

Management of primary squamous cell carcinoma of the pancreas with a nanosomal paclitaxel lipid suspension-based regimen: A case report

SAROJ KUMAR DAS MAJUMDAR¹, DILLIP KUMAR MUDULY², SUBHASIS MISHRA², CHINMAYA RASHMI RANJAN MOHAPATRA², DEEPAK BUNGER³ and MUJTABA A. KHAN³

Departments of ¹Radiotherapy and ²Surgical Oncology, All India Institute of Medical Sciences, Bhubaneswar, Odisha 751019; ³Department of Medical Affairs and Clinical Development, Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat 380054, India

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Abstract. Squamous cell carcinoma (SCC) of the pancreas is a rare tumor with only a few case reports available. It is an aggressive form of pancreatic cancer with a poor prognosis. The diagnosis and optimal management of SCC of the pancreas is poorly defined due to the lack of standard treatment or guidelines and owing to the rarity of this malignancy. Patients suffering from SCC of the pancreas do not respond well to chemotherapy or radiotherapy and isolated reports are available on the use of gemcitabine and newer taxane formulations. Surgical resection of the tumor is the most effective modality; however, due to a delay in diagnosis, the majority of pancreatic SCCs remain unresectable. Herein, a case of SCC of the pancreatic tail is reported in a 60-year-old patient who was managed with a combination of albumin-free nanosomal paclitaxel lipid suspension (NPLS) and gemcitabine in a neoadjuvant setting. To the best of our knowledge, this is the first such case report of a locally advanced SCC of the pancreatic tail showing an overall survival of 1 year following treatment with an NPLS based regimen. The treatment was well tolerated with no serious safety concerns.

Introduction

Pancreatic cancer is a highly lethal malignancy with short-term survival rates (1) and is associated with a high mortality rate that closely parallels its incidence (2). It is generally considered as a 'silent disease' (3) as there are no signs and symptoms

in its early stages, and is generally diagnosed at an advanced stage (2,3). The number of new cases of pancreatic cancer were 12.6 per 100,000 men and women per year according to the National Cancer Institute Surveillance, Epidemiology, and End Results Program (NCI SEER) data from 2011-2015 (4). In India, the incidence of pancreatic cancer is comparatively low at 0.5-2.4 per 100,000 men and 0.2-1.8 per 100,000 women (5). Squamous cell carcinoma (SCC) of pancreas is a subtype of ductal carcinoma, a non-endocrine part (6). Primary pancreatic SCC is a rare malignancy, accounting for 0.5-2% of all malignant pancreatic tumors (7) and is considered as an aggressive subtype with a poor prognosis (8). The diagnosis and optimal management of SCC of pancreas remains poorly defined (9). Furthermore, there is no standard treatment or guidelines available for the management of SCC of pancreas owing to the rarity of this malignancy (10,11).

We report here, a case of locally advanced SCC of the pancreatic tail. The patient was treated with neoadjuvant nanosomal paclitaxel lipid suspension (NPLS) and gemcitabine chemotherapy followed by surgery.

Case report

A 60-year-old man, a known case of diabetes, presented at the Department of Oncology, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, Odisha, India, in February 2017, with complaints of abdominal pain (epigastric pain radiating to back), vomiting, weight loss (10 kg over the last 6 months) and weakness. He was a non-smoker and non-alcoholic. Investigations revealed that his baseline serum amylase (17.49 IU/l), lipase (16.76 U/l) and CA 19-9 (29.9 U/ml) levels were within normal limits. An upper gastrointestinal endoscopy (UGIE) showed a submucosal swelling which measured 10x10 cm. A computed tomography (CT) scan of the abdomen revealed a heterogeneously enhancing cystic and necrotic mass lesion, measuring 8.1x6.8x6.4 cm in the pancreatic tail, with chronic calcific pancreatitis, diffuse parenchymal calcification and multiple studded intraductal calculi; the pancreatic tail region was lobulated near the hilum with splenic vessel encasement, and a secondary splenic

Correspondence to: Dr Saroj Kumar Das Majumdar, Department of Radiotherapy, All India Institute of Medical Sciences, Bhubaneswar, Odisha 751019, India
E-mail: sarojmajumdar@gmail.com

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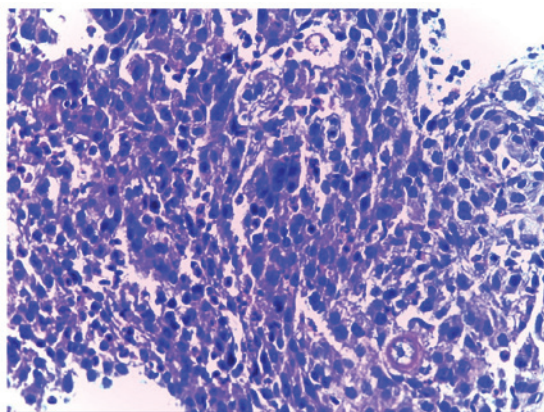


Figure 1. Markedly pleomorphic tumor cells in diffuse sheets (magnification, x200).

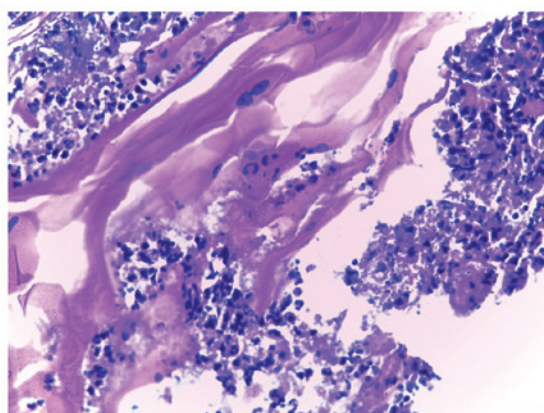


Figure 2. Large areas of keratinisation and necrosis (magnification, x400).

parenchymal infarct (images not available). A CT guided core needle biopsy of the pancreatic mass was performed, and histologic examination revealed markedly pleomorphic tumor cells in diffuse sheets (Fig. 1) and large areas of keratinization and necrosis (Fig. 2). The patient was diagnosed as a case of primary SCC of pancreas, a rare entity, which arises from the pancreatic duct in the background of chronic calcific pancreatitis or a pre-existing pancreatic stone. The staging was confirmed as Stage III (T4N1M0). Extensive workup performed to evaluate other primary sources and metastatic disease did not reveal any head and neck malignancy. The final diagnosis was confirmed as primary SCC of pancreatic tail.

The Eastern Cooperative Oncology Group (ECOG) performance status was 1, and neoadjuvant chemotherapy with a combination of NPLS 120 mg (70 mg/m²) and gemcitabine 1400 mg (800 mg/m²) intravenously (IV) was initiated on days 1, 8 and 15 every 4 weeks. Premedication with IV ranitidine (50 mg), dexamethasone (8 mg), chlorpheniramine maleate (10 mg), and ondansetron (8 mg) was given. On day 1 of the 1st cycle, NPLS 120 mg was reconstituted in 250 ml of 5% dextrose solution and was administered over 1.5 h; gemcitabine 1.4 was reconstituted in 250 ml normal saline and was administered over 45 min. The patient complained of nausea and was administered ranitidine 50 mg IV and ondansetron 8 mg IV. The patient received the same premedications and chemotherapy on days 8 and

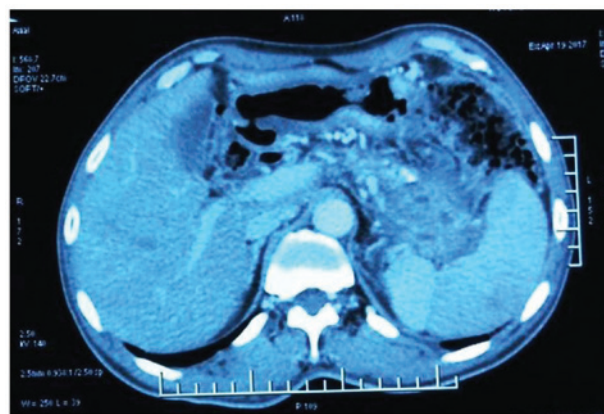


Figure 3. Positron emission tomography-computed tomography image following 2 cycles of chemotherapy, showing a 2.3x1.5x2.1 cm mass in the tail of pancreas.

15 of Cycle 1. The patient tolerated the treatment well; vital signs, liver and renal functions were normal, and the patient was hemodynamically stable. Similarly, the second cycle of NPLS-gemcitabine chemotherapy was administered on days 1, 8 and 15. On day 1 of the second cycle, the patient's random blood sugar (RBS) level was found to be high (517 mg/dl), which was managed with insulin. On day 15 of the second cycle, the patient's hemoglobin (Hb) levels became low (8.6 gm%) and he was administered 1 unit of packed red blood cells.

Post completion of 2 cycles of chemotherapy, a positron emission tomography-CT (PET CT) performed in April 2017 showed hypodense areas in the region of the splenic hilum and pancreatic tail, along with diffuse peritoneal stranding (2.3x1.5x2.1 cm), and with standardized uptake values (SUV) of 4.2, suggestive of a good tumoral response with the regression of tumor mass (Fig. 3). There was no hypermetabolic abdominal or retroperitoneal lymphadenopathy, and no definite abnormal hypermetabolic distant metastases were observed. The treatment was well-tolerated, and the patient received a third cycle of NPLS-gemcitabine combination therapy in May 2017 without any new complaints.

Post 3 cycles of chemotherapy, the patient was asymptomatic and tolerated the treatment with NPLS and gemcitabine well with normal complete blood counts (CBC), liver and renal function tests. Peripheral neuropathy (grade II) and anemia (grade III) were the adverse events reported in this patient.

Based on the tumoral response on the PET-CT, the patient was offered surgical exploration. He underwent distal pancreatico-splenectomy with enblock resection of the involved stomach and colon in June 2017 and R0 resection was achieved. Biopsy specimens from the pancreatic margin, celiac lymph node and right common hepatic lymph node confirmed a well-differentiated SCC of the tail of pancreas infiltrating into the wall of stomach and colon. The staging was confirmed as Stage IIA (pT3N0Mx) within the limitations of metastatic work-up, and the patient was discharged in stable condition.

Post-surgery, the patient received 2 cycles of gemcitabine 1 gm IV (day 1, 8 and 15 of each cycle) in combination with capecitabine 1,000 mg orally (day 1 to 21) as adjuvant therapy. The patient became asymptomatic and tolerated the treatment well.

Outcome and follow-up. Seven months post completion of NPLS and gemcitabine therapy, an ultrasound (USG) performed in December 2017 revealed multiple metastatic lesions in the liver, a segment 5 lesion causing infiltration of the common bile duct and resultant bilobar intrahepatic biliary radical dilatation (IHBRD) and minimal ascites. The patient underwent percutaneous transhepatic biliary drainage (PTBD) with stenting, but succumbed after 2 months, leading to an overall survival (OS) of approximately 1 year after having started NPLS treatment.

Discussion

Pancreatic cancer is one of the deadliest malignancies, and is associated with a poor prognosis (12). The symptoms can vary depending upon the anatomic location of the tumor. The head of the pancreas (78%) is most commonly affected, followed by the body (11%) and tail (11%) (3). Cancers of the pancreatic head are located near the common bile duct, may cause jaundice even if they are small, and can be diagnosed at an early stage. However, cancers of the pancreatic body or tail don't impinge on the duct until they have spread through the pancreas and are at an advanced stage (13). The survival rates are also lower in patients with pancreatic cancers of the body and tail as compared with head lesions (14). Primary SCC of pancreas is an extremely rare entity, with an incidence of 0.5 to 2% of all exocrine pancreatic neoplasms (15). The clinical presentation of SCC of pancreas is similar to that of adenocarcinoma; it may arise from chronic inflammation leading to malignant transformation of squamous metaplasia, or from mixed adenosquamous carcinoma in which the glandular components have disappeared, or from an adenocarcinoma with squamous metaplasia where the tumor has a potential to drift into both adenocarcinoma or SCC (16). The correct diagnosis of SCC of pancreas requires a thorough workup to exclude another possible primary metastatic SCC (10).

There is no standard therapy established for the management of pancreatic SCC (10). These tumors generally do not respond to chemotherapy or radiotherapy and are very aggressive. Majority of the tumors may not be resectable due to a delay in diagnosis (15). Published literature is available only as case reports, and comprehensive clinical trials are not available (17).

The cure rate for pancreatic cancer is very low at 7%, which makes the disease a vexing treatment challenge (18). Surgical resection is regarded as the only potentially curative treatment and Stage I, IIA and IIB pancreatic cancers are considered resectable (19). Neoadjuvant chemotherapy followed by surgical exploration has been studied in patients with locally advanced pancreatic cancer (20). Gemcitabine is considered as the standard of care despite its limited activity and modest treatment outcomes (12). It was shown to be effective in a 49-year-old patient with a metastatic SCC of the pancreas. Given as a second line therapy after radiotherapy plus 5 FU and cisplatin, gemcitabine improved the patient's health leading to an OS of 8 months (21). In an inoperable patient, first-line therapy with gemcitabine and cisplatin followed by second-line 5-FU and leucovorin showed a good survival rate (22). Reports have shown improved outcomes in patients with pancreatic

cancer with a taxane and gemcitabine combination (12,18). The novel formulations of taxanes penetrate tumor cell mass at higher concentrations due to their unique structure and may exert better activity than conventional taxanes (12). Nab-paclitaxel, an albumin bound formulation of paclitaxel, has been studied in pancreatic adenocarcinoma (23,24) but no data is available on its use in SCC. Kataoka *et al* demonstrated that nab-paclitaxel plus gemcitabine combination therapy was effective in a 60-year-old patient with adenosquamous carcinoma of the pancreas. However, disease progression was noted after the completion of 4 cycles, with an OS of 7 months (25).

Previous reports have shown a median OS of 7 months in 8 patients with pancreatic SCC undergoing curative resection (26,27). Brown *et al* (28) demonstrated a median OS of 7 months (range 6-16 months) for patients who underwent curative resection. A recent systematic review and pooled survival analysis conducted by Ntanasis-Stathopoulos *et al* showed a median OS of 7 months in 54 patients with pancreatic SCC. This is the largest pool of data regarding pancreatic SCC available in public domain till date (29). The median age of patients at diagnosis was 63 years (range 33-80 years); majority (61.1%) of them were males; pain (77.8%) and weight loss (57.4%) were the most common presenting symptoms. Most of the patients were nonsmokers (77.8%) and most did not consume alcohol (70.4%). Majority of the tumors were in the head of the pancreas (52.9%) followed by tail (21.6%) and body (5.9%). Resectable cases had significantly better OS when compared with non-resectable cases (10 months versus 4 months, respectively) (29). OS without any treatment has been dismal and has been reported as 3 months (22). Furthermore, there were 11 cases of SCC of pancreatic tail in the pooled analysis, and the OS ranged from 2 to 8 months. In comparison, our patient initially presented with abdominal pain and weight loss, was a non-smoker and non-alcoholic and showed a higher OS of 1 year. This is the first case report on the use of NPLS in the treatment of primary SCC of pancreatic tail. In the current report, the patient had a locally advanced SCC of the pancreatic tail and was treated with an NPLS and gemcitabine combination therapy followed by surgery, thereby achieving a partial response. Overall, the treatment was well-tolerated, and no serious adverse events (SAEs) were reported. Neuropathy and anemia were observed, which resolved with appropriate treatment.

PacliAqualip is an albumin-free NPLS formulation, which is made from Lipids Generally Regarded As Safe (GRAS) by the US Food and Drug Administration (30). NPLS has been formulated based on 'Aqualip Technology', which is patented in Europe, Japan and Canada, while the filed US patent is under review. The Aqualip technology results in the drug particles being nano-sized (~100 nm) that allows the drug to penetrate the tumor tissue through leaky vasculature without being attacked by the immune system. NPLS is devoid of cremophor EL and ethanol, thus potentially reducing the toxicities associated with cremophor for example severe anaphylactoid hypersensitivity reactions, hyperlipidemia, abnormal lipoprotein patterns, aggregation of erythrocytes and peripheral neuropathy (31). Furthermore, corticosteroid premedication is also not

required. NPLS has been shown to be effective in the treatment of metastatic breast cancer (30). It is approved for the treatment of metastatic or node-positive breast cancer, metastatic ovarian cancer, metastatic non-small cell lung cancer, and AIDS-related Kaposi's sarcoma.

In our case, the patient with locally advanced SCC of pancreatic tail was treated with a novel nanosomal formulation of paclitaxel, NPLS, in combination with gemcitabine in a neoadjuvant setting followed by surgery. Overall, the current report highlights the potential efficacy and safety of NPLS in the treatment of SCC of pancreatic tail.

Presently, there is no definitive treatment available for squamous cell carcinoma of pancreas. This case report shows that NPLS, a novel albumin-free nanosomal paclitaxel formulation devoid of cremophor EL and ethanol, can be a potential treatment option for the treatment of locally advanced squamous cell carcinoma of pancreatic tail.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SKDM, DKM, SM and CRRM planned and conducted the study, performed the procedures, acquired the data and wrote the manuscript. SKDM, DKM, SM, CRRM, DB and MAK conceived and designed the case report. SKDM, DKM, SM, CRRM, DB and MAK reviewed the manuscript, and SKDM served as the guarantor.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient's next of kin for the publication of this report as the patient was deceased.

Competing interests

Drs. Deepak Bungler and Mujtaba A. Khan are employees of Intas Pharmaceuticals Ltd.

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