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Immunotherapy in Advanced Biliary Tract Cancer

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QUESTION: A 65-year-old female patient visited our hospital complaining of abdominal pain and dyspepsia. Abdominal computed tomography (CT) revealed a mass of approximately 6 cm in the left lobe of the liver (Fig. 1A). Percutaneous needle biopsy confirmed adenocarcinoma, and positron emission tomography-CT revealed peritoneal carcinomatosis (Fig. 1B). Therefore, the patient was diagnosed with stage IV intrahepatic cholangiocarcinoma with peritoneal metastasis, and her performance status was good, indicating that palliative chemotherapy was an option. Considering the 2024 National Comprehensive Cancer Network (NCCN) guidelines, what are the two most recommended preferred regimens for first-line therapy for this patient?

ANSWER: (1) Durvalumab + gemcitabine + cisplatin or (2) Pembrolizumab + gemcitabine + cisplatin.

REVIEW: Biliary tract cancer (BTC) is a malignant tumor originating from epithelial cells involved in bile production. The major types include extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer. BTC predominantly affects the elderly and has a particularly high incidence in East Asia, including South Korea. The incidence of BTC is increasing in many countries, including Korea, and most patients present at an advanced stage at diagnosis, posing significant treatment challenges [1]. Currently, no effective screening tests for early detection of BTC have been established, and the disease often remains asymptomatic during the early stages, complicating early diagnosis. Consequently, the five-year survival rate remains alarmingly low at less than 10%.

Radical surgery offers the only curative treatment for BTC; however, operability is limited as most patients are diagnosed at an advanced stage. In these cases, chemotherapy becomes the primary treatment option. The standard regimen had been a combination of gemcitabine and cisplatin for more than a decade [2]. Nevertheless, the overall survival with this combination remains a mere 11.7

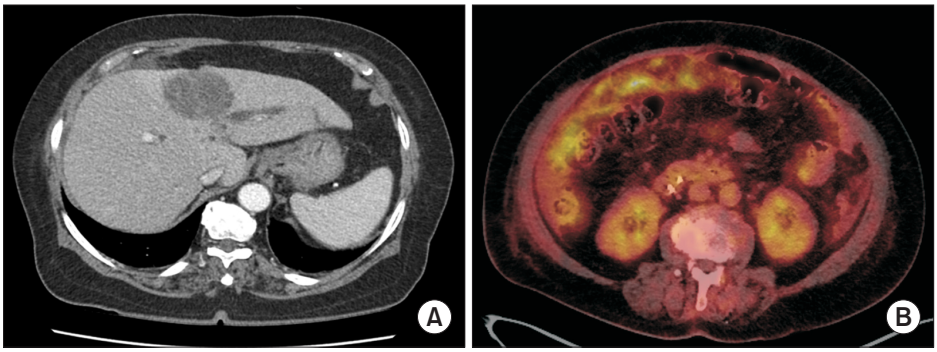

Fig. 1. Initial imaging findings of the patient. (A) Abdominal computed tomography (CT). (B) Positron emission tomography-CT.

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months. Immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway have primarily been studied as a second-line treatment for patients who progress after first-line therapy [3,4]. Clinical trials have utilized pembrolizumab and nivolumab, showing therapeutic responses in some patients, although the increase in survival time has been minimal, and without a definitive biomarker, ICIs have not been established as a standard treatment.

The integration of ICI and cytotoxic chemotherapy combination therapy as first-line treatment has significantly altered the BTC treatment paradigm. The TOPAZ-1 study, published in 2022, demonstrated that the combination of the PD-L1 inhibitor durvalumab with gemcitabine and cisplatin improved survival rates in patients with advanced BTC compared to the previous standard therapy [5]. The 24-month overall survival rate was 24.9% for the durvalumab group versus 10.4% for the placebo group (hazard ratio, 0.80; 95% confidence interval, 0.66–0.97). The Keynote-966 study, published in 2023, showed similar results with the combination of the PD-1 inhibitor pembrolizumab with gemcitabine and cisplatin, demonstrating improved survival compared to standard therapy (hazard ratio, 0.83; 95% confidence interval, 0.72–0.95) [6]. These findings have led the recent NCCN guidelines to recommend gemcitabine/cisplatin/ICIs (durvalumab or pembrolizumab) combination therapy as first-line treatment for advanced BTC in patients with good performance status (Eastern Cooperative Oncology Group performance status 0 or 1). In Korea, as of April 2024, the use of gemcitabine/cisplatin/ICIs (durvalumab or pembrolizumab) is feasible for advanced BTC (excluding ampulla of Vater cancer), although the high cost of ICIs remains a barrier to widespread adoption.

Identifying effective biomarkers is essential for the successful application of ICIs in advanced BTC. While PD-L1 expression in tissue and microsatellite instability-high status are the primary biomarkers currently used, their efficacy has not been clearly established. A recent meta-analysis indicated that PD-L1 expression in tissue may predict improved survival following ICI therapy in BTC, but it does not predict response rates, limiting its role as a definitive biomarker [7]. Researches are expanding into other potential biomarkers, such as tumor mutational burden, which could enable more precise treatment selection and prognostic assessments.

The introduction of immunotherapy in the treatment of advanced BTC signifies a crucial advancement, and ongoing clinical trials and research are likely to provide further insights and treatment strategies. Future research should focus on optimal ICI combinations, effective patient selection criteria, and the management of adverse effects. Additionally, the development of biomarkers and a precision medicine approach will enhance personalized treatment strategies, improving survival rates and quality of life for BTC patients. These efforts are expected to open new horizons in the treatment of advanced BTC.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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