Observational Study

Medicine

OPEN

# Do antihypertensive drugs really have antitumor effects? Baseline differences in hypertensive and non-hypertensive patients with advanced pancreatic cancer

Kiyotsugu Iede, MD[a], Terumasa Yamada, MD, PhD[b,*], Masami Ueda, MD, PhD[b], Yujiro Tsuda, MD[b], Shinsuke Nakashima, MD, PhD[b], Katsuya Ohta, MD, PhD[b], Tsukasa Tanida, MD, PhD[b], Jin Matsuyama, MD, PhD[b], Masakazu Ikenaga, MD, PhD[b], Shusei Tominaga, MD, PhD[a]

**Abstract**

Although the antitumor effects of antihypertensive drugs for patients with advanced pancreatic cancer (APC) have been investigated, their efficacy remains unclear. Previous studies suggest that hypertensive (HT) patients with APC are significantly older than non-HT patients with APC, and that other major baseline differences in patient characteristics which may affect prognosis exist between HT and non-HT patients. It is also possible that antihypertensive drugs lack antitumor activity. Therefore, we herein retrospectively investigated the baseline differences between HT and non-HT patients with APC. From January 2015 to April 2020, 56 patients with APC received nab-paclitaxel plus gemcitabine as first-line chemotherapy at Higashiosaka City Medical Center (Higashiosaka, Japan). Of these 56 patients, 30 were diagnosed with hypertension (HT group); the remaining 26 did not have hypertension (non-HT group). Differences between the two groups were compared and prognostic factors were evaluated. Patients in the HT group had significantly less sarcopenia, a significantly larger body mass index, were significantly older, and significantly more likely to have a regular doctor and primary site in the body and tail of the pancreas than those in the non-HT group. Although no significant difference was found in the treatment response, patients in the HT group were significantly more likely to move to second-line chemotherapy than those in the non-HT group. Survival curves showed that median overall survival (OS) in the HT group was significantly longer (10.5 months) than in the non-HT group (6.8 months, $P = .04$). Multivariate analysis did not identify the use of antihypertensive drugs as an independent prognostic factor of OS. We identified key baseline differences in the characteristics of APC patients with and without HT, suggesting that major selection bias could occur when investigating the efficacy of antihypertensive drugs in all populations. Therefore, it is possible that antihypertensive drugs lack antitumor activity. To determine the true efficacy of antihypertensive drugs for APC, HT, and non-HT patients in another population should be investigated, or a prospective, randomized, controlled trial conducted that is stratified by HT or non-HT status.

**Abbreviations:** 1L = first-line, 2L = second-line, ACEIs = angiotensin I-converting enzyme inhibitors, AG = nab-paclitaxel plus gemcitabine, APC = advanced pancreatic cancer, ARBs = angiotensin II type-1 receptor blockers, BMI = body mass index, CCBs = calcium channel blockers, CI = confidence interval, CT = computed tomography, FOLFORINOX = fluorouracil/leucovorin plus irinotecan plus oxaliplatin, GEM = gemcitabine, HCMC = Higashiosaka City Medical Center, HT = hypertensive, L3 = third lumbar vertebra, LAPC = locally advanced pancreatic cancer, nab-PTX = nab-paclitaxel, OS = overall survival, PC = pancreatic cancer, PS = performance status.

**Keywords:** angiotensin II type 1 receptor blocker, calcium channel blocker, hypertension, pancreatic cancer, sarcopenia

*Data availability statement.*

*The authors of this work have nothing to disclose.*

*The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.*

*This work was supported by HCMC clinical research aid.*

*[a]Departments of Clinical Oncology and Higashiosaka City Medical Center, Higashiosaka, Japan, [b]Gastroenterological Surgery, Higashiosaka City Medical Center, Higashiosaka, Japan.*

**Correspondence: Terumasa Yamada, Department of Gastroenterological Surgery, Higashiosaka City Medical Center, 3-4-5 Nishiiwata, Higashiosaka 578-8588, Japan (e-mail: yamada-t@higashiosaka-hosp.jp).*



*How to cite this article: Iede K, Yamada T, Ueda M, Tsuda Y, Nakashima S, Ohta K, Tanida T, Matsuyama J, Ikenaga M, Tominaga S. Do antihypertensive drugs really have antitumor effects? Baseline differences in hypertensive and non-hypertensive patients with advanced pancreatic cancer. Medicine 2022;101:29(e29532).*

*Received: 6 October 2021 / Received in final form: 6 May 2022 / Accepted: 10 May 2022*

*http://dx.doi.org/10.1097/MD.0000000000029532*

## 1. Introduction

Pancreatic cancer (PC) is a fatal malignancy and the fourth major cause of cancer-associated mortality in Japan.[1,2] Compared with fluorouracil treatment of patients with advanced PC (APC), gemcitabine (GEM) has been associated with improved clinical outcome and longer overall survival (OS) (4.41 vs 5.65 months, respectively).[3] Further study of GEM-based combination regimens revealed nab-paclitaxel (nab-PTX) plus GEM (AG) to have a survival benefit over GEM monotherapy among patients with metastatic PC (8.5 vs 6.7 months, respectively) (MPACT trial).[4] Since this finding, AG has been administered as a first-line (1L) chemotherapeutic regimen in patients with APC.

New treatments are urgently required for patients with APC to improve survival. Recently, attention has focused on repurposing non-anticancer drugs for use in oncology.[5] The antitumor effects of antihypertensive drugs, such as calcium channel blockers (CCBs), angiotensin I-converting enzyme inhibitors (ACEIs), and angiotensin II type-1 receptor blockers (ARBs), for patients with APC have been investigated.[6–12] However, prospective, randomized, controlled phase III trials on the efficacy of those antihypertensive drugs have not been performed so their true efficacy remains unclear. Previous studies suggest that hypertensive (HT) patients with APC are significantly older than non-HT patients with APC,[7,12] and that other major baseline differences in characteristics which can affect prognosis exist between HT and non-HT patients. It is also possible that antihypertensive drugs lack antitumor activity. Therefore, we herein retrospectively investigated the baseline differences between HT and non-HT patients with APC.

## 2. Materials and Methods

### 2.1. Patients

From January 2015 to April 2020, 56 patients with APC received AG as 1L chemotherapy at Higashiosaka City Medical Center (HCMC, Higashiosaka, Japan). Of these patients, 30 were diagnosed with hypertension (HT group) and 26 did not have hypertension (non-HT group). Patient baseline characteristics and subsequent clinical courses were retrospectively compared between the two groups, and prognostic factors for OS were analyzed. The clinical research was approved by the institutional review board (02-0706-A). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent for study participation and publication was obtained from all individual participants included in the study.

### 2.2. Evaluation

HT patients either had a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg (or both), or had taken antihypertensive drugs. Performance status (PS) was determined according to the Eastern Cooperative Oncology Group scale.[13] Computed tomography (CT) was performed at diagnosis in all patients using a 64-multidetector row CT scanner (Aquilion TSX-101A; Toshiba Medical Systems, Tokyo, Japan) or 128-slice helical CT scanner (Brilliance iCT SP; Philips, Amsterdam, the Netherlands). CT images were analyzed using SYNAPSE VINCENT software version 5.3 (Fujifilm, Tokyo, Japan) to evaluate the total skeletal muscle area in a single axial image at the third lumbar vertebra (L3). Hounsfield unit thresholds of −29 to +150 were used for skeletal muscle. The cross-sectional skeletal muscle area was standardized by the square of the height to calculate the L3 skeletal muscle index. The cutoff line for the skeletal muscle index was 43.75 $cm^2/m^2$ for men and 38.5 $cm^2/m^2$ for women.[14,15]

These cutoffs were used to diagnose sarcopenia. The tumor response was assessed by CT using Response Evaluation Criteria in Solid Tumors version 1.1. Imaging evaluation was repeated every two cycles of AG treatment. The objective response was defined as a complete response or partial response maintained for ≥4 weeks. Disease control was defined as a complete response, partial response, or stable disease maintained for ≥4 weeks.

### 2.3. Treatment

Beginning in January 2015, AG was administered as 1L chemotherapy for APC until disease progression or intolerance because of adverse events. The initial dose of AG was chosen according to a previous Phase III trial[4]: intravenous infusions of nab-PTX (125 $mg/m^2$) and concomitant GEM (1000 $mg/m^2$) on days 1, 8, and 15, followed by a 7-day rest. This regimen was adjusted at the discretion of the physician and patient. After AG, the indications for second-line (2L) chemotherapy were determined according to the general status and willingness to continue treatment of the patient.

### 2.4. Statistical analysis

Differences between the two groups were compared using the chi-square test and the Mann–Whitney *U* test. OS was calculated from initiating treatment to the patient's death or censored time. OS was estimated using the Kaplan–Meier method and compared using the Wilcoxon test. Prognostic factors with clinical importance were entered into the multivariate Cox proportional hazards model to analyze independent factors. $P < .05$ was considered statistically significant. Statistical analyses were performed using JMP software version 13.0 (SAS Institute, Cary, NC).

## 3. Results

### 3.1. Patient characteristics and subsequent clinical course

Baseline patient characteristics and subsequent clinical courses are shown in Table 1. Of the 30 patients in the HT group, 19 used CCBs, 13 used ARBs, and 10 used both CCBs and ARBs at baseline. None of the patients in the non-HT group used any antihypertensive drugs. Patients in the HT group were significantly older, had a significantly larger body mass index (BMI), had significantly less sarcopenia, and were significantly more likely to have a regular doctor and primary site in the body and tail of the pancreas than those in the non-HT group. Although no significant difference was found in the treatment response, patients were significantly more likely to move to 2L chemotherapy in the HT group than in the non-HT group. Thirty-two (57%) patients received 2L chemotherapy. S-1 (oral 5-FU derivative) was mainly used (23 patients, 72%), followed by modified fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX; 7 patients, 22%). Twenty-three (41%) patients did not receive 2L chemotherapy. One patient continued AG for >30 months in the HT group.

### 3.2. OS in HT and non-HT groups

Figure 1 shows the duration of OS in HT and non-HT groups. The median duration of OS was 10.5 months (95% confidence interval [CI], 8.6–15.0) in the HT group and 6.8 months (95% CI, 3.9–11.2) in the non-HT group. This difference was significant ($P = .04$).

### 3.3. Univariate and multivariate analyses of OS

Univariate and multivariate analyses were undertaken to clarify the prognostic factors of OS (Table 2). Univariate analysis

**Table 1**

**Baseline patient characteristics and subsequent clinical course.**

| Patient characteristic | HT (n = 30) | Non-HT (n = 26) | *P* |
|---|---|---|---|
| Male:female ratio | 13:17 | 13:13 | .62 |
| Age, yr (range) | 73 (42–80) | 66.5 (42–79) | **.02** |
| PS (0:1–2) | 20:10 | 16:10 | .69 |
| Body mass index (median, kg/m$^2$) | 23.5 | 20.2 | **.01** |
| Skeletal muscle index (median, cm$^2$/m$^2$) | 43.1 | 39.1 | **.04** |
| Sarcopenia (yes:no) | 11:19 | 18:8 | **.02** |
| Symptoms at diagnosis (yes:no) | 19:11 | 22:4 | .07 |
| Use of a regular doctor (yes:no) | 28:2 | 9:17 | **<.001** |
| Distant metastasis (yes:no) | 22:8 | 22:4 | .30 |
| Site of the primary tumor (head vs body and tail) | 7:23 | 15:11 | **.009** |
| Albumin (>/=3.3 vs <3.3 g/dL) | 24:6 | 18:8 | .35 |
| CRP (>1.0 vs </=1.0 mg/dL) | 9:21 | 8:18 | .95 |
| CA19-9 (median, U/mL) | 901 | 934.5 | .50 |
| Clinical course | | | |
| Objective response (yes:no) | 9:21 | 4:22 | .20 |
| Disease control (yes:no) | 21:9 | 15:11 | .61 |
| Discontinuation of AG because of adverse events (yes:no) | 5:25 | 9:17 | .12 |
| Induction of 2L chemotherapy (yes:no)* | 22:7 | 10:16 | **.005** |

Bold values are statistically significant.

2L = second-line, AG = nab-paclitaxel plus gemcitabine, CA19-9 = carbohydrate antigen 19-9, CRP = C-reactive protein, HT = hypertension, PS = performance status.

*One patient continued AG for >30 months in the HT group.

identified PS (0 vs 1–2), CCB use, and distant metastasis as significant prognostic factors. Multivariate analysis performed with clinically important variables identified PS (0 vs 1–2) and distant metastasis as independent prognostic factors.

## 4. Discussion

In the present study, we investigated baseline differences in characteristics of APC patients with and without HT. Patients in the HT group had significantly less sarcopenia, had a significantly larger BMI, were significantly older, and significantly more likely to have a regular doctor and primary site in the body and tail of the pancreas than those in the non-HT group. Although there was no significant difference in the AG treatment response, patients were significantly more likely to move to 2L chemotherapy and had significantly longer OS in the HT group than in the non-HT group. Multivariate analysis did not identify the use of antihypertensive drugs as an independent prognostic factor of OS.

Following extensive preclinical data, many studies have investigated the association between use of antihypertensive drugs and OS in different types of cancer. For example, both ACEIs and ARBs were revealed to be associated with

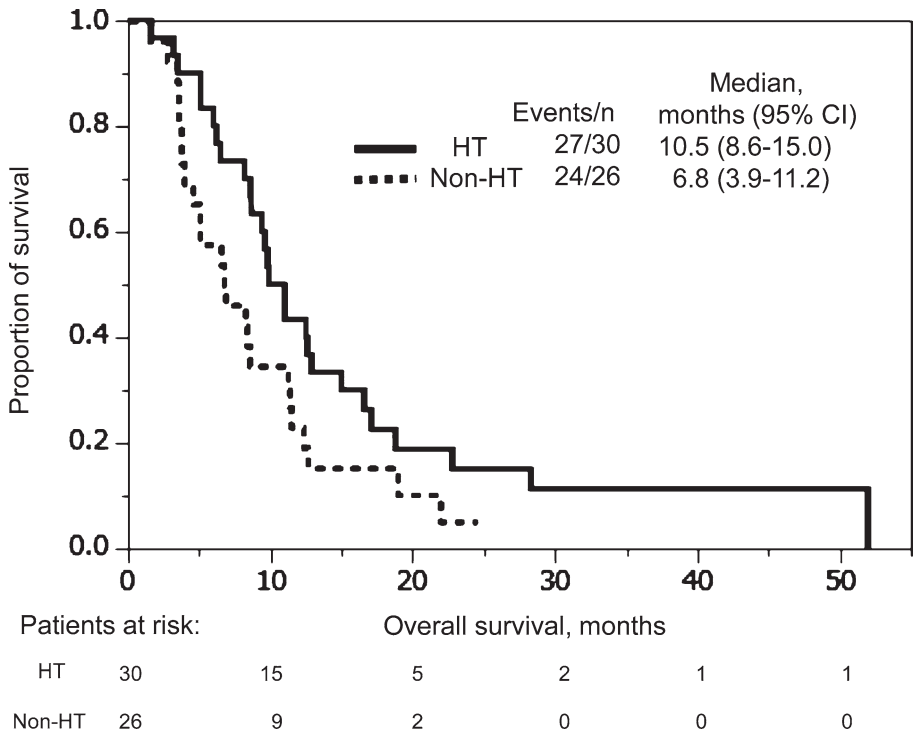


**Figure 1.** Kaplan–Meier curves for overall survival in HT and non-HT groups of patients with APC. *P* = .04. APC = advanced pancreatic cancer, HT = hypertension.

**Table 2**

**Univariate and multivariate analyses of overall survival.**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| **Factor** | **HR** | **95% CI** | ***P*** | **HR** | **95% CI** | ***P*** |
| Sex (male vs female) | 0.99 | 0.57–1.74 | .98 | | | |
| Age (>/=65 vs <65 yr old) | 1.35 | 0.73–2.65 | .34 | 1.71 | 0.76–3.97 | .20 |
| PS (0:1–2) | 0.34 | 0.18–0.63 | **<.001** | 0.33 | 0.17–0.66 | **.002** |
| HT (yes:no) | 0.60 | 0.34–1.06 | .08 | | | |
| CCB use (yes:no) | 0.55 | 0.29–0.98 | **.04** | 0.60 | 0.30–1.17 | .13 |
| ACEI/ARB use (yes:no) | 0.77 | 0.39–1.45 | .43 | | | |
| CCB and ACEI/ARB use (yes:no) | 0.65 | 0.29–1.28 | .22 | | | |
| Symptoms at diagnosis (yes:no) | 1.73 | 0.95–3.48 | .08 | | | |
| Presence of a regular doctor (yes:no) | 0.63 | 0.36–1.15 | .13 | | | |
| Body mass index (>/=21 vs <21) | 0.81 | 0.46–1.45 | .48 | | | |
| Sarcopenia (yes:no) | 1.28 | 0.73–2.25 | .38 | 0.90 | 0.51–1.62 | .73 |
| Primary tumor (head vs body and tail) | 1.37 | 0.77–2.41 | .28 | 1.93 | 0.94–3.94 | .07 |
| Distant metastasis (yes:no) | 2.70 | 1.27–6.65 | **.008** | 2.52 | 1.14–6.47 | **.02** |

Bold values are statistically significant.

ACEIs = angiotensin I-converting enzyme inhibitors, ARBs = angiotensin II type-1 receptor blockers, CCBs = calcium channel blockers, CI = confidence interval, HR = hazard ratio, HT = hypertension, PS = performance status.

improvement in OS in patients with non-small cell lung cancer and in patients with advanced gastric cancer.[16,17] The survival benefits of ACEIs/ARBs in combination with GEM in patients with APC were revealed in a previous retrospective study.[12] Based on these findings, they conducted a phase I trial of GEM and candesartan combination therapy to determine the recommended dose of candesartan in normotensive patients with APC (GECA1).[11] This proceeded to a single-arm multicenter phase II trial (GECA2) which explored the antitumor efficacy of candesartan in combination with GEM.[10] However, GEM and candesartan combination therapy failed to demonstrate activity against APC.[10] It is unclear why the results of these prospective and retrospective studies differ.[10,12]

The survival benefits of CCBs in combination with chemo and/or radiotherapy in patients with APC were investigated in another retrospective study.[7] Both retrospective studies found that patients with APC who were receiving antihypertensive drugs were more likely to be older and have hypertension than those without antihypertensive drugs; baseline demographics were otherwise similar between the two groups.[7,12] A single-arm phase II clinical trial was performed to investigate the potential of losartan to improve success in surgical tumor resection among locally APC (LAPC) patients receiving FOLFIRINOX followed by chemoradiotherapy.[8] This proceeded to a current 4-arm randomized phase II clinical trial investigating the effects of losartan and/or immunotherapy (nivolumab) in combination with FOLFIRINOX and stereotactic body radiotherapy on improving success in surgical resection in patients with LAPC (NCT03563248).[18] Although patients already receiving ACEI or ARB treatment for HT or renal protection at the time of enrollment were excluded in the test arms, the HT status was not set as a stratified factor.

The present study is a new report revealing major baseline differences in the characteristics of patients with APC with and without HT. Our finding that patients in the HT group had less sarcopenia and a larger BMI in spite of their older age suggests that they might perform antihypertension exercise to maintain their skeletal muscles. APC might be detected in these patients slightly earlier than in non-HT patients because of more regular medical checks. Conversely, the likely reduced medical checks of non-HT patients could mean that they endure APC symptoms such as stomachache, fatigue, appetite loss, or reduced body weight and skeletal muscle until they become severe. This could explain why HT patients have more physical strength to undergo 2L chemotherapy than non-HT patients. The induction of 2L chemotherapy is considered important for improved survival,[19–26] so the higher induction rates of 2L chemotherapy observed in the HT group might lead to a longer OS.

In the present study, HT patients were likely to be diagnosed with APC without symptoms during a regular medical check. In general, patients with APC in the head of the pancreas are more likely to be have symptoms such as obstructive jaundice or duodenal invasion than patients with APC in the body or tail of the pancreas. This could explain why the primary tumor site was more commonly identified in the body and tail of the pancreas in patients with HT than in those without HT in the present study. Consequently, we identified key baseline differences in the characteristics of APC patients with and without HT, suggesting that major selection bias could occur when investigating the efficacy of antihypertensive drugs in all populations. Therefore, it is possible that antihypertensive drugs lack antitumor activity.

This study has several limitations. We were unable to eliminate potential selection bias because this was a single-center retrospective study, and the statistical power was limited by the small sample size. Nevertheless, some major baseline differences were still identified between patients with and without HT, which could mean that antihypertensive drugs lack strong antitumor activity. To determine the true efficacy of antihypertensive drugs for APC, a prospective, randomized, controlled trial stratified by HT status should be conducted, or HT and non-HT patients should be investigated in another population.

## Acknowledgments

We thank Sarah Williams, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

## Author contributions

Conceptualization: Kiyotsugu Iede.
Data curation: Kiyotsugu Iede.
Formal analysis: Kiyotsugu Iede, Terumasa Yamada.
Funding acquisition: Kiyotsugu Iede, Shusei Tominaga, Terumasa Yamada.
Investigation: Kiyotsugu Iede.
Methodology: Kiyotsugu Iede.
Project administration: Kiyotsugu Iede.
Resources: Jin Matsuyama, Katsuya Ohta, Kiyotsugu Iede, Masakazu Ikenaga, Masami Ueda, Shinsuke Nakashima, Terumasa Yamada.
Software: Kiyotsugu Iede.
Supervision: Shusei Tominaga, Terumasa Yamada.
Validation: Terumasa Yamada.

Visualization: Kiyotsugu Iede.
Writing – original draft: Kiyotsugu Iede.
Writing – review & editing: Terumasa Yamada.

## References


[1] Iede K, Yamada T, Kato R, et al. Multiple liver metastases rather than the presence of liver metastasis is a significantly poor prognostic factor for patients with advanced pancreatic cancer. Pancreas 2020;49:e63–5.
[2] Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan. Available at: https://ganjoho.jp/reg_stat/statistics/dl/index.html [database on the Internet]. 2019.
[3] Burris HAIII, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403–13.
[4] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.
[5] Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov 2019;18:41–58.
[6] Keith SW, Maio V, Arafat HA, et al. Angiotensin blockade therapy and survival in pancreatic cancer: a population study. BMC Cancer 2022;22:150.
[7] Tingle SJ, Severs GR, Moir JAG, et al. Calcium channel blockers in pancreatic cancer: increased overall survival in a retrospective cohort study. Anticancer Drugs 2020;31:737–41.
[8] Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: a phase 2 clinical trial. JAMA Oncol 2019;5:1020–7.
[9] Nakai Y, Isayama H, Sasaki T, et al. The inhibition of renin-angiotensin system in advanced pancreatic cancer: an exploratory analysis in 349 patients. J Cancer Res Clin Oncol 2015;141:933–9.
[10] Nakai Y, Isayama H, Ijichi H, et al. A multicenter phase II trial of gemcitabine and candesartan combination therapy in patients with advanced pancreatic cancer: GECA2. Invest New Drugs 2013;31:1294–9.
[11] Nakai Y, Isayama H, Ijichi H, et al. Phase I trial of gemcitabine and candesartan combination therapy in normotensive patients with advanced pancreatic cancer: GECA1. Cancer Sci 2012;103:1489–92.
[12] Nakai Y, Isayama H, Ijichi H, et al. Inhibition of renin-angiotensin system affects prognosis of advanced pancreatic cancer receiving gemcitabine. Br J Cancer 2010;103:1644–8.
[13] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
[14] Ninomiya G, Fujii T, Yamada S, et al. Clinical impact of sarcopenia on prognosis in pancreatic ductal adenocarcinoma: a retrospective cohort study. Int J Surg (London, England) 2017;39:45–51.
[15] Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009;15:2920–6.
[16] Wilop S, von Hobe S, Crysandt M, et al. Impact of angiotensin I converting enzyme inhibitors and angiotensin II type 1 receptor blockers on survival in patients with advanced non-small-cell lung cancer undergoing first-line platinum-based chemotherapy. J Cancer Res Clin Oncol 2009;135:1429–35.
[17] Kim ST, Park KH, Oh SC, et al. How does inhibition of the renin-angiotensin system affect the prognosis of advanced gastric cancer patients receiving platinum-based chemotherapy? Oncology 2012;83:354–60.
[18] ClinicalTrials.gov. Losartan and nivolumab in combination with FOLFIRINOX and SBRT in localized pancreatic cancer (NCT03563248). [Updated 2/24/2022]; Available at: http://clinicaltrials.gov/ct2/show/NCT03563248.
[19] Matsumoto T, Kurioka Y, Okazaki U, et al. FOLFIRINOX for advanced pancreatic cancer patients after Nab-paclitaxel plus gemcitabine failure. Pancreas 2020;49:574–8.
[20] Iede K, Yamada T, Kato R, et al. Predictive implications of decreased CA19-9 at 8 weeks during nab-paclitaxel plus gemcitabine for the induction of second-line chemotherapy for patients with advanced pancreatic cancer. Cancer Rep (Hoboken, NJ) 2020;3:e1289.
[21] Iede K, Yamada T, Kato R, et al. Efficacy of S-1 in second-line chemotherapy after nab-paclitaxel plus gemcitabine for patients with advanced pancreatic cancer. Cancer Rep (Hoboken, NJ) 2020;3:e1215.
[22] Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet (London, England) 2016;387:545–57.
[23] Chiorean EG, Von Hoff DD, Tabernero J, et al. Second-line therapy after nab-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. Br J Cancer 2016;115:188–94.
[24] Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol 2014;32:2423–9.
[25] Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer (Oxford, England: 1990) 2011;47:1676–81.
[26] Iede K, Yamada T, Koh M, et al. Optimal relative dose intensity in the first 4 weeks during Nab-paclitaxel plus gemcitabine for older patients with advanced pancreatic cancer in Japan. Pancreas 2022;51:e4–6.