Successful treatment of advanced pancreatic leiomyosarcoma treated with gemcitabine plus *nab*-paclitaxel: a case report and literature review

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Abstract

Pancreatic leiomyosarcoma (PLMS) is an extremely rare tumor that accounts for 0.1% of pancreatic malignancies, and its chemotherapy has yet to be established. Generally, soft-tissue sarcoma chemotherapy is standard treatment with doxorubicin (DXR) alone. However, the effectiveness of gemcitabine (GEM) plus docetaxel (DOC) has been shown in uterine leiomyoma. In contrast, the GEM plus nab-paclitaxel (PTX) regimen has been established as first-line chemotherapy for unresectable pancreatic cancer. For this study, we selected the GEM plus nab-PTX regimen for patients with PLMS, achieving success in approximately 10 months. From a search on PubMed, we found only 12 cases of PLMS (including this case) that underwent chemotherapy. Our case is the first reported patient to have survived more than 2 years with chemotherapy alone. In a nude mouse model, the GEM plus DOC regimen was shown to significantly decrease tumor size when compared with DXR in leiomyosarcoma, and the GEM plus nab-PTX regimen was reported to significantly reduce necrosis when compared with DXR alone, GEM alone, DOC alone, nab-PTX alone and GEM plus DOC in soft-tissue sarcoma. GEM plus nab-PTX therapy might therefore be the first choice for soft-tissue sarcoma and leiomyosarcoma. This is the first reported case of PLMS treated with GEM plus nab-PTX.

Keywords Pancreatic leiomyosarcoma · Chemotherapy · Gemcitabine · Nab-paclitaxel

Introduction

Primary pancreatic leiomyosarcoma (PLMS), first reported in 1951 by Ross CF [1], is an extremely rare mesenchymal pancreatic tumor that accounts for 0.1% of pancreatic malignancies [2]. PLMS has a dismal prognosis; Xu et al. reported

that the median survival time and 3-year survival rate were 12 ± 6.3 months and 0%, respectively [3]. Almost all cases of PLMS are from diagnostic and surgical reports, with very few reports on its chemotherapy, of which there were only three cases, including our case, on effective chemotherapy. Our case is the first patient reported to survive more than 2 years with chemotherapy alone.

Doxorubicin (DXR) is recommended as the standard first-line regimen for soft-tissue sarcoma [4–6] but is generally not employed for pancreatic cancer, whereas GEM plus nanoparticle albumin-bound paclitaxel (nab-PTX) is the standard regimen for pancreatic cancer [7]. We treated our patient with GEM plus nab-PTX regimen for their PLMS. To date, there are only 12 reported cases of PLMS (including our case) that, to our knowledge, have been treated with chemotherapy (Table 1) [8–17]. In this article, we report the first effective treatment of PLMS with GEM plus nab-PTX.

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Table 1 Primary pancreatic leiomyosarcoma with chemotherapy in the scientific literature

Case	Author	Year	Age / Sex	Surgery	Chemotherapy Regimen	Treatment Response	Survival time (months)	Outcome
1	Ishikawa et al. [8]	1981	44/M	+	DXR, CPA, BLM	No effective	48	Death
2	Ishii et al. [9]	1994	66/M	None	CDDP, DXR, MMC, etc	Unknown	33	Death
3	Aranha et al. [10]	1995	46/F	+	DXR	No effective	9	Death
4	Shimizu et al. [11]	1997	49/F	None	Unknown	Unknown	3	Death
5	Chawla et al. [12]	1998	45/F	None	CBDCA + VCR + CPA + EPI	Effective	2	Alive
6	Srivastava et al. [13]	2000	38/M	None	Unknown	Unknown	3	Death
7		2000	45/M	None	Unknown	Unknown	Unknown	Unknown
8	Muhammad et al. [14]	2008	73/M	None	Unknown	Unknown	3	Death
9	Vanderpuye et al. [15]	2012	59/M	+	Capecitabine (adjuvant)	Unknown	24	Alive
10	Moletta et al. [16]	2012	54/F	+	DXR (1st line)	Effective	37	Alive
					Myocet + ifosfamide (1st line)	Stable disease		
					GEM + DOC (2nd line)	Unknown		
					Trabectedin (3rd line)	Unknown		
11	Reyes et al. [17]	2016	72/F	None	Dacarbazine (4th line)	Unknown	2	Alive
					GEM + DOC	Unknown		
					GEM + nab-PTX (1st line)	Effective		
12	Present case	2015	55/F	None	Trabectedin (2nd line)	No Effective	29	Death
					Eribulin (3rd line)	Effective		

DXR doxorubicin; CPA cyclophosphamide; BLM bleomycin; CDDP cisplatin; MMC mitomycin C; CBDCA carboplatin; VCR vincristine; EPI epirubicin; myocet, liposome-encapsulated doxorubicin citrate; GEM gemcitabine; DOC docetaxel; nab-PTX nanoparticle albumin-bound paclitaxel

Case report

A 55-year-old woman was referred to our hospital by her primary care physician for multiple metastatic liver tumors on December 2014. The patient's medical history included cardiopulmonary arrest due to pulmonary artery thrombosis in 2009, glaucoma and gastric ulcer. The patient's laboratory measurements were normal, except for slightly elevated levels of aspartate transaminase (42 IU/L), alanine transaminase (37 IU/L), lactate dehydrogenase (238 U/L), alkaline phosphatase (446 IU/L), gamma-glutamyl transpeptidase (222 U/L) and total cholesterol (259 mg/dL). The other tumor markers (alpha-fetoprotein, carbohydrate antigen 19–9, carcinoembryonic antigen, duke pancreatic monoclonal antigen type 2, s-pancreas antigen-1, protein induced by vitamin K absence-II, serum soluble interleukin 2 receptor) were normal.

Contrast-enhanced abdominal computed tomography (CT) showed a 33-mm mass in the pancreatic tail and multiple liver masses (Fig. 1a), and chest CT showed multiple metastases (Fig. 1b). 2-[18F] fluoro-2-deoxy-D-glucose-positron emission tomography showed increased metabolic activity in the left ribs (yellow arrow), liver (red triangular arrow), and lumbar spine (white bold arrow) (Fig. 1c), while an endoscopic ultrasound confirmed the presence

of a large hypoechoic pancreatic tail mass. We performed endoscopic ultrasound-fine needle aspiration using 19G and 25G fine-needle biopsy on the pancreatic tail tumor to determine the diagnosis. A histological examination was suggestive of spindle cell neoplasm (Fig. 2a), with the spindle cells showing mild to moderate nuclear pleomorphism and anisocytosis. The immunohistochemical studies revealed positivity for desmin (Fig. 2b) and smooth-muscle-specific actin (Fig. 2c) and were negative for S-100 protein (Fig. 2d), c-kit (Fig. 2e) and CD34 (Fig. 2f). The histological and immunohistochemical analysis confirmed leiomyosarcoma of pancreatic origin.

In January 2015, the patient underwent the first chemotherapy with GEM (1000 mg/m²) plus nab-PTX (125 mg/m²) on days 1, 8 and 15 every 28 days. The therapeutic effect on the tumor was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. After two cycles, the tumor showed a 14% increase in size; however, we continued the same regimen because the tumor remained in the RECIST category of stable disease (Fig. 3a). We observed a 22% reduction in tumor size after four cycles (Fig. 3b) and a maximum 44% reduction in size (partial response) after seven cycles (Fig. 3c). After ten cycles, the tumor unfortunately became a progressive disease in October 2015 (Fig. 3d); however, we continued with the same regimen until December 2015.

Fig. 1 Axial abdominal CT, chest CT and FDG scan (**a**, **b**, and **c**). Contrast-enhanced abdominal CT scan reveals 35-mm mass in the tail of the pancreas (yellow arrow) and liver metastasis (red triangular arrow) (**a**). **b** Chest CT scan reveals several small masses (**b**).

FDG scans showed increased metabolic activity in the left ribs (yellow arrow), liver (red triangular arrow), and lumbar spine (white bold arrow) (**c**)

Fig. 2 Histological features of a pancreatic tumor biopsy. Hematoxylin and eosin-stained section of tumor showed fascicles of spindle-shaped cells ($\times 400$) (**a**). Immunohistochemistry showed positive

staining for desmin (**b**), smooth-muscle-specific actin (SMA) (**c**), S-100 (**d**), c-kit (**e**), and CD34 (**f**)

Fig. 3 Contrast-enhanced abdominal CT during therapy with GEM plus nab-PTX. **a** After two cycles, **b** after four cycles, **c** after seven cycles, **d** after ten cycles

We did not select pazopanib and doxorubicin as the second chemotherapy, because the patient experienced cardiopulmonary arrest due to pulmonary artery thrombosis and was prescribed rivaroxaban. The patient was therefore treated with trabectedin (1.2 mg/m^2 every 21 days) as the second chemotherapy starting in February 2016. Although the tumor began to slightly increase after three cycles, we continued the same regimen. Once again, the tumor began to progress in June 2016 after five cycles. We therefore treated the patient with eribulin (1.4 mg/m^2 on day 1 and 8 every 21 days) as the tertiary chemotherapy starting in June 2016. The tumor showed a partial response in August 2016 after three cycles but began to progress in November 2016 after eight cycles. We re-selected the GEM plus nab-PTX regimen in February 2017; however, the patient presented with vomiting of blood in March 2017. Through upper gastrointestinal endoscopy, we observed that the patient had multiple gastric metastases. We provided the patient and their family with the best supportive care possible, but the patient died at another hospital in May 2017.

Discussion

This is the first reported case of PLMS treated with GEM plus nab-PTX therapy, a regimen that was effective in 10 months. The patient survived 29 months from the start of the GEM plus nab-PTX therapy.

There have been a few clinical studies on unresectable leiomyosarcoma treated by GEM plus DOC therapy [18–21], a therapy with a high response rate (31.5–35.8%) against uterine leiomyosarcoma [20, 21]. The standard treatment for soft-tissue sarcoma is DXR; however, Miyake et al. reported that GEM plus DOC therapy significantly reduced tumor size when compared with DXR in leiomyosarcoma using a nude mouse model [22]. We therefore recommend GEM plus DOC therapy as the standard first-line therapy for leiomyosarcoma.

nab-PTX is the first nanotechnology-based drug developed for cancer treatment. In nab-PTX, paclitaxel binds to the human protein albumin and is contained in nanoparticles [23]. The mechanism of nab-PTX is through the same

microtubule inhibitor as DOC. Recently, Higuchi T et al. reported that soft-tissue sarcoma treated with GEM plus nab-PTX resulted in more necrosis than DXR alone, GEM alone, DOC alone, nab-PTX alone and GEM plus DOC when employed in a nude mouse model [24]. Therefore, GEM plus nab-PTX could become the first-line chemotherapy for soft-tissue sarcoma.

Our patient experienced efficacy with eribulin, which showed a capacity to prolong overall survival in liposarcoma and leiomyosarcoma [25]. Eribulin is a microtubule inhibitor that has the same mechanism as taxane, a drug that blocks cell growth by impeding mitosis. Microtubule inhibitors can be effective drugs for leiomyosarcoma.

In conclusion, GEM plus nab-PTX was effective against PLMS and might therefore be considered as effective chemotherapy for PLMS.

We reported this patient at the 53rd Annual Meeting of the Japan Society of Clinical Oncology in 2015.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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