum relative risk (RR) of 20% (3/15) was achieved, the study will continue to enroll another 18 patients for the second stage.

OS and PFS were estimated using Kaplan-Meier method. Statistical analysis was performed using SPSS 11.5 statistical software (SPSS Inc, Chicago, IL). A value of $P \leq 0.05$ was considered to be statistically significant.

RESULTS

Patient Characteristics

Between February 2006 and August 2010, a total of 15 eligible patients with pancreatic adenocarcinoma received the combination of radiochemotherapy with rAd-p53. A total of 85 times of intratumoral injection was performed in the trial. The median GTV dose was 55 Gy (38-60). The median time of Gem by intravenous administration was 2 times (0-5). Five of them who had peritonitis carcinomatosa received intraperitoneal perfusion of rAd-p53 combined with abdominal thermochemotherapy. The median time of intraperitoneal perfusion of rAd-p53 was 5 times (1-14). Three patients received intraperitoneal perfusion of Gem and cisplatin, and the other 2 patients received Gem alone. Patient characteristics are listed in Table 1. The median age was 62 (38-72) years old. There were 7 and 8 patients diagnosed as stage III and IV (4 with abdominal cavity metastasis, 4 with liver metastasis), respectively.

Table 1. Patient characteristics (n=15)

Characteristic	Data
Gender [n (%)]	
Male	10 (66.7)
Female	5 (33.3)
Age [median (range)] (y)	62 (38-72)
Average baseline pain intensity score*	
Median	5
Range	0-7
Karnofsky performance score**	
Median	80
Range	60-90
Disease [n (%)]	
Locally advanced	7 (46.7)
Metastatic	8 (53.3)
Primary tumor (cm)	
Median	4.8
Range	2.9-7.3
CA19-9 (U)	
Median	2955
Range	86.4-8489.0
GTV dose (Gy)***	
Median	55
Range	38-60

*Patient self-estimation on visual analog scale (range, 0 to 10 from least to worst possible pain). **According to the judgment of the treating physician. ***GTV: gross tumor volume.

Table 2. Acute toxicity (n=15)

Toxicity	n (%)
Hematologic	
Neutropenia	
Grade 1-2	9 (60)
Grade 3	6 (40)
Anemia	
Grade 1-2	12 (80)
Thrombocytopenia	
Grade 1-2	4 (26.7)
Nonhematologic	
Nausea and vomiting	
Grade 1-2	6 (40)
Fever	
Grade 1-2	13 (66.7)
Grade 3	1 (6.7)
Fatigue	
Grade 1-2	12 (80)
Grade 3	1 (6.7)
All Grade 3 toxicity*	8 (53.3)

*No Grade 4 toxicity was observed.

Safety

The majority of treatment-related adverse events were grade 1 or 2 toxicities. Toxicities are summarized in Table 2. Grade 3 toxicities were neutropenia (6 patients, 40%), fever (1 patient, 6.7%) and fatigue (1 patient, 6.7%). No grade 4 toxicity was observed. Fever (14 patients, 93.3%) was the most frequent toxicity in the trial. All fever events were transient and self-limited. One patient experienced the grade 3 fatigue after finishing the intratumoral injection of rAd-p53 four times and GTV dose of 40 Gy. There was no serious adverse related with intratumoral injection events, such as massive hemorrhage, pancreatitis and pancreatic fistula. There was no treatment-related death in this trial.

CBR and DCR

In this trial, only one patient had slight improvement in weight, nine patients had loss of weight during the treatment. Eight patients (53.3%) had a CBR. Of these 8 patients, 5 patients (62.5%) got improvement in pain (≥50% improvement to baseline level in subjective pain intensity or ≥50% decrease to baseline level in analgesic consumption). The remaining 3 patients (37.5%) had improvement in KPS.

The overall response rate was 13.3% (2 of 15): 0 CR and 2 PR. SD was 66.7% (10 of 15). The disease control rate (CR + PR + SD) was 80% (12 of 15). Other 3 patients had progress in liver metastasis during treatment.

CA19-9

All patients were available for CA19-9 assessment. Ten patients' (10/15, 66.7%) CA19-9 level decreased, and five patients' (5/15, 33.3%) increased. While, 26.7% (4 of 15) and 46.7% (7 of 15) experienced >90% and >70% decrease of CA19-9 level, respectively. One's CA19-9 level was dramatically decreased from 5,115 U/ml to the normal level, 31 U/ml.

PFS and OS

The median PFS and OS were 6.7 and 13.8 months, respectively. One-year PFS and OS rate were 40.0% and 51.1%, respectively (Figure 3A and 3B).

One-year OS rates were 41.7% and 38.1% for the CRB group and the non-CRB group, respectively (P=0.277). One-year PFS rates were 50.0% and 20.0% for the CA19-9 improved group and the CA19-9 un-improved group, respectively (P=0.059); and one-year OS rates were 74.1% and 0% for these two groups, respectively (P=0.002).

Nine patients were dead at the last follow-up. Seven patients died of disease progress (5 with systemic progress and 2 with regional progress), and the other two died of upper gastrointestinal bleeding and heart attack, respectively.

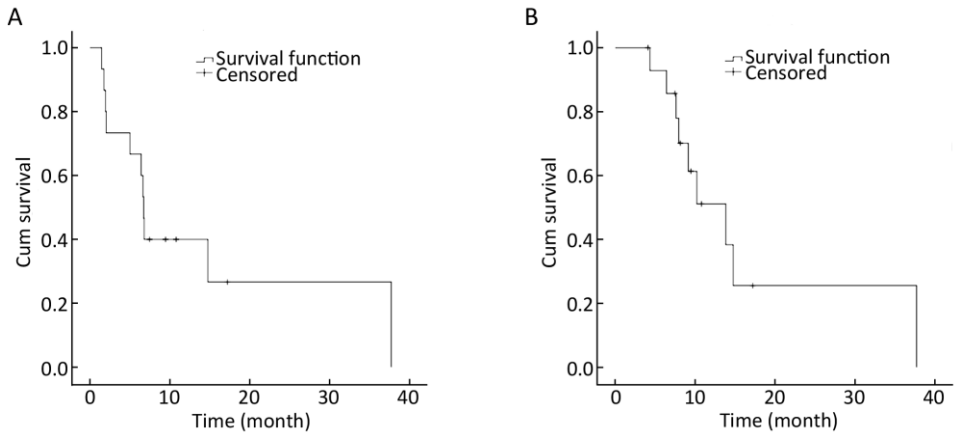

Figure 3. PFS and OS of the trial. A: Progression free survival; B: Overall survival.

DISCUSSION

Although more than 80% pancreatic cancer patients presented locally advanced disease or metastatic disease, the treatment for them remains palliative[7]. This trial was designed to improve CBR, DCR, PFS and OS with tolerable toxicities for the patients with unresectable pancreatic carcinoma. The preliminary results showed the feasibility of

this combining strategy with promising survival benefit and low rate of ≥ grade 3 toxicities.

Gem has been the first-line therapy for patients with advanced pancreatic cancer, considering the improvements in survival and clinical benefit[8]. Multiple new agents with different mechanisms of action in combination with Gem

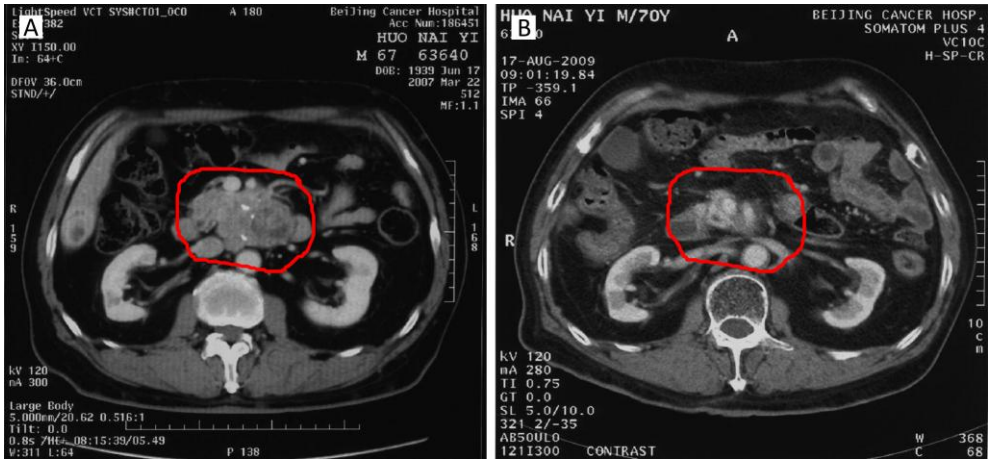

Figure 4. One patient's primary tumor experienced obviously response to the combined treatment after 15 months of enrollment. A: The diameter of the primary tumor was 6.7 cm before treatment; B: There was no obvious disease after the treatment.

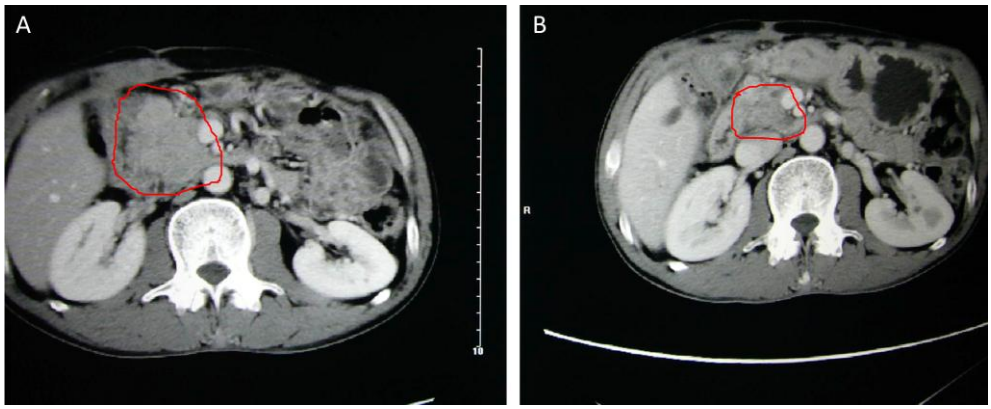

Figure 5. Here is another patient in the study with nearly complete response after 12 months of enrollment. A: The diameter of the primary tumor was 4.9 cm before treatment; B: There was also no obvious disease after the combined treatment.

Table 3. The treatment of each patient in the trial

Patient	Gender	Age (y)	Stage	Injection[a]	Perfusion[b]	GTV[c]	Hyper[d]	Gem[e]	OS[f]
1	Male	71	IV	4	0	60	0	1	14.8
2	Female	48	IV	4	0	40	0	0	6.4
3	Female	72	IV	7	0	55	0	2	10.2
4	Male	68	IV	2	5	45	5	3	37.7
5	Male	42	III	6	1	60	1	5	7.6
6	Male	44	IV	6	0	59	0	1	9.1
7	Female	65	III	6	6	60	6	4	13.8
8	Male	38	IV	6	6	56	14	1	17.2
9	Male	66	IV	5	0	38	0	2	4.4
10	Male	72	III	6	0	55	0	5	8.0
11	Male	53	IV	0	5	60	5	5	10.8
12	Female	62	III	6	0	56	0	3	9.5
13	Male	54	III	6	0	54	0	2	8.1
14	Female	53	III	6	0	54	0	4	7.5
15	Male	68	III	6	0	44	0	2	4.1

[a]The intratumoral injection of rAd-p53 to the primary tumor (times); [b]Intraperitoneal perfusion of rAd-p53 (times); [c]Gross tumor volume (Gy); [d]Hyperthermia (times); [e]Gemzar (times); [f]Overall survival.

have been tested in randomized clinical trials, with no improvement in outcome[21-23]. Erlotinib, a small-molecule inhibitor of the epidermal growth factor receptor (EGFR), is the only agent that, in combination with Gem, has shown a small, but statistically significant improvement in survival among patients with advanced pancreatic cancer[24]. The median OS and 1-year survival rate for the combination of erlotinib and Gem group were 6.24 months and 23%, respectively. While in our trial, the preliminary results are comparable with this trial (the median OS was 13.8 months and the 1-year OS rate was 51.1%).

One notable aspect of this study is the applying of rAd-p53. More than 50% of pancreatic cancer patients have mutations in the p53 gene[25]. Basic researches had found the important function of p53 in the development of pancreatic cancer[11-19]. Tumors with p53 mutation are highly malignant and are resistant to many conventional therapies. And rAd-p53, a recombinant replication-incompetent human serotype 5 adenovirus, had been confirmed to have long-term survival benefit in NPC[12]. This design tried to confirm that rAd-p53 acts as a radiosensitizer, just as the previous trial's results in NPC. Nowadays, the multidisciplinary treatment is recommended for malignant tumor, especially for advanced pancreatic cancer. In order to control the abdominal cavity metastasis, the intraperitoneal perfusion of rAd-p53 in combination with peritoneal thermochemo-therapy was applied. The results showed that DCR was 80%, in accord with our purpose. What's more, most patients (12 of 15, 80%) experienced the decrease of tumor density on CT. The change of tumor density on CT could be the complementarity for RECIST, which named Choi response criteria[26]. The change of tumor density on CT helped us to find out whether the combined treatment was effective on the primary tumor, while the tumor size didn't have obvious change. The safety of intratumoral injection would be an important item in this new design. However, this trial, with 85 times of intratumoral injection, didn't show any severe intratumoral injection events, such as massive hemorrhage, pancreatitis or pancreatic fistula. And no treatment-related death was observed in this trial. These results might approve the safety and efficacy of rAd-p53 for advanced pancreatic cancer.

The therapy regimen in this trial was well tolerated. All grade 3 toxicity rates were 53.3% (8 of 15). And no grade 4 toxicity was observed. Neutropenia (40%), fever (6.7%) and fatigue (6.7%) were the major grade 3 toxicities. The patients with grade 3 neutropenia should be given hematopoietic growth factors. Fever could be the special toxicities relative to rAd-p53, and 93.3% patients developed different degree of fever. All fever events were under control, without special treatment.

Considering the poor prognosis of advanced pancreatic cancer, Burris and Rothenberg et al.[8, 27] introduced the concept of CBR. A recent trial compared CBR in patients receiving Gem plus capecitabine versus single-agent Gem for advanced/ metastatic pancreatic cancer. The CBR was 25% and 27% in the assessable patients of these two groups, respectively[19]. While in our trial, more than half patients (53.3%) achieved CBR. The most common improvement item in CBR was pain. Benefit in weight during treatment was rarely observed.

CA19-9 is the most commonly used marker for pancreatic cancer. It has a sensitivity of 70%–90% and specificity of 90%[28]. CA19-9 is the only biomarker with demonstrated clinical usefulness and is particularly useful for assessing response and identifying early recurrence after treatment in patients with known pancreatic cancer[29-33]. In this design, we took the change of CA19-9 level as one important factor for therapeutic monitoring and prognosis. The results showed that 66.7% (10 of 15) patients experienced CA19-9 level decreasing. In these patients, 70% (7/10) patients had obvious decrease (>70%). Two patients' CA19-9 level decreased to the normal level. These results could further confirm the benefit of this prospective trial.

For the survival benefit, the preliminary results showed the promising median survival time of 13.8 months. One-year and two-year OS were 51.1% and 25.6%, respectively. These results are obviously better than previous data[2, 4]. There was also no significant difference between the CRB group and the non-CRB group for one-year PFS (P=0.718) and OS rate (P=0.277). Nevertheless, there was significant difference between the CA19-9 decreasing group and the non- CA19-9 decreasing group for one-year OS rate (P=0.002). And one-year PFS rate in the CA19-9 decreasing group was obviously better (50.0% vs. 20.0%). It was in accord with the change of CA19-9 in this trial.

Table 3 lists the details of each patient. No. 4 patient with liver and retroperitoneal lymph metastasis had a survival time of 37 months (Figure 4). He received two times of intratumoral injection of rAd-p53 combined with radiotherapy of 45 Gy for primary tumor and five times of intraperitoneal perfusion of rAd-p53 combined with intraperitoneal perfusion of cDDP 50 mg for retroperitoneal lymphocyte metastasis. After 15 months of enrollment, there was no obvious primary tumor and retroperitoneal lymphocyte node through CT scan. A node liver metastasis received radiotherapy of 60 Gy. He died of upper gastrointestinal bleeding at 37 months after treatment. No. 8 patient with greater omentum metastasis has lived for 20 month after enrollment. He received six times of intratumoral injection combined with radiotherapy of 55 Gy and fourteen times of intraperitoneal perfusion of rAd-p53 combined with thermochemotherapy. He is still alive with the normal CA19-9. His primary tumor nearly reached CR at the 12 months after enrollment (Figure 5).

However, the limitations of this study should also be noticed. Firstly, the enrolled sample was small. Next step, we need more patients to prove our conclusion. Secondly, the follow-up is short. We need longer time to observe the survival benefit. Lastly, it is a single-arm, non-randomized single-institution prospective trial. And a phase III trial is further needed to confirm the results above.

In conclusion, the preliminary results of the combination of recombinant adenovirus-p53 (rAd-p53) with radiochemotherapy showed encouraging survival benefit for unresectable pancreatic carcinoma with well tolerance. Long-term follow-up is needed to confirm the improvement of PFS and OS. And a randomized control-labeled phase III trial based on this design would be warranted.

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