

Gemcitabine and Triapine Co-Delivery Using Calcium Carbonate Nanoparticles for the Treatment of Chemo-resistant Pancreatic Cancer

Tiaqing Li*

NICM Health Research Institute, Western Sydney University, Westmead, Australia

Abstract

Chemotherapy is the primary component of the systemic treatment strategy for pancreatic cancer, which is a fatal disease. However, patients with pancreatic cancer still have a very poor overall prognosis and a low survival rate. Gemcitabine (GEM) is a chemotherapeutic agent that is frequently used to treat pancreatic cancer. However, the primary obstacle remains GEM chemoresistance. To address the issue of Triapine's poor solubility and suppress the GEM resistance of pancreatic cancer cells (PANC-1/GEM), we prepared calcium carbonate nanoparticles (CaCO₃ NPs) loaded with a nucleotide reductase inhibitor (Triapine). Using both 2D PANC-1/GEM cells and 3D tumor spheroids, CaCO₃-GEM-Triapine NPs nano-formulations inhibited cancer cell proliferation, migration, and resistance to GEM, enhancing the therapeutic effect of GEM-based chemotherapy. According to the findings of the study, CaCO₃ NPs containing GEM and Triapine may be an efficient treatment option for overcoming drug resistance in pancreatic cancer.

Keywords: Calcium carbonate nanoparticles; Gemcitabine; Drug resistance; Triapine; Pancreatic cancer

Introduction

Because of its poor prognosis after diagnosis, pancreatic cancer is the leading cause of cancer-related deaths worldwide, with a five-year survival rate of about 5%. The most common treatment for pancreatic cancer is chemotherapy. In particular, Gemcitabine (GEM) is a common first-line systemic treatment for patients with advanced or metastatic pancreatic cancer [1]. However, despite initial drug treatment, GEM chemoresistance remains the main obstacle, reducing survival. Although numerous studies have been carried out to investigate GEM-based combination therapies, no significant therapeutic outcomes have yet been achieved in clinics. Therefore, it is crucial to develop novel strategies or effective delivery systems capable of overcoming GEM resistance and increasing survival rates [2].

Drug transport regulation, DNA damage and repair, and the renewability of cancer stem cells are just a few of the many factors that contribute to GEM resistance. It has been demonstrated that ribonucleotide reductase (RR), which acts as a catalyzer in the process of converting ribonucleotides to deoxyribonucleotides during DNA replication and repair, is a significant contributor to the emergence of GEM chemoresistance. It has been demonstrated that RR's two subunits, M1 (RRM1) and M2 (RRM2), influence the adjuvant treatment of pancreatic cancer [3]. In particular, RRM2 articulation level has a positive relationship with DNA harm fix and replication. A poor prognosis is correlated with a poor response to GEM-based chemotherapy and a high level of RRM2 expression. GEM chemosensitivity was found to be significantly enhanced by deferasirox-induced inhibition of RRM2 expression in a previous study. As a result, inhibiting RRM2 might be a good way to boost chemotherapy's ability to fight cancer. Triapine, an anticancer thiosemicarbazone and iron-binding compound, inhibits human ribonucleotide reductase (RNR) by selectively blocking the synthesis of nucleotides required for DNA synthesis and replication in cancer cells by consuming large quantities of deoxy-ribonucleoside triphosphate (dNTP). By reducing the iron complex and providing an electron, Triapine can also directly quench the tyrosine diiron group on the M2 subunit, inhibiting RRM2 expression [4]. In patients who had previously failed gemcitabine treatment, a combination of Triapine and GEM was found to improve anticancer efficacy in a phase 1 trial. Be that as it may, the unfortunate solvency and short plasma half-existence of

Triapine limit its application against Jewel safe disease. As a result, the creation of the ideal platform for efficiently delivering it to tumor sites is urgent.

Methods

Patients and study design

The Samsung Medical Center's institutional review board granted approval (approval number) for this study. 2022-07-082), and prior to the procedure, each patient gave their informed consent. Between May 2012 and June 2021, 84 patients went through pancreatic malignant growth medical procedure with entryway vein (PV) or unrivaled mesenteric vein (SMV) remaking at a tertiary reference community. From electronic medical records, clinical data and patient characteristics were gathered retrospectively. A radiologist read the images from contrast-enhanced computed tomography (CT) with portal venous phase for each and every patient. According to NCCN guidelines², all pancreatic tumors in the PMV group were categorized as having no TVI, a TVI of 180°, a TVI of >180°, or thrombosis based on preoperative image reading. Clinical tumor stage, locally advanced status, and tumor-vein interface (TVI) degree were also evaluated. 1). Neoadjuvant chemotherapy was administered by an oncologist when necessary, depending on the clinical stage [5].

The division of Hepato-Biliary-Pancreatic Surgery and Liver Transplantation carried out the operation, and if PMV invasion occurred prior to or during the procedure, resection and reconstruction were carried out in conjunction with a vascular surgeon. In our center, pylorus preserving pancreaticoduodenectomy (PPPD) is the most

*Corresponding author: Tiaqing Li, NICM Health Research Institute, Western Sydney University, Westmead, Australia, E-mail: tiaqing.li@gmail.com

Received: 28-Mar-2023, Manuscript No. ijm-23-95207; **Editor assigned:** 31-Mar-2023, PreQC No. ijm-23-95207(PQ); **Reviewed:** 14-Apr-2023, QC No. ijm-23-95207; **Revised:** 21-Apr-2023, Manuscript No. ijm-23-95207(R); **Published:** 28-Apr-2023, DOI: 10.4172/2381-8727.1000212

Citation: Li T (2023) Gemcitabine and Triapine Co-Delivery Using Calcium Carbonate Nanoparticles for the Treatment of Chemo-resistant Pancreatic Cancer. Int J Inflamm Cancer Integr Ther, 10: 212.

Copyright: © 2023 Li T. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

common type of pancreatic cancer surgery. Depending on the anatomy of the patient, pylorus resecting pancreaticoduodenectomy (PRPD), standard Whipple, total pancreaticoduodenectomy (PD), or distal pancreatectomy were carried out. A vascular surgeon performed venous resection and reconstruction if venous adhesions were found after the PD specimen was handled. When the primary repair was anticipated to be difficult based on preoperative imaging, reconstruction techniques and graft types were primarily designed for interposition through autologous great saphenous vein (GSV) harvest [6]. At the point when it was hard to utilize an autologous GSV because of a size confound of the PMV affirmed in the employable field, reproduction was performed utilizing a size-matched cryopreserved AG. For both the proximal and distal anastomoses, the same procedure was followed, and either 5-0 or 6-0 polypropylene was used to make a continuous-running suture. Since the reconstruction length was determined in the operating field, the operator (vascular surgeon) determined the reconstruction technique during surgery. PMV resection was carried out in accordance with the degree of venous invasion or adhesion of pancreatic cancer [7]. When the remaining PMV cut surface allowed for tension-free end-to-end anastomosis, EA reconstruction was only carried out. GSV or AG harvesting prepared prior to surgery was used by all patients to begin the procedure. PMV reconstruction using autologous GSV or AG was carried out if EA reconstruction was not feasible.

To verify the resection margin status, frozen biopsy was carried out in each and every pancreatic cancer surgery. The R0 resection margin was defined as greater than 1 mm, and we tried to perform R0 resection whenever possible. In consultation with an oncologist, adjuvant or palliative chemotherapy was prescribed based on histologic pathology [8]. On post-employable the very beginning, a ultrasound assessment was performed to affirm unite patency, and a half portion of low-subatomic weight heparin was utilized to forestall early join disappointment during hospitalization. Depending on the primary underlying disease, the patient received lifelong antiplatelet or anticoagulation therapy. After discharge, contrast-enhanced CT follow-up was performed at 1, 4, and 12 weeks.

Endpoint

Graft patency, disease recurrence, and patient mortality were the primary endpoints. Stenosis greater than 50% and occlusion or thrombosis of the reconstructed PMV were used to estimate graft patency. As disease-free survival rates and overall survival rates, respectively, data on disease recurrence and patient mortality were gathered and analysed [9].

Results

During pancreatic cancer surgery, 84 patients underwent PMV resection and reconstruction, with 65 receiving EA and 19 receiving AG reconstruction. The resectability of the patients' pancreatic cancer was assessed after their diagnosis, and surgery was attempted whenever possible. Our comparison of EA and AG by perioperative factors revealed that EA recipients had a significantly younger median age. Pancreatic ductal adenocarcinoma was the preoperative diagnosis for all patients, with the exception of one pancreatic neuroendocrine tumor. The group that received neoadjuvant therapy had significantly more AG reconstruction, but there was no significant difference between the two groups in terms of the type of procedure or the tumor-vein interface. The activity times and blood misfortune sums were altogether higher in the AG patients.

Discussion

This study compared EA and AG interposition in patients with

borderline resectable pancreatic cancer who underwent resection and reconstruction during PMV surgery. Consequently, EA had significantly superior primary patency, but the recurrence-free survival rate and overall survival rate did not differ significantly between the two groups. Pancreatic cancer is categorized as resectable, borderline resectable, or locally advanced (unresectable) by the National Comprehensive Cancer Network (NCCN) [10]. Among these classifications, borderline resectability status includes PV/SMV tumor-vessel interface 180° of the vessel wall circumference and/or reconstructable occlusion; superior mesenteric artery tumor-vessel interface less than 180 degrees of the circumference of the vessel wall; celiac course cancer vessel interface $<180^\circ$ of the vessel wall boundary; and the tumor-vessel interface of the common hepatic artery without involvement of the appropriate hepatic artery or celiac artery [11].

The most widely used PMV reconstruction techniques are segmental resection and primary anastomosis. However, primary anastomosis is typically only considered for segmental defects smaller than 2 cm due to the requirement that it be performed without tension. The operator (vascular surgeon) determined the reconstruction method during surgery in our study [12]. However, due to the fluidity of the intra-abdominal organs and the redundancy of the vascular structure, it is necessary to determine whether tension-free anastomosis is possible in the surgical field. This is not just a matter of the length of the segmental defect. Interposition ought to be taken into consideration if a longer segmental resection is required; various conduits have been used for interposition, but none are clearly recommended. Therefore, the length of the PMV resection or defect may not necessarily indicate the use of EA or AG. However, in order to estimate EA, the TVI length was measured and compared during the stage of preoperative planning [13]. In the actual data, the length of TVI for the AG group was mostly between 2 and 3 cm, whereas the length of TVI for the EA group was between 2.8 and 3.6 cm, with a deviation. ($p = .131$) In particular, despite a length of TVI greater than 3.5 cm, EA anastomosis was possible in three instances. As a result, the length of the lesion cannot be the sole determinant of reconstruction techniques; instead, all options should be considered and surgery should be planned. Intervention utilizing autologous veins (saphenous veins) is the most helpful choice, yet fringe veins are frequently out of place because of size befuddle with the PMV. A few examinations have suggested autologous vein mediation considering size matching utilizing the interior jugular vein or left renal vein [14]. However, harvesting a major vein may not be an easy procedure because of other related factors like surgical length, additional incisions, and postoperative complications.

Acknowledgement

None

Conflict of interest

None

References

1. Winter JM, Cameron JL, Campbell KA (2006) Pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg* 10: 1199-1210.
2. Tempero MA, Malafa MP, Al-Hawary M (2021) Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 19: 439-457.
3. Muller SA, Hartel M, Mehrabi A (2009) Vascular resection in pancreatic cancer surgery: survival determinants. *J Gastrointest Surg* 13: 784-792.
4. Tseng JF, Raut CP, Lee JE (2004) Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg* 8: 935-949.

5. Han SS, Park SJ, Kim SH (2012) Clinical significance of portal-superior mesenteric vein resection in pancreatoduodenectomy for pancreatic head cancer. *Pancreas* 41: 102-106.
6. Ravikumar R, Sabin C, Abu Hilal M (2017) Impact of portal vein infiltration and type of venous reconstruction in surgery for borderline resectable pancreatic cancer. *Br J Surg* 104: 1539-1548.
7. Dua MM, Tran TB, Klausner J (2015) Pancreatectomy with vein reconstruction: technique matters. *HPB* 17: 824-831.
8. Lee DY, Mitchell EL, Jones MA (2010) Techniques and results of portal vein/superior mesenteric vein reconstruction using femoral and saphenous vein during pancreatic oduodenectomy. *J Vasc Surg* 51: 662-666.
9. Umino Y, Mizuma M, Akamatsu D (2021) Reconstruction of portal vein and superior mesenteric vein using superficial femoral vein graft in surgical resection of pancreatic head cancer-A case report. *Gan To Kagaku Ryoho* 48: 1783-1785.
10. Kostov G, Dimov R (2021) Portal vein reconstruction during pancreaticoduodenal resection using an internal jugular vein as a graft. *Folia Med (Plovdiv)* 63: 429-432.
11. Smoot RL, Christein JD, Farnell MB (2007) An innovative option for venous reconstruction after pancreaticoduodenectomy: the left renal vein. *J Gastrointest Surg* 11: 425-431.
12. Tran TB, Mell MW, Poultides GA (2017) An untapped resource: left renal vein interposition graft for portal vein reconstruction during pancreaticoduodenectomy. *Dig Dis Sci* 62: 68-71.
13. Kleive D, Berstad AE, Verbeke CS (2016) Cold-stored cadaveric venous allograft for superior mesenteric/portal vein reconstruction during pancreatic surgery. *HPB* 18: 615-622.
14. Zhang XM, Fan H, Kou JT (2016) Resection of portal and/or superior mesenteric vein and reconstruction by using allogeneic vein for pT3 pancreatic cancer. *J Gastroenterol Hepatol* 31: 1498-1503.