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LETTER TO THE EDITOR

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ABOUT COVER

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

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CASE REPORT

Long survival after immunotherapy plus paclitaxel in advanced intrahepatic cholangiocarcinoma: A case report and review of literature

Meng-Ye He, Fei-Fei Yan, Kai-Li Cen, Peng Shen

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Abstract

BACKGROUND

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary hepatic malignancy worldwide. However, currently available systemic therapies are of limited effectiveness, and the median overall survival of patients treated with first-line standard chemotherapy is less than one year. Immune checkpoint inhibitors have been used to treat solid tumors. Clinical studies recently explored the combination of chemotherapy and immunotherapy for CCA. However, the clinical significance of predictive biomarkers for chemo-immunotherapy in CCA remains unclear. It is also worth exploring whether a combination of chemotherapeutic agents can increase the sensitivity of CCA immunotherapy.

CASE SUMMARY

This study reports a case of advanced iCCA in which clinical complete remission had been achieved using a programmed death 1 (PD-1) inhibitor and paclitaxel without known predictive biomarkers, but with *BRCA1*, *KRAS*, and *NTRK3* mutations after rapid progression to first-line chemotherapy, and has remained in clinical complete remission for more than two years. This case suggests that chemo-immunotherapy is a potential therapeutic option for patients with iCCA and few known predictive biomarkers for immunotherapies as well as synergistic effect of the combination of paclitaxel and PD-1 monoclonal antibody.

CONCLUSION

The combination of paclitaxel and PD-1 monoclonal antibodyr can be explored in patients with advanced iCCA.

Key Words: Intrahepatic cholangiocarcinoma; Programmed cell death protein-1 inhibitor; Paclitaxel; Chemo-immunotherapy; Predictive biomarker; Case report

Core Tip: The first-line standard treatment for advanced intrahepatic cholangiocarcinoma has been programmed cell death ligand 1 antibody combined with gemcitabine + cisplatin therapy, but the median overall survival time still could not break 1 year. However, this patient achieved clinical complete remission after second-line treatment with paclitaxel combined with programmed death 1 antibody and has survived for more than 32 mo. And we performed genetic testing of tissue specimens and found that this patient was without known predictive biomarkers related to immunotherapy efficacy but with *BRCA1*, *KRAS* and *NTRK3* mutation, and whether there is a therapeutic efficacy correlation deserves further exploration.

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INTRODUCTION

As of 2020, primary liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related death worldwide[1]. Cholangiocarcinoma (CCA) is the second most common primary liver malignant tumor after hepatocellular carcinoma, accounting for 10%–20% of all primary liver cancers. According to anatomical location, it can be divided into intrahepatic CCA (iCCA), hilar CCA, and distal CCA. The incidence of iCCA has been increasing over the past few decades[2]. Owing to the characteristics of hidden onset and lack of typical clinical symptoms, iCCA is often diagnosed at an advanced stage. Only 30%–40% of patients receive surgical treatment after diagnosis, and the postoperative recurrence rate is high[3]. There is an urgent need to develop new strategies for the predictive diagnosis of biliary tract cancer (BTC) at an early, resectable stage. Liquid biopsy has received increasing attention over the years, given its promising application in cancer patients. In CCA the detection of circulating tumor cell, circulating free DNA and extracellular vesicles has tremendous potential applications in the early diagnosis of CCA and monitoring of treatment response[4,5]. But now due to the limitations of diagnostic tools, even after radical surgery, the 5-year overall survival rate is less than 40%, and the median overall survival (mOS) time is approximately 28 mo[6]. Also, local treatments include transarterial radioembolization, hepatic artery infusion, transarterial chemoembolization and radiofrequency ablation, which have been shown to improve the survival of ICC[7,8].

So far, chemotherapy is the primary treatment for patients with locally advanced or metastatic iCCA. A phase III clinical trial (ABC-02) reported that the mOS time and median progression-free survival time of patients with advanced CCA treated with the gemcitabine + cisplatin (GemCis) regimen were significantly longer than those treated with gemcitabine monotherapy (mOS time: 11.7 mo *vs* 8.1 mo; hazard ratio, 0.64; 95% confidence interval, 0.52–0.80; $P < 0.001$)[9]. Because of the ABC-02 results, the GemCis regimen was promoted as the standard first-line chemotherapy for advanced CCA. In addition, clinical trials reported the efficacy of albumin paclitaxel combined with gemcitabine as the first-line treatment[10,11]. Immunotherapy targeting programmed death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 was recently approved for the treatment of different types of cancers, especially those with high PD-L1 expression, high tumor mutation load (TMB), or microsatellite instability (MSI)[12-14]. TOPAZ-1 is the first phase III clinical study using immunotherapy in combination with chemotherapy as the first-line treatment of CCA, with a significant improvement in mOS resulting in a breakthrough in 1-year survival in the chemo-immunotherapy group[15]. Considering the response of BTC to immunotherapy, reliable biomarkers of response to PD-1/PD-L1 inhibitor in BTC are still not identified and developed, clarifying the role of PD-L1 expression, MSI, mismatch repair, TMB and other emerging predictors[16]. However, after progression on first-line therapy quality evidence of second-line treatment is lacking, preventing standardized follow-up treatment after disease progression. The phase III clinical trial ABC-06 study showed that, as second-line treatment, the FOLFOX or Nal-IRI + 5-FU/LV regimen prolonged the survival of patients after the GemCis compared to palliative treatment (mOS time, 6.2–8.6 mo)[17,18], but the survival benefit was very limited.

Potentially actionable molecular alterations are identified in about 50% of iCCA cases[19,20]. Molecular profiling should be considered for all biliary tract cancer patients who may benefit from the discovery of a potentially actionable mutation, especially *FGFR2* fusions or rearrangements and *IDH1* mutations[20,21]. However, the benefit of using immunotherapy combined with chemotherapy as

second-line therapy for these biomarker-negative iCCA patients is unclear, and the choice of chemotherapy regimen has a variable impact on the efficacy of immunotherapy. Here we report a case of metastatic iCCA treated with anti-PD1 monoclonal antibody combined with paclitaxel after first-line GemCis chemotherapy failure. After six treatment cycles, the best effect achieved was clinical complete remission with mild adverse reactions.

CASE PRESENTATION

Chief complaints

An elevated carbohydrate antigen 199 (CA199) level (579.9 U/mL; reference range, 0–37 U/mL) but no discomfort.

History of present illness

A 67-year-old man was admitted to the hospital with an elevated CA199 level (579.9 U/mL; reference range, 0–37 U/mL) but no discomfort. Enhanced computed tomography (CT) of the abdomen revealed a mass with a maximum diameter of 5.7 cm in S8 of the liver, and pulmonary CT showed multiple small nodules in both lungs (Figure 1A and B).

History of past illness

No history of biliary stones, no history of hepatitis, no history of hepatic schistosomiasis.

Personal and family history

Denied smoking, drinking and history of epidemic disease. No family history of tumors.

Physical examination

The abdomen was soft, without pain, and no obvious masses were palpated in the abdomen.

Laboratory examinations

CA199 level (579.9 U/mL; reference range, 0–37 U/mL).

Imaging examinations

Enhanced CT of the abdomen revealed a mass with a maximum diameter of 5.7 cm in S8 of the liver, and pulmonary CT showed multiple small nodules in both lungs.

FINAL DIAGNOSIS

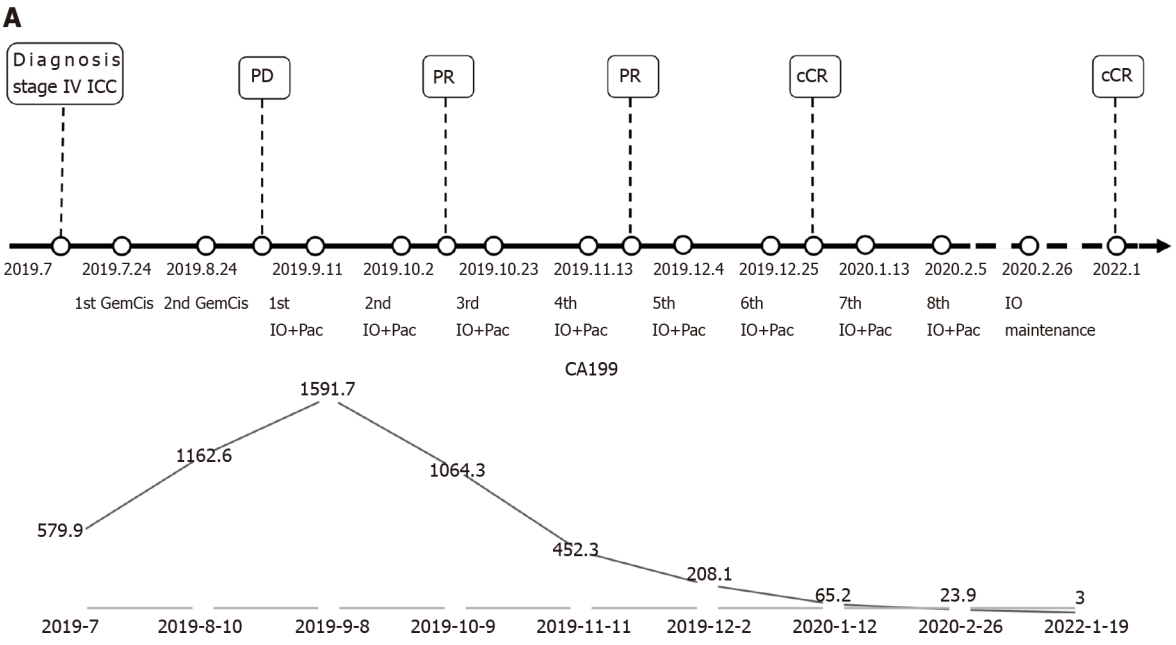
Liver mass: iCCA considered.

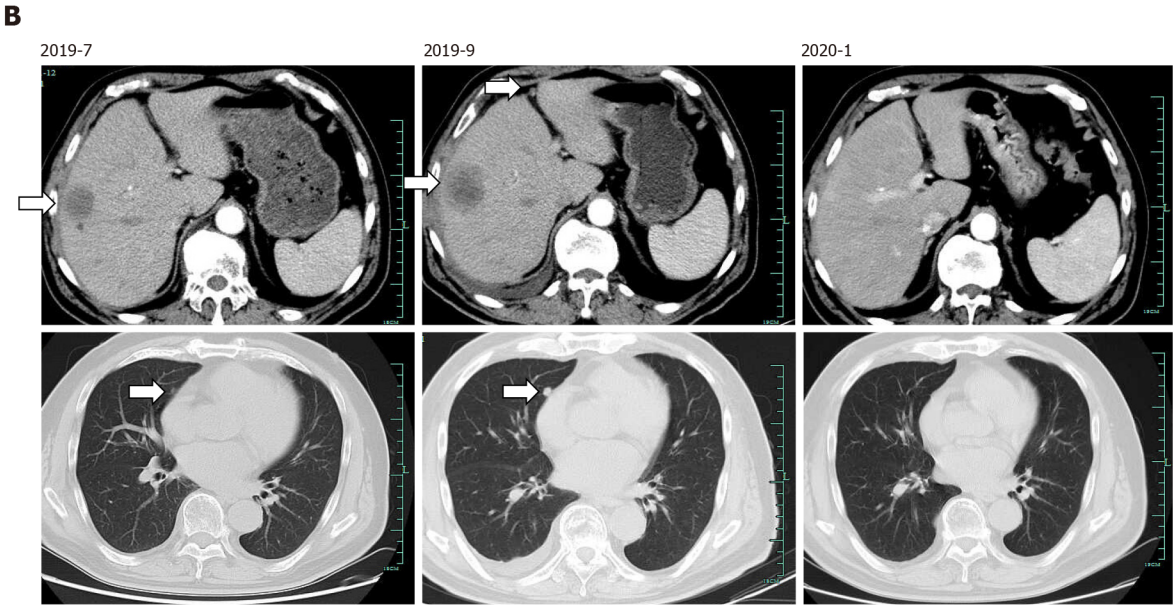
TREATMENT

After evaluation subsequent intrahepatic mass was proposed for resection. During surgery, the tumor was found to be located in segments V and VIII, approximately 6 cm, with multiple metastases in the diaphragm and peritoneum; therefore, radical resection was not suitable, and a peritoneal nodule biopsy was performed. Pathology revealed a moderately differentiated adenocarcinoma. An immunohistochemical examination showed the following: CK7(+), CK19(+), hepatocyte(-), AFP(-), GPC3(-), Arginase-1(-), MUC-1(local+), CDX2(-). The final clinical diagnosis, according to the American Joint Committee on Cancer, was stage IV iCCA (cT4N0M1).

Referring to the ABC-02 clinical trial, the patient was given first-line chemotherapy with GemCis for two cycles. But the patient presented with right-sided chest pain on breathing and no significant decrease in CA199, so an evaluation was performed upfront. However, the response evaluation suggested disease progression with CT showing an increased number and size of metastases in the abdomen and lungs (Figure 1A and B). Genomic alteration testing was performed to explore the potential drug targets using the next-generation sequencing assay, which contains 520 genes that are related to cancer mechanism and targeted therapy. The results showed three somatic mutations, including *BRCA1*, *KRAS*, and *NTRK*, with MSI being stable and TMB 3.2 mut/Mb defined as TMB-low (Figure 1C). PD-L1 expression was detected by immunohistochemical staining (Dako 22C3) with tumor proportion score (TPS) 0% and combined positive score 5.

The second-line treatment was changed to camrelizumab 200 mg in combination with paclitaxel 175 mg/m^2 every three weeks. The serum concentrations of CA199 and CA125 decreased to 452.3 U/mL and normal, respectively, and partial response was maintained based on CT scans after two cycles of





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Gene	Mutation Type	Mutation Result
BRCA1	Shift mutation	p.Tyr655fs germline heterozygous
KRAS	Missense mutation	p.Gly12Ala 18.89%
NTRK3	Missense mutation	p.Gly633Glu 8.06%
MSI	NA	Low
TMB	NA	3.2mut/Mb

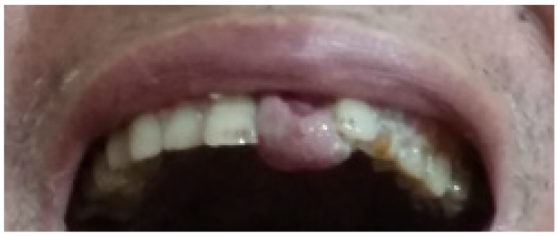

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Figure 1 Patient's treatment history and outcome. A: Timeline: Treatment regimens with response assessment and carbohydrate antigen 199 change; B: Computed tomography (CT) of the abdominal and lung lesions throughout therapy. July 2019, CT images of lung and liver on presentation, benign proliferative lesion of lung was considered at that time; September 2019, CT images of lung and liver after 2 cycles of GemCis chemotherapy, the intrahepatic and intrapulmonary lesions were significantly larger than before, and the peritoneal lesions were increased and pleural effusion appeared; January 2020, CT images of lung and liver after 6 cycles of paclitaxel and programmed death 1 monoclonal antibody, lesions of liver and lung were clinical complete remission; C: Genomic alteration assay result; D: The Reactive cutaneous capillary endothelial proliferation developed in the oral gingiva after the third cycle of camrelizumab with paclitaxel and was surgically removed after 2 mo. iCC: Intrahepatic cholagiocarcinama cancer; PR: Partial response; PD: Progressive disease; cCR: Clinical complete remission; GemCis: Gemcitabine and cisplatin; IO: Immunotherpay; Pac: Paclitaxel; PD-1: Programmed death 1.

combination chemotherapy and immunotherapy. After six cycles of therapy, both intrapulmonary and intra-abdominal lesions achieved clinical complete remission on CT (Figure 1A and B). After eight cycles of combination therapy, the treatment was changed to camrelizumab 200 mg every three weeks until the completion of 1 year of anti-PD-1 antibody treatment.

OUTCOME AND FOLLOW-UP

This patient has now been followed-up for 32 mo (until May 2022), and no disease progression has been observed at regular follow-ups. Reactive cutaneous capillary endothelial proliferation (RCCEP) developed in the oral gingiva and facial skin with bleeding after the third cycle of chemo-immunotherapy. The RCCEP in the gingival area (Figure 1D) was surgically removed after 2 mo, while that on the facial area self-exfoliated with no other serious adverse effects during treatment.

DISCUSSION

There is currently no standard second-line treatment for advanced iCCA. mFOLFOX has been recommend as the preferred second-line regimen, but its survival benefit is very limited, with an mOS time of 6.2 mo *vs* 5.3 mo, $P = 0.031$[17]. Immunotherapy has shown relatively good efficacy against a variety of solid tumors, and data from small samples of cholangiocellular carcinoma suggest the efficacy of PD-1 monoclonal antibody in advanced cholangiocellular carcinoma[22,23]. Approximately 11% of cholangiocellular carcinomas have an immunoinflammatory phenotype, as defined by comprehensive genomic analysis, which may be predictive of the effectiveness of PD-1 or PD-L1 monotherapy[24]. Other recent studies have explored the molecular typing of CCA by genomics and proteomics, which show the different expression patterns of immune checkpoints, highlight the need to design personalized checkpoint inhibitors for use, and provide clues to explain the differential response of advanced iCCA to anti-PD-1 monotherapy[25].

In this case, MSI, TMB, and PD-L1 TPS expressions were low, but mutations in *BRCA1* and *KRAS* were present. *BRCA* mutations were detected in approximately 3.6% of CCA samples (*BRCA1*, 0.6%; *BRCA2*, 3%)[26]. PARP inhibitors are expected to be the next category of targeted agents as breakthrough treatments for advanced CCA, but the research data are not sufficient[27]. The available genetic test results for this patient suggested that he was not sensitive to immunotherapy.

To improve the anticancer effect, many chemotherapeutic agents have been tested in combination with immunotherapy to modify the antitumor activity[28,29]. The TOPAZ-1 trial is the first phase III clinical study using immunotherapy plus a chemotherapy regimen of gemcitabine and platinum for the first-line treatment of biliary tract cancer to show a significant difference in mOS obtained in the treatment group[15]. Table 1 lists the reported cases of PD-1/PD-L1 inhibitors and chemotherapy in patients with CCA, and the chemotherapeutic drugs are mainly platinum and fluorouracil alone or in combination. Chemotherapeutic drugs can destroy tumor tissues and overcome immune rejection, causing antigen shedding and increasing tumor neoplastic antigens to improve immunotherapy efficacy. There is growing evidence that some chemotherapeutic agents, such as platinum and taxanes, induce apoptosis in tumor cells and cause immunogenic cell death, which activates the immune system [30,31]. The immunomodulatory effects of chemotherapeutic agents are summarized in Table 2. Chemotherapy-induced tumor cell death may release immunostimulatory signals that promote dendritic cell activation and induce T-lymphocyte-mediated immune tumor cell killing. Chemotherapy induces the upregulation of major histocompatibility complex I (MHC-I), which helps T cells recognize tumor cells. Furthermore, chemotherapeutic agents upregulate PD-L1 expression, and chemotherapy-enhanced immunosuppression induced by PD-L1 upregulation can be abolished when immunotherapy is added to the treatment strategy, which is expected to produce a synergistic anti-cancer effect.

Based on these theories and the summary in Table 2, paclitaxel in combination with anti-PD-1 is a very favorable option for improving the activated immune response (upregulating MHC-I, dendritic cell maturation, and T cell effectors) and reducing immunosuppressive cells (myeloid derived suppressor cell, T-regulatory cells, and tumor-associated macrophage type 2). According to a preclinical study, most iCCA cell lines were resistant to platinum drugs, whereas most cell lines were sensitive to gemcitabine and paclitaxel[25]. Available clinical studies show that triple negative breast cancer patients who are expected to have greater *BRCA* mutations and urothelial cancer patients with *BRCA1* mutations receive immune-combination chemotherapy regimens; PD-1 monoclonal antibody combined with paclitaxel has very good efficacy[32,33]. A hypnosis regarding these findings suggests that paclitaxel may be a better chemotherapeutic agent in combination with PD-1/PD-L1 immunotherapy for paclitaxel-sensitive solid tumors with or without *BRCA* gene mutations. This mechanism has been the focus of published research, where treatment with polyethylene glycol-sheddable nanodrugs containing paclitaxel and anti-PD-1 enhanced the tumor infiltration of cytotoxic T lymphocytes as well as local immune checkpoint blockade[34].

Table 1 Reported cases of programmed death 1 inhibitors and chemotherapy in patients with cholangiocarcinoma

Ref.	Biomarker	Drug	Patient population	Sample size	Best effect	PFS
Ma *et al*[35], 2021	NA	FOLFOX6 + Camrelizumab + Fruquintinib	fourth line	1	PR	2 mo
Liu *et al*[36], 2020	TMB-H	Sintilimab + S-1	third line	1	PR	5 mo
Sui *et al*[37], 2019	High insertion-deletion ratio	Tegafur + Pembrolizumab	first line	2	cCR	16 mo; 13 mo
Mou *et al*[38], 2018	TMB-H; PD-L1	Pembrolizumab + SOX	second line	1	cCR	11 mo

NA: Not available; TMB: Tumor mutation load; PR: Partial remission; PFS: Progression free survival; PD-L1: programmed cell death ligand 1; cCR: Clinical complete remission.

Table 2 Immunomodulatory effects of chemotherapeutic agents

	Immunogenic cell death	PD-L1 ↑	MDSC ↓	Treg ↓	M2↓	MHC class I ↑	Dendritic cells mature	T-cell effectors ↑
Gemcitabine[39-41]	×	√	√	√	×	√	√	√
Platinum[42-45]	?	√	√	√	×	√	√	√
Paclitaxel[44,46-49]	√	√	√	√	√	√	√	√
Fluorouracil[50-53]	√	√	√	√	√	√	√	?

↑: Increase; ↓: Decrease; ?: Unsure; √: Modulate mechanism; ×: Does not modulate mechanism; MDSC: Myeloid derived suppressor cell; MHC: Major histocompatibility complex; PD-L1: Programmed death ligand 1; M2: Tumor-associated macrophage type 2; Treg: T-regulatory cell.

This case describes a potential clinical option for combination immunotherapy in patients with iCCA with or without *BRCA1* mutations. This is the first study to investigate paclitaxel combined with a PD-1 inhibitor in patients with advanced iCCA, which signified the benefit of chemo-immunotherapy in advanced iCCA patients with low TMB, PD-L1, TPS, and microsatellite stability. Obviously, in iCCA and other types of cancer, predictive biomarkers are lacking for many patients. Thus, this case suggests that the paclitaxel and PD-1 inhibitor combination is a potential effective therapeutic option for the management of these patients.

In conclusion, chemo-immunotherapy offers a potential therapeutic option for patients with iCCA and few or no predictive biomarkers for immunotherapies, and the combination of paclitaxel as an effective chemotherapeutic agent with PD-1 monoclonal antibody may have a better synergistic effect. Future studies should better elucidate the therapeutic efficacy and potential mechanisms of action of chemo-immunotherapy in iCCA as well as the optimal combination strategy for immunotherapy.

CONCLUSION

For patients with advanced iCCA without predictive biomarkers, a regimen of immunotherpay combined with paclitaxel may be considered for treatment. And a more complex analysis will be performed to screen the population that really benefits from this treatment.

FOOTNOTES

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