Use of Hapten Combined Cytotoxic Drugs for Enhancing Therapeutic Effect in Advanced Stages of Pancreatic Cancer

Abstract

Aim: To evaluate the clinical effectiveness of double cytotoxic drugs enhanced chemo immunotherapy in the treatment of advanced pancreatic cancer compared to single cytotoxic drugs by ultra-minimum incision personalized intra-tumoral chemo immunotherapy (UMIPIC-Therapy).

Method: In study of UMIPIC with double drugs, 41 patients of pancreatic cancer were randomly divided into UMIPIC and ITCT groups, UMIPIC-D (n=30) treated with a proprietary therapeutic regimens including two cytotoxic drugs (Cytosine Arabinoside: Ara-C and Bleomycin: BLM) plus an oxidant and hapten, and ITCT-D (n=11) treated with same regimens intra-tumoral without the hapten. In UMIPIC with single drug, 45 patients of pancreatic cancer were randomly divided into two groups. UMIPIC-S (n=25) treated with a proprietary therapeutic regimens, it is composed of three intra-tumoral injections of a compound with an oxidant, a cytotoxic drug (Ara-C) and hapten. ITCT-S (n=20) uses an oxidant and a cytotoxic drug (Ara-C) without hapten. Both UMIPIC and ITCT use the same clinical therapeutic procedure.

Results: For single drug, median survival was 6.45 months for UMIPIC-S vs 4.98 months for ITCT-S, ($P<0.05$), one year survival rate was 28% for UMIPIC-S vs 5% for ITCT-S ($P<0.05$). For double drugs, median survival was 15.5 months for UMIPIC-D vs 3 months in ITCT-D ($P<0.01$). The 6-month survival rate was 76.67% for UMIPIC-D vs 18.18% for ITCT-D ($P<0.01$) and 1-year survival rate for 56.67% UMIPIC-D vs 9.09% ITCT ($P<0.01$).

Conclusion: UMIPIC for pancreatic cancer is a non-invasive and potentially effective therapy, and double cytotoxic drugs applied in the UMPIC-D revealed a significant advantage in prolonging the survival time.

Keywords: Intra-tumoral chemo immunotherapy; Cytotoxic drugs; Ultra-minimum incision therapy; Pancreatic cancer; Percutaneous intra-tumoral drug delivery

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Abbreviations: UMIPIC-Therapy: Ultra-Minimum Incision Personalized Intra-tumoral Chemo immunotherapy; BLM: Bleomycin; Ara-C: Cytosine Arabinoside; OS: Overall Survival; ITCT: Intra-Tumoral Chemotherapy; DT: Diameter of the Tumor; CR: Complete Response; PR: Partial Response; SD: Stable Disease; EM: Extracellular Matrix

Introduction

Pancreatic cancer, with only a 6% five-year survival rate, and a median survival of 6-9 months, remains one of the most malignant and aggressive cancers. It is the 10th most commonly diagnosed cancer, the 4th leading cause of cancer death in the U.S. [1]. In 2015 approximately 48,960 people were diagnosed with this malignancy, with 40,560 attributed deaths in United States during the period [1]. The lack of progress in prevention, early detection, and diagnosis of this disease is putting the most patients at advanced stage at the time of diagnosis, with only about 15-20% of all pancreatic cancer patients having borderline resectable tumors. Since the most patients are non-operable, the only remaining options of treatment are generally conventional chemotherapy, radiation and targeted therapy separately or combined. Gemcitabine is the current standard chemotherapy regimen for advanced pancreatic cancer. It has shown to have proven efficacy in phase II trials [2], however phase III trials exploring gemcitabine-based combinations have failed to improve overall survival (OS) [3]. Thus the need for optimal treatments in advanced pancreatic cancer remains high, which motivates us to make additional strides to improve therapeutic options.

The concept of intra-tumoral drug delivery has been known for several decades [4]. Some successful examples have clearly shown the clinical feasibility of such treatment options, with significant reduction in both toxicity and tumor growth, but not in pancreatic cancer patients. Pancreatic cancer is located in a crucial organ surrounded by vital tissues and organs such as the duodenum, gallbladder, portal vein, and aorta. Tumor invasion of these organs by pancreatic cancer is most common and could lead to unresectability.

Our published data suggests that UMIPIC (ultra-minimum incision personalized intra-tumoral chemo immunotherapy) offers an ideal percutaneous intra-tumoral approach for chemical de-bulking of advanced lung cancer and advanced hepatocellular carcinoma and the hapten plays an important role in prolonging patients' survival [5,6]. The article herein describes the results for 86 patients with late stages of pancreatic cancer. These patients whose treatment failed with conventional and traditional therapy were treated with UMIPIC and ITCT (Intra-tumoral Chemotherapy: ITCT) with single and double cytotoxic drugs. This data has not been previously reported. The data using single drug and double drugs and oxidant with or without hapten in the study of pancreatic cancer treatment were collected and analyzed. We evaluated UMIPIC-Therapy to possibly provide a new option for clinical effectiveness of hapten-enhanced chemo immunotherapy (a likely cancer autologous vaccine) compared with ITCT. We further analyzed the role of hapten's role as an immune booster in prolonging patients' survival time of pancreatic cancer.

Methods

Patient selection

The patients selected were diagnosed with at least one solid pancreatic cancer tumor at least 1.5 cm in diameter, confirmed by CT imaging, biopsy and pathologic examination to be malignant. Pancreatic cancer patients studied were those whose treatment failed with conventional and traditional therapy and had locally advanced and/or metastatic tumor(s) , they were treated with UMIPIC therapy (single marked as UMIPIC-S and double cytotoxic drugs marked as UMPIC-D) or intra-tumoral chemotherapy (ITCT, single marked as ITCT-S and double cytotoxic drugs marked as ITCT-D). The study was conducted in China from November 1999 to August 2012 in a total of 86 cases. All patients signed the informed consent forms and classified into therapy groups of UMIPIC and ITCT with single during 1999 to 2006 (45 cases) and therapy groups of UMIPIC and ITCT with double drugs during 2007 to 2012 (41 cases), the hospital Ethics Committee with external members approved the study (EC approval letter No. TMBFZLLY001). At the end of follow-up a total of 86 patients remained, UMIPIC-Therapy group (n=55, UMIPIC-S=25; UMIPIC-D=30) had 55 with response data and survival data. The ITCT group (n=31, ITCT-S=20; ITCT-D=11) had 31 with response data and survival data. The baseline characteristics of the patients were well balanced between the two groups with no significantly difference (Table 1) (P>0.05). All of patients had non-operable tumors and had conventional chemotherapy that had failed.

Table 1: Patient Baseline Characteristics.

		Single Drug				Double Drugs			
		ITCT		UMIPIC		ITCT		UMIPIC	
		N	%	N	%	N	%	N	%
Enrolled patients		20	100	25	100	11	100	30	100
Sex	Male	11	55	14	56	6	54.55	15	50
	Female	9	45	11	44	5	45.45	15	50
Age rang		35-68		28-72		50-72		40-80	
Diabetes		8		3		6		1	
Cigarette smoking		5		6		9		3	
Alcohol intake		4		9		8		2	
Cytological diagnosed cancer		20		25		11		30	
Stage of disease	Stage I	0	0	0	0	0	0	0	0
	Stage II	4	20	5	20	1	9.09	1	3.33
	Stage III	4	20	6	24	4	36.36	9	30
	Stage IV	12	60	14	56	6	54.55	20	66.67
Tumor size	<2cm	0	0	0	0	0	0	0	0
	2-5cm	13	65	16	64	7	63.64	16	53.33
	>5cm	7	35	9	36	4	36.36	14	46.67
Disease status	Locally advanced	9	45	12	48	5	45.46	12	40
	Metastatic disease	11	55	13	52	6	54.54	18	60

Indication and contraindications for UMIPIC and ITCT: The following contraindications excluded some patients from the study. Contraindications for treatment with UMIPIC and ITCT were poor performance status (Karnofsky status, ≤ 40%), nutritional impairment, high serum total bilirubin level [>3 mg/dL (51.3 μmol/L)], and renal failure [serum creatinine level >2 mg/dL (176.8 μmol/L)]. Cardiovascular or respiratory failure was a further exclusion criterion for the procedure, as not were partial or complete thrombosis of the main portal vein.

Preparation of agents: As pancreatic tissue is quite fragile, Concerns for injections is bleeding and it may limit the application. Fine needle biopsy is performed in clinical practice for diagnosis and evaluation of treatment for pancreatic organs, requiring a fine needle with sharp tip. Both the 25 gauge spinal needles and the inflators (inflation device, 30 atm/bar) were purchased from Merit-Medical, South Jordan, UT. The UMIPIC (Single & Double drugs) and ITCT (Single & Double drugs) solutions were freshly prepared before each injection. UMIPIC contains clinically approved agents (an oxidant, it can oxidate matrix tissue of tumor, a cytotoxic drug: Cytosine Arabinoside (Ara-C) or Bleomycin (BLM) & Ara-C and hapten, it can bind antigen and enhance anti-gencity) for percutaneous intra-tumoral delivery, ITCT contains a clinically approved oxidant with the cytotoxic drug Ara-C or BLM & Ara-C without hapten (both drugs were saturated concentration) [5-7].

Treatment design: Routine examination of cardiopulmonary function and peripheral complete blood count were done to rule out liver and/or pancreas puncturing or related contraindications, some blood samples were taken before and after treatment for analysis of T cell function.

Patients with pancreatitis, intestinal obstruction and other heavy infections were not allowed to receive this therapy. Prior to UMIPIC-Therapy the patients were asked to fast without water intake for 14 hours pre-treatment in order to avoid side effects and infections. In order to control pain during the treatment, 50 mg of morphine was injected intramuscularly at least 30 minutes pretreatment. The skin was cleansed and local anesthesia performed in the area of injection.

The spinal needle was inserted into the tumor under CT guidance. After insertion the core was taken out of the needle (which was connected to the inflator used as a high pressure syringe), then the injection performed (Figure 1). UMIPIC and ITCT have the same therapeutic procedure, which is minimally invasive. UMIPIC-Therapy or ITCT was delivered by a spinal needle inserted into the tumor and connected with the inflator for injection under pressure (at the level of atmospheric pressure) to obtain full distribution of clinically approved regimens in the tumor. Ultrasound or CT (Picker IQ, Phillips Healthcare, Bothell WA) guidance was used for scanning and monitoring of the density changes at a point or area of interest in the pancreatic tumor (Figure 2A). Special attention was paid to monitoring the CT value changes in the margins of surrounding tumor to ensure full distribution of drugs to the edge of the tumor (Figure 2B,2C). Biopsies were done in patients after treatment for studying of drug distribution and immunohistochemistry. The average time of the procedure took approximately 30-45 minutes, however if the tumor was hard to inject, more pressure was needed to overcome the difficulty to penetrate into the tumor, and a repeat CT would be needed for monitoring. The volume of the injection was calculated based on the diameter of the tumor (Dt) x2 for 1-5 cm of tumor, and (Dt) x1.5 for 6 cm of tumor or more. Each therapy was based on this calculation to deliver adequate dosage into the tumors [5,6,8].

The size of the tumor (tumor mass) is closely re-examined by CT Scanning once a week for 3 weeks; the treatment is repeated each week. Three treatments in total included the initial treatment as one treatment cycle of UMIPIC and ITCT. If the tumor was not stable in size, or smaller after 8-9 weeks when the tumor was re-examined, additional treatment was added to maintain better efficacy. Distant tumors were treated the same as primary pancreatic tumors if the tumor size was larger than 2 cm in other organs, such as liver or abdomen, as determined by CT or ultrasound. Patients were closely monitored for 2 days post-treatment, to determine if significant systemic or local adverse effects needed to be evaluated or treated.

Assessment

The response to treatment in the solid tumor's effect was evaluated as per evaluation criterion of EROTC (European Organization for Research and Treatment of Cancer) and RECIST (NCI, US and Canada) in October 1998 [9]. All case report forms (CRF) were filled by treating physicians. All physicians were trained with standard protocols in each hospital.

Statistical analysis

The statistical analysis was done by experts in a medical college. Overall survival (OS) was defined as the duration from the date of first treatment (not the date of diagnosis) to the date of death, plotted according to the Kaplan-Meier method. Comparisons of effective rates were calculated with the Chi-square test. Statistical analysis was done with SPSS 17.0 statistical software and a P value of <0.05 was considered statistically significant.

Results

Efficacy evaluation

The therapeutic effects were analyzed in 45 patients (Table 2). For single drug of UMIPIC-Therapy, the effective rate [complete remission (CR) + partial remission (PR) / total patients] was 12 % and 21% respectively, beneficial rate [complete response (CR) + partial response (PR) + stable disease (SD) / total patients] was 88% and 95% in the UMIPIC-Therapy and ITCT groups, respectively (Table 2). For the double drug of UMIPIC-therapy, the effective rate was lower than single drug in UMIPIC-Therapy without significant difference while beneficial rate was no different compared to single drug in UMIPIC-Therapy.

The single drug of UMIPIC-Therapy (Table 3) demonstrated comparable efficacy with first line treatments, and showed the longer of median survival time was 6.45 months in UMPIC-S vs 4.98 months in ITCT-S (P<0.05); significantly longer of overall survival for one year was 28% in UMIPIC-S VS 5% in ITCT-S (P<0.05) with minimal disruption of quality of life. The double drug of UMIPIC-Therapy (Table 4) demonstrated remarkable efficacy and significantly longer of median survival time was 15.5

months in UMIPIC-D vs 3 months in ITCT-D (P<0.01); significantly longer of 6-months OS was 76.67% in UMIPIC-D vs 18.18% in ITCT-D (P<0.01) and one-year OS was 56.67% in UMIPIC-D VS 9.09% in ITCT-D (P<0.01). Comparison UMIPIC-D Therapy with UMIPIC-S Therapy (Table 5), it showed significant improvement in the median survival time (15.5 months vs 6.45 months, P<0.01) and one-year survival time (56.67% vs 28%, P<0.01, Figure 3). The improvement of survival time for UMIPIC-D group is relatively promising compared to the survival time reported in other studies. In this study one patient with pancreatic cancer was found with partial remission (Figure 2A & Figure 2B), but two years after the first cycle of UMIPIC treatment, partial remission (PR) was found changed to complete remission (CR) (Figure 2A). Partial remission and tumor stabilization were found in most patients including distant tumors (Figure 2C & 2D). The UMIPIC-S group had an additional 1.5 months of median survival time compared with the ITCT-S group with significant difference (P<0.05) while the UMIPIC-D had an additional 12.5 months of median survival time compared with the ITCT-D group with most significant improvement (P<0.01) and an additional 9 months of median survival time compared to the UMIPIC-S (P<0.01).

Cancer cells dying with debris, dendritic cells, and drug crystals from saturated concentration of drugs in UMIPIC therapy were observed under electronic microscopy in samples of biopsies (Figure 4). Patient's $CD4^+$ and $CD8^+$ changed before and after UMIPIC therapy (Table 6). The ratio indicated that the level of $CD4^+$ T-cells increases after UMIPIC therapy.

The patients had temporary mild fever (not over 38 °C) for a few hours and minor injection pain after the intra-tumoral injection of UMIPAC-Therapy solution, but no severe complications. No other significant systematic or local adverse effects were observed. No bleeding in the needle track or side effects such as myelosuppression, neutropenia, thrombocytopenia, GI toxicity, or apparent loss of hair/ loss of appetite was noted.

Table 2: Comparison of response rate between UMIPIC and ITCT with single or double drugs.

	N	CR	PR	SD	PD	Effective Rate (%)	Chi square	P value	Benefit Rate (%)	Chi square	P value
ITCT-S	25	0	3	19	1	12	0.541	0.462	88	0.672	0.412
UMIPIC-S	20	0	4	15	3	20			95		
ITCT-D	30	0	3	25	2	10	1.187	0.276	93	0.07	0.792
UMIPIC-D	11	0	0	10	1	0			90		

Table 3: Comparison of survival time between UMIPIC-S and ITCT-S.

Group	N	Mean (M)	Median (M)	Log-Rank		6-Month Survival Rate			1-Year Survival Rate		
				χ^2	*P*	%	χ^2	*P*	%	χ^2	*P*
UMIPIC-S	25	6.95	6.45	5.586	0.018	64	1.62	>0.05	28	4.02	0.045
ITCT-S	20	5.37	4.98			45			5		

Table 4: Comparison of survival time between UMIPIC-D and ITCT-D.

Group	N	Mean (M)	Median (M)	Log-Rank		6-Month Survival Rate			1-Year Survival Rate		
				χ^2	*P*	%	χ^2	*P*	%	χ^2	*P*
UMIPIC-D	30	19.97	15.5	12.589	0.000	76.67	11.570	0.001	56.67	7.379	0.007
ITCT-D	11	4.91	3			18.18			9.09		

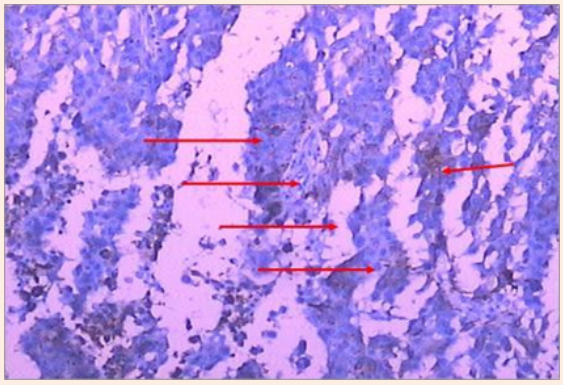

Figure 1: Insertion of Spinal needle in to tumor.

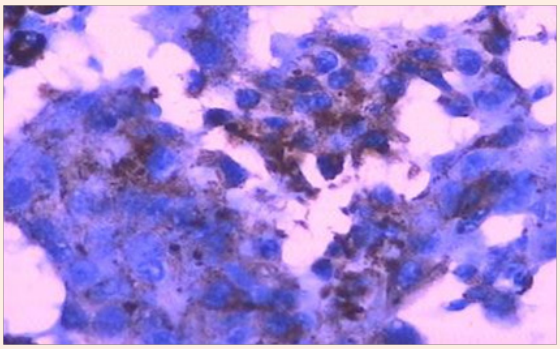

Figure 2A: Density changes at a point in the pancreatic tumor.

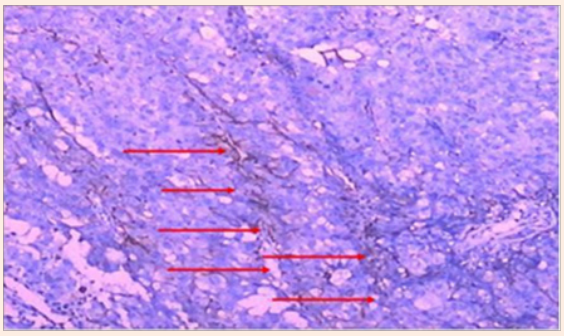

Figure 2B: Distribution of drugs to the edge of the tumor.

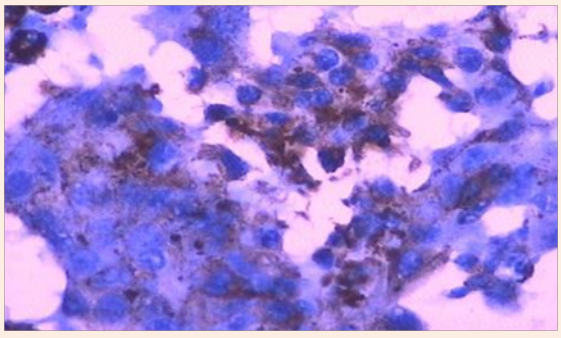

Figure 2C: Cancer Cell interaction with White Blood Cells.

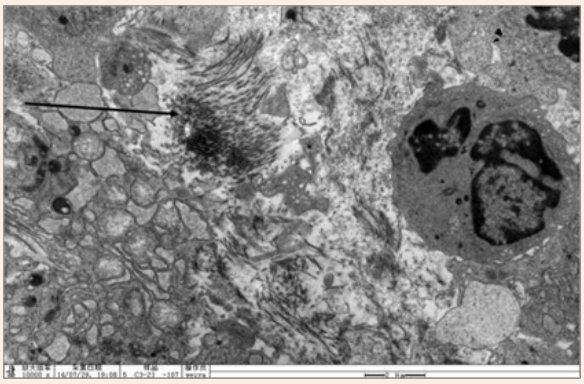

Figure 2D: Fibrosis.

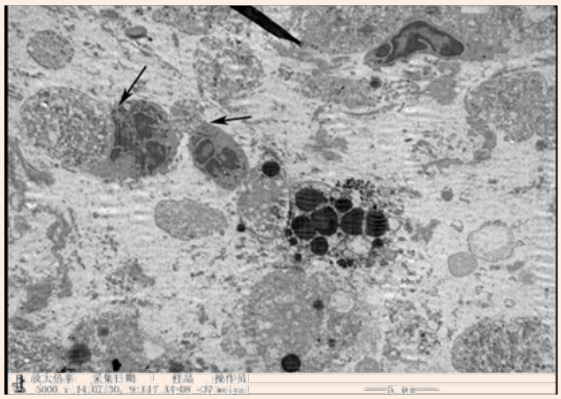

Figure 3: Cancer Cell.

Discussion

Pancreatic cancer is an aggressive carcinoma characterized by marked invasiveness and a propensity for distant metastasis. Less than 20% of patients with pancreatic carcinoma are candidates for surgical treatment on resectable borderline pancreatic cancer, surgery-associated complications are very common. Pancreatic carcinoma is also associated with high tissue concentrations of multidrug-resistant genes, therefore advanced pancreatic cancers can be resistant to conventional treatment protocols, leading to suboptimal therapeutic outcome [10,11]. Therefore, in order to minimize toxicities and maximize therapeutic efficacy, alternative drug-delivery routes may be vital to achieve such clinically therapeutic goals. Of all the drug-delivery routes, the percutaneous intra-tumoral approach combined with hapten-cytotoxic drugs in our studies has been regarded as a new direction of choice, with the greatest potential for prolonging survival time and enhancing the quality of life in these unresectable pancreatic cancer patients [12]. This is achieved by increasing drug concentration levels at the tumor site while minimizing systematic drug exposure and toxicity to the whole body [13].

UMIPIC in this clinical study is a patented combination of therapeutic method for solid tumors [5,6,14], and was explored in this clinic with personalized dosage based on tumor-size while utilizing patient-specific *in-vivo* modified autologous tumor antigens of patient as a self-vaccination to tumor-specific response. The regimens is a personalized and freshly prepared

compound solution containing an oxidant, a cytotoxic drug and hapten. Each component plays a vital role in the therapy. Since the combination is composed of water-soluble drugs with higher pressure for injection into the tumor mass, it is different from oil-drug emulsion which is sticky and hard to injection which resulted in the poor distribution in tumors. The combination of drugs in UMIPIC and ITCT could penetrate into the full matrix of the tumor, even into tumor cells, with sustained release in the tumor for an extended time with the help of an oxidant [5,6,8]. The oxidant of intra-tumoral injection can effectively coagulate the tumor mass by disturbing the micro blood vessel in the tumor, which ultimately leads to a higher concentration of the injected drug sealed within the coagulated tumor mass for a long time. The coagulation can effectively change the extracellular matrix (EM) and alter the morphological and biochemical components of the tumor such as collagen, elastic fibers, reticular fibers, fibronectin, proteoglycans, hyaluronic acid and other large molecules, obtaining a soft, semisolid [5]. It also destroys the environmental condition for tumor cell growth while the inflammation occurs. This was likely due to inflammatory response induced by coagulation or interaction with the malignant cells and the extremely high concentration of the cytotoxic drug locally injected [4,15]. The inflammation in tumors was induced by intra-tumoral chemo immunotherapy in animal research and lung cancer and liver patients were treated by same UMIPIC-Therapy with similarly effective rate [5,6,8], but the most tumors include distant tumors found in stable condition in these group of patients. This transformation is shown in earlier animal studies and clinical research [5,8]. In fact UMIPIC therapy integrated with surgery, multi drugs chemotherapy, and hapten induced immunotherapy into one new therapy (UMIPIC), has the three functions in one at the same time [5,8].

Creating an *in-situ* vaccine depot in tumor due to tumor-specific antigen is another intriguing factor in the process of intra-tumoral chemotherapy [15]. Furthermore, UMIPIC can not only induce the tumor *in-vivo* vaccine-like effect, but also enhance systematic immunity due to addition of hapten [11,12]. When multiple autologous tumor antigens were released from the tumor coagulation, cell death can be a priming event for T cell response and can induce potent immunity. These cell deaths were called a "good death" [7,16,17], which elicit a weak immune response as an *in-vivo* self-vaccination promoted by immunologic modulator, i.e., small molecule hapten inlaying the denatured tumor; and the modified cell debris or matrixes with tumor antigens became a new complex, more specific to the host immune system. Therefore, the role of hapten is important in enhancing the immunological response of tumor-associated antigens.

In addition, the $CD4^+$, $CD25^+$, $FoxP3^+$ regulatory T (Treg) cells are some of the most important immunosuppressive factors. They are greatly inhibited by the cytotoxic drug, leading to enhanced anti-tumor immunity. Chemotherapy can up-regulate CD95 expressed in Treg cells, which further induces apoptosis (compared to the effect of T cells). This indicates that Treg cells may take part in the anti-tumor immune response as a new target [18]. Instant coagulation in tumors can kill the Treg cells in tumor mass following UMIPIC-Therapy, and enhance up-regulation of T cells.

Our clinical data and animal studies have shown the immune response significantly improves after UMIPIC-Therapy, especially the $CD4^+$ T cell immunity (Figure 4, Table 6) [8].

In view of the optimistic survival advantage of UMIPIC with double drug compared to single drug (Table 5), significant improvement in the median survival time (15.5 months VS 6.45 months, $P<0.01$) and one-year survival time (56.67% vs 28%, $P<0.01$), indicated the UMIPIC with double drugs sufficiently prolong the survival time and survival rate compared to UMIPIC with single drug. It may be attributed to the long term immunological memory and more effective antitumor response from constitutive releasing of antigens in UMIPIC with double drugs, correlative with dendritic cell and $CD4^+$, $CD8^+$ improvement we found (Figure 4 & Table 6) and T cell subgroup characterization and measurement should be added in the future clinical study.

Our unpublished data showed that inflammatory tumor cells attract different lymphocytes including APC, macrophages and DC (Figure 4), and the activated B cells which react with tumor-associated antigens such as mesothelin tumor antigen, DNA, RNA and other cell lysates [14,19]. Other inflammatory mediators such as TNF and IFN-γ are also involved in anti-tumor growth [20]. The lymphocytes exposed to these tumor-associated antigens, especially the antigens modified with hapten (generated from the tumor cell lysis) elicit a tumor-specific immune response. This can encompass hormonal, cellular and complement-mediated responses which further act against the presence of adjacent live neoplastic cells not initially killed by the coagulation effect. Other inflammatory mediators such as TNF and IFN-γ are also involved in anti-tumor growth. Yue-Mei et al. [20] constructed a new mouse tumor model, incorporating a manufactured surgical wound representative of acute inflammation. They found the inhibitory effects of tumor cells in the early phase to be related to IFN-γ secretions in the wound [20]. Consequently, as the "invisible scalpel", tumor-specific immune response is enhanced and affected on the vegetative tumor cells, blocking recurrence and metastasis.

Table 5: Comparison of survival time between UMIPIC-S and UMIPIC-D.

Group	N	Mean (M)	Median (M)	Log-Rank		6-Month Survival Rate			1-Year Survival Rate		
				χ^2	*P*	%	χ^2	*P*	%	χ^2	*P*
UMIPIC-D	30	19.97	15.5	16.531	0.000	76.67	1.061	0.303	56.67	4.556	0.033
UMIPIC-S	25	6.95	6.45			64			28		

Table 6: T cells in blood changed in 22 patients before and after UMIPIC Therapy.

	n	Average	T Value	P Value
1. CD3+T				
Before UMIPIC	22	70.90%	1.313	0.203
After UMIPIC	22	72.89%		
2. CD3+CD4+T				
Before UMIPIC	22	37.29%	2.509	0.020
After UMIPIC	22	45.62%		
3. CD3+CD8+T				
Before UMIPIC	22	30.51%	2.566	0.018
After UMIPIC	22	27.26%		
4. CD3+CD4+T /CD3+CD8+T				
Before UMIPIC	22	1.65	2.804	0.011
After UMIPIC	22	2.18		

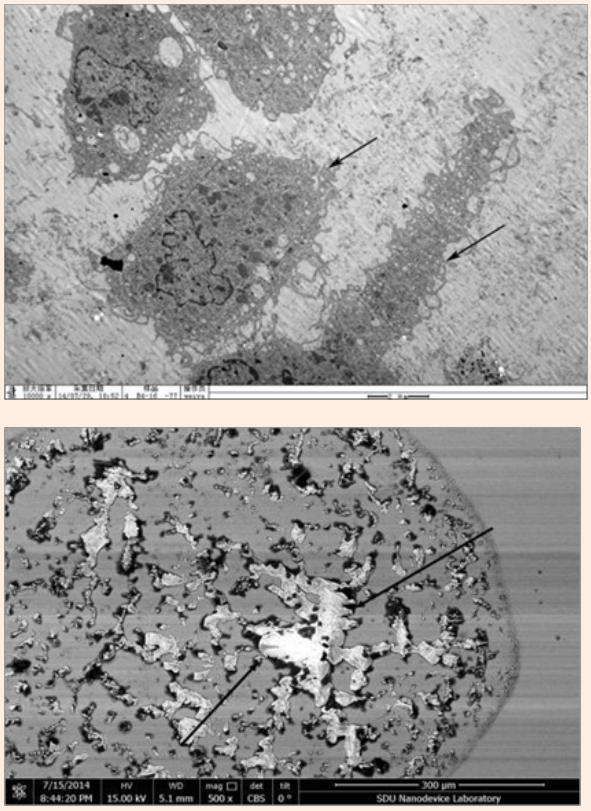

Figure 4: Dendritic Cells & Drug Crystals.

Conclusion

In summary, UMIPIC with double drugs is a comprehensive procedure and a new method for treating pancreatic cancer. It is not only de-bulking or chemical surgery for big tumor mass, but also slow release drugs intratumorally continue to kill the residual tumor cells. It also has the effect of induced systemic immunotherapy to synergistically eradicate the residual tumor cells of whole body in the guardianship to defend against the tumor recurrence and metastasis. This idea seems counterintuitive, even unconventional, and meets the resistance with misunderstanding from varied views of each expert in the past years, but now it will likely meet the improvement of freedom in the medical environment since cancer immunotherapy is garnering interest every day. It is a potentially effective therapy and has a long way to go to reach a recognized reality with experts such as medical oncologists, radiation oncologists and surgeons. In fact, it offers a prospect of tailoring treatments much more precisely and could lead to a better response, especially in patients in advanced stages of inoperable or drug-resistant types of pancreatic cancer. More effective control of the disease and mechanism for defense of the tumor recurrence or metastasis is needed for us to investigate the UMIPIC with not only double cytotoxic drugs but also double hapten's into clinical study. It may produce stronger and varied types of immunological responses to eradicate the residual ones of tumors and give more effective cancer treatment.

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