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CASE REPORT

Combination chemotherapy with gemcitabine and nab-paclitaxel for a metastatic pancreatic ductal adenocarcinoma patient undergoing hemodialysis

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Abstract

In cancer patients, impairment of kidney function is not uncommon. Recently, the efficacy of the combination of gemcitabine and nab-paclitaxel for pancreatic ductal adenocarcinoma (PDAC) patients has been reported, however, there is no recommendation for dose and administration to patients undergoing hemodialysis (HD). A 66-year-old man began receiving HD for chronic renal failure 4 years previously. He suffered from diarrhea, back pain, and loss of appetite, and his weight gradually decreased. Abdominal dynamic computed tomography showed a 45-mm hypodense mass in the pancreatic body and a 30-mm hypodense mass in the liver. The patient was diagnosed with metastatic PDAC. He started combination chemotherapy of gemcitabine and nab-paclitaxel without dose modification. He developed pneumonia and neutropenia in the first and second courses, so we modified to a 60% dose of gemcitabine and nab-paclitaxel on day 1 every 2 weeks. After dose modification, he continued combination chemotherapy for over 7 months without severe adverse events or tumor progression. Combination chemotherapy using gemcitabine and nab-paclitaxel was effective in a PDAC patient undergoing HD. While it is possible to originally administer these drugs with no dose modification, early dose modification was needed for our patient because of severe adverse events.

Keywords Pancreatic cancer · Hemodialysis · Gemcitabine · Nab-paclitaxel · Combination chemotherapy

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most fatal cancers, and the 5-year overall survival (OS) rate for metastatic pancreatic cancer remains at 2%, with a median life expectancy of < 1 year [1]. One reason for this low survival rate is that chemotherapy using gemcitabine (GEM) has been the only available treatment for a long time. Recently, however, the efficacy of multi-agent chemotherapy for metastatic PDAC has been examined [2, 3]. The median OS of PDAC patients receiving a combination chemotherapy regimen comprising oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) was 11.1 months, compared with an OS of 6.8 months in patients receiving gemcitabine, and the response rate of FOLFIRINOX was 32% [2]. In the gemcitabine plus nab-paclitaxel trial (the MPACT trial), the median OS of patients in the experimental arm was 8.5 months, compared with an OS of 6.7 months in patients receiving gemcitabine, and the response rate of gemcitabine plus nab-paclitaxel was 23% [3]. Moreover, in Japanese patients, the objective response rate of gemcitabine plus nab-paclitaxel therapy was 58.8%, and the median OS was 13.5 months [4]. However, patients with impaired renal function or undergoing hemodialysis (HD) were excluded from these studies. Moreover, there are only a few reports about chemotherapy for PDAC patients receiving HD [5, 6], and these reports dealt with monotherapy using gemcitabine

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only, so there is no report about the combination of gemcitabine plus nab-paclitaxel.

Several studies have reported that patients with chronic kidney disease are at a higher risk of developing various cancers than the general population [7–10]. Moreover, patients receiving long-term dialysis are at a significant risk for all cancers [9]. Therefore, reports on the treatment of cancer in patients receiving hemodialysis (HD) are important.

We treated a patient with metastatic PDAC concurrently undergoing HD. The patient was administered chemotherapy of gemcitabine plus nab-paclitaxel, and we report the clinical course here.

Case report

A 66-year-old man was undergoing peritoneal dialysis for chronic renal failure due to chronic glomerulonephritis 5 years previously and had switched to HD three times weekly beginning 4 years previously. He also had coexisting diseases, including hypertension and angina. The patient suffered from diarrhea and back pain since 1 month before. The patient experienced loss of appetite and gradual weight decrease, and he was referred to our department. His serum carbohydrate antigen 19-9 (CA 19-9) levels were elevated to 26061.7 U/mL. Abdominal dynamic computed tomography (CT) showed a 45-mm hypodense mass with distal dilatation of the main pancreatic duct in the pancreatic body (Fig. 1). This mass extended to the portal vein, splenic artery, common hepatic artery, and celiac artery. Ascites was found in the pelvic cavity. Moreover, a 30-mm hypodense mass was found in the liver. The patient underwent endoscopic ultrasound-guided fine needle aspiration of the pancreatic body mass, which revealed adenocarcinoma, class V. He was diagnosed with metastatic PDAC.

We planned to administer nab-paclitaxel (125 mg per square meter of body-surface area) in combination with gemcitabine (1000 mg per square meter) on days 1, 8, and 15, on a 4-week cycle [3, 4]. Laboratory findings before administration of chemotherapy showed mild leukocytopenia and anemia, including the following: white blood cells, 3300/μL; neutrophils, 1914/μL; hemoglobin, 11.6 g/dL; and platelets, 18.5×10^4/μL. The levels of aspartate aminotransferase, alanine aminotransferase, and C-reactive protein were within the normal range. Chemotherapy was administered in the afternoon and he received HD on the next day in the morning.

During the first course of chemotherapy, he developed a fever on day 7, and was diagnosed with pneumonia after CT. Antibiotics were administered, and chemotherapy was not administered on day 8. On day 15, his pneumonia had improved, but his granulocyte count was < 1000/μL, so chemotherapy was also not administered on day 15.

For the second course of chemotherapy, we administered an 80% dose of nab-paclitaxel and gemcitabine on day 1, because of the adverse events that occurred during the first course. However, he developed a fever and was ill with pneumonia again on day 6, and administration of nab-paclitaxel and gemcitabine was skipped on day 8. After administration of antibiotics, he recovered from pneumonia. Because he developed pneumonia despite the 20% reduction in dose, we further reduced the dose of nab-paclitaxel and gemcitabine to 60% on day 1 every 2 weeks. After that, he received 14 cycles of chemotherapy at that dose. During this time, the patient did not experience pneumonia or any other grade 3 or higher adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0) [11].

To determine the effectiveness of chemotherapy, abdominal CT was performed (Fig. 2). Both the pancreatic mass and the liver metastasis had expanded at the beginning of treatment compared to the time of diagnosis; the liver metastasis had increased in size to 45 mm. After 2 cycles of chemotherapy, the liver metastasis had reduced to 30 mm, and we assessed the patient as having stable disease according to the Response Evaluation Criteria in Solid Tumor guidelines. While the serum CA 19-9 levels had increased to 92590.7 U/mL before the start of chemotherapy, they decreased

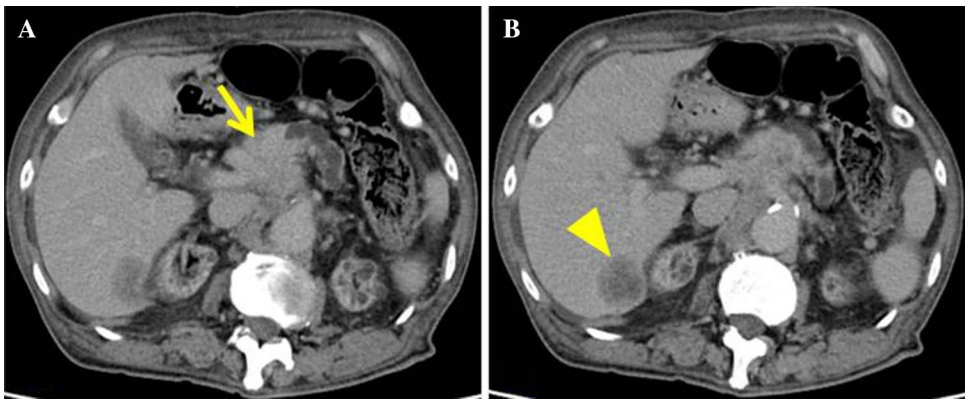

Fig. 1 **a** Abdominal dynamic computed tomography showed a 45-mm hypodense mass with distal dilatation of the main pancreatic duct at the pancreatic body (arrow). **b** A 30-mm hypodense mass was found in the liver (arrow head)

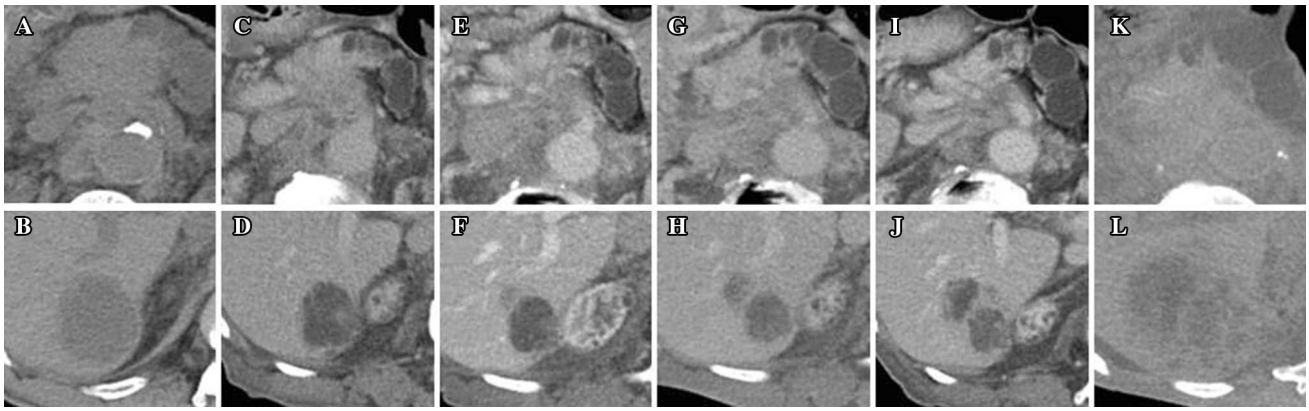

Fig. 2 Computed tomography images in the upper row show the pancreatic mass and those in the lower row show the liver metastasis. **a**, **b** At the start of chemotherapy; **c**, **d** after 2 cycles; **e**, **f** after 8 cycles; **g**, **h** after 12 cycles; **i**, **j** after 16 cycles; and **k**, **l** after 18 cycles of chemotherapy. While the liver metastatic mass expanded to 45 mm in diameter at the beginning of chemotherapy, the mass reduced to 30 mm after chemotherapy administration, and remained this size for about 5 months

with treatment, and were 2211.8 U/mL after 10 cycles of chemotherapy (Fig. 3). After 8 cycles of chemotherapy, a new liver metastasis appeared next to the previous metastasis. Although this new lesion appeared, we assessed that this chemotherapy regimen was clinically effective because of the reduction in size of the previous metastasis and the decrease in serum CA19-9 levels, and this treatment was continued for another 8 cycles.

After 16 cycles of chemotherapy, 8 months after the start of chemotherapy, the liver metastasis had re-expanded to 40 mm, and the serum CA 19-9 levels had increased to 10190.2 U/mL. At the same time, the patient developed infection of the arteriovenous graft. He had undergone shunt construction because of shunt obstruction 2 months ago. He recovered with administration of antibiotics and drainage, but he could not receive chemotherapy for 1.5 months. After that, he received another two cycles of chemotherapy. However, he developed poor physical health and emaciation, and the liver metastasis increased in size to 60 mm. He died of the disease 2 weeks after the last administration of chemotherapy. He survived over 10 months in total from the beginning of chemotherapy.

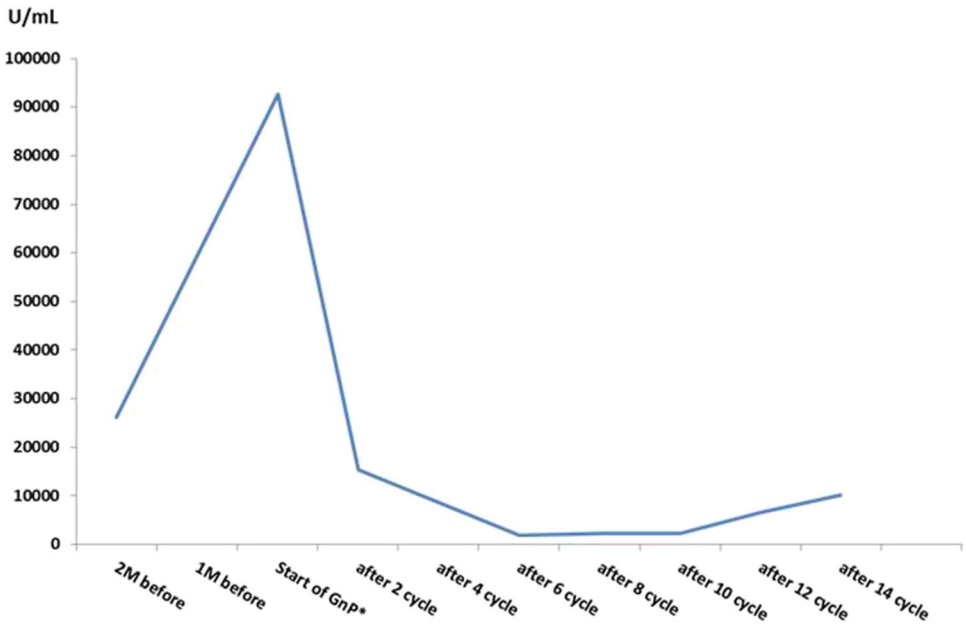

Fig. 3 The serum carbohydrate antigen 19-9 levels increased to 92590.7 U/mL before starting chemotherapy. After 10 cycles of chemotherapy, they decreased to 2211.8 U/mL in February. However, they started rising again in spite of continued chemotherapy. (GnP*: combination chemotherapy with gemcitabine and nab-paclitaxel)

Discussion

Recent advances in drug development have yielded effective chemotherapies, including molecular targeted drugs, for patients with other cancers, but there are currently only two chemotherapies (FOLFIRINOX and gemcitabine plus nab-paclitaxel) for patients with PDAC. Therefore, it is very important to examine the effectiveness and safety of a combination chemotherapy regimen of gemcitabine and nab-paclitaxel for patients with PDAC undergoing HD.

To the best of our knowledge, this is the first case examining the combination of gemcitabine plus nab-paclitaxel for a patient with PDAC undergoing HD.

In cancer patients, impairment of kidney function is not uncommon. However, patients with renal dysfunction are excluded in many clinical trials. Therefore, there are few data on the efficacy of almost all chemotherapeutic agents for patients with renal dysfunction, and no recommendation for dose and administration.

We administered gemcitabine and nab-paclitaxel to our PDAC patient undergoing HD, based on past case reports about the administration of gemcitabine and/or paclitaxel or nab-paclitaxel for patients undergoing HD.

Gemcitabine is metabolized intracellularly by deoxycytidine kinase to its active products, difluorodeoxycytidine diphosphate and triphosphate nucleoside, and has a half-life of 42–94 min, with a time to peak in the plasma of 30 min after infusion [12]. There are few reports on the administration of gemcitabine in patients undergoing HD [5, 6, 13]. In previous studies, there were no differences in pharmacokinetic parameters of gemcitabine, such as the $t_{1/2}$, AUC, and C_{max}, between patients undergoing HD and those with normal renal function, indicating that there may be no need for dose modification for patients undergoing HD [6, 13]. Gemcitabine is metabolized by cytidine deaminase to 2′,2′-difluorodeoxyuridine (dFdU) in both plasma and cells [14], and 80–90% of gemcitabine is excreted as dFdU in the urine within the first 6 h of administration [6, 14]. Masumori et al. [13] reported that dFdU showed a sustained level until HD was initiated, and Kiani et al. [6] reported that the AUC of dFdU in patients receiving HD was approximately 10-fold that in a historical control with normal renal function until undergoing HD. dFdU has been considered to be the major inactive metabolite of gemcitabine. However, Veltkamp et al. reported that its triphosphorylated form, dFdUTP, may contribute to cytotoxicity by inhibiting cell cycle progression in vitro [15]. Therefore, the frequency and severity of adverse events are considered to be higher in patients undergoing HD than in patients with normal renal function. In a past case report about a patient with PDAC undergoing HD, standard dose gemcitabine monotherapy was administered at first, but because of severe hematological toxicity, he required early dose reduction to 60%, which was administered every 2 weeks [5].

Nab-paclitaxel is metabolized in the liver and excreted predominantly through the feces (20%), with a small amount excreted in the urine (4%) [12]. Nab-paclitaxel's half-life is approximately 27 h. Although there is no report about the pharmacokinetics of nab-paclitaxel in patients undergoing HD, it has been reported that the paclitaxel pharmacokinetics in patients undergoing HD are similar to those in patients with normal renal function, and paclitaxel has good tolerance in several studies [16, 17]. Therefore, Janus et al. [18] proposed that no dose reduction in paclitaxel is needed for patients undergoing HD, and we believe that the same is true of nab-paclitaxel. There is only one report about the use of nab-paclitaxel in a patient undergoing HD [19]. They administered nab-paclitaxel 200 mg/body every 3 weeks with tegafur/gimeracil/otracil to a gastric cancer patient undergoing HD. The combination chemotherapy was continued for 1 year with no severe adverse events.

As mentioned above, there is no report of patients undergoing HD receiving combination chemotherapy with gemcitabine and nab-paclitaxel, but there are a few case reports of patients with urothelial carcinoma undergoing HD receiving combination chemotherapy with gemcitabine and paclitaxel [20, 21]. Although the dosage and administration interval were different in these reports, they administered these drugs to patients undergoing HD without dose modification. Moreover, there was no severe toxicity.

Incidentally, Von Hoff et al. reported that the combination therapy of gemcitabine and nab-paclitaxel increased apoptosis, and combination treatment with nab-paclitaxel promoted intratumoral gemcitabine levels in mice [22]. Frese et al. showed that nab-paclitaxel decreased protein levels of cytidine deaminase, which metabolizes gemcitabine, in mice [14]. This reaction may be one of the main mechanisms of the efficacy of the combination of gemcitabine and nab-paclitaxel.

Because of not only the accumulation of dFdU and the synergistic effect of combination of gemcitabine and nab-paclitaxel, but also the increased risk of infection in patients undergoing HD [23], it is believed that adverse events occur easily in PDAC patients receiving HD. Although we started chemotherapy with gemcitabine and nab-paclitaxel at the full dose and with no dose delay, as compared with the MPACT trial [3], severe adverse events occurred in our patient. He developed pneumonia and grade 3 neutropenia during the first course, and again in the second course, in spite of a reduction to 80% dose in both drugs. Hence, we administered a 60% dose of gemcitabine and nab-paclitaxel on day 1 every 2 weeks. After that, there were no severe adverse events for over 7 months. Although previous reports have found that no dose reduction of gemcitabine and/or

paclitaxel is needed for patients with various cancers who are receiving HD, early dose modification may be needed for PDAC patients.

In terms of the efficacy of combination chemotherapy with nab-paclitaxel and gemcitabine, the median progression-free survival (PFS) and OS were 5.5 months and 8.5 months, respectively, in the MPACT trial [3]. Moreover, in a Japanese patient cohort, the median PFS and OS were 6.5 months and 13.5 months, respectively [4]. In our patient, the PFS was about 7 months and the OS was about 10 months, so we believe that combination chemotherapy with nab-paclitaxel and gemcitabine was effective for this PDAC patient undergoing HD when compared with previous reports.

The relative dose intensity of combination therapy in our patient was approximately 42.5%. In contrast, the median relative dose intensities in the MPACT trial were 81% for nab-paclitaxel and 75% for gemcitabine [3, 24]. In spite of the lower rate in our report, the efficacy of combination chemotherapy was similar to that of the MPACT trial. Therefore, dose reduction may be preferable when starting chemotherapy with gemcitabine and nab-paclitaxel, allowing continuation of treatment without severe adverse events.

In conclusion, combination chemotherapy of gemcitabine and nab-paclitaxel was effective in our PDAC patient undergoing HD, similar to what has been seen in patients with normal renal function. While it may be possible to administer these drugs to patients undergoing HD with no dose modification for the first administration, early dose modification was needed in our patient because of the development of severe adverse events. However, this patient undergoing HD was able to continue gemcitabine combination chemotherapy for a long time with appropriate dose modification. Further clinical studies are needed to recommend this method.

Compliance with ethical standards

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

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Informed consent was obtained from all patients for being included in the study.

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