Treatment Outcomes of Durvalumab Combination Therapy in Patients with Biliary Tract Cancer

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Objectives: This study aimed to evaluate the efficacy and safety of gemcitabine, cisplatin, and durvalumab (GCD) combination therapy in patients with biliary tract cancer treated at our hospital.
Methods: Nineteen patients diagnosed with biliary tract cancer and treated with durvalumab combination therapy at Tokai University Hachioji Hospital between February 1, 2023, and May 31, 2024, were included in this retrospective study.
Results: The median overall survival was 13.7 months, and the median progression-free survival was 7.3 months, comparable to outcomes reported in the TOPAZ-1 trial.
Conclusion: GCD therapy demonstrated efficacy and safety similar to those observed in the TOPAZ-1 trial.

Key words: durvalumab, biliary tract cancer, GCD therapy

INTRODUCTION

Biliary tract cancer carries a poor prognosis. Cytotoxic antitumor drugs, such as gemcitabine and cisplatin (GC) combination therapy, have long been used for unresectable cases [1]. Recently, the immune checkpoint inhibitor (ICI) durvalumab was approved for insurance coverage in Japan, leading to its increasing use.

However, much remains unknown about the efficacy and adverse events of existing treatments in Japanese clinical practice compared with those reported in the TOPAZ-1 trial [2]. This study aimed to evaluate the efficacy and safety of gemcitabine, cisplatin, and durvalumab (GCD) combination therapy in patients treated at our hospital.

PATIENTS AND METHODS

Consecutive nineteen patients (11 men and 8 women) histologically diagnosed with biliary tract cancer and treated with durvalumab combination therapy at Tokai University Hachioji Hospital between February 1, 2023, and May 31, 2024, were included in this study. The following parameters were retrospectively evaluated: age, tumor markers (carcinoembryonic antigen (CEA) and carbohydrate antigen 19−9 (CA19−9)), performance status, primary tumor location, tumor condition (unresectable or postoperative recurrence), disease stage (distant metastasis or local recurrence), timing of GCD therapy (first-line or second-line), post-GCD therapy course (conversion to durvalumab monotherapy, treatment discontinued, or treatment modification), best overall response, adverse events, overall survival, and progression-free survival. Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) criteria. Primary tumor location was classified as intrahepatic bile duct, perihilar bile duct, common bile duct, gallbladder, or papilla. The best overall response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), categorized as complete response, partial response, stable disease, or progressive disease. Adverse events of grade 3 or 4 based on the Common Terminology Criteria for Adverse Events (CTCAE) were considered significant.

Survival curves were estimated using the Kaplan–Meier method, and confidence intervals for survival times were calculated using Greenwood's formula. Statistical analyses were performed using JMP version 12 (JMP International Offices, Tokyo, Japan).

RESULTS

The ages of the 19 patients ranged from 54 to 83 years, with a median age of 73 years. Serum CEA levels ranged from 1.4 to 976 ng/mL (median, 4 ng/mL), and CA19−9 levels ranged from 14.9 to 66,453.1 U/mL (median, 153 U/mL). The ECOG performance status was 0 in 13 patients, 1 in four patients, and 2 in two patients. Primary tumor locations were the intrahepatic bile duct in five patients (26%), perihilar bile duct in two (10%), common bile duct in three (16%), gallbladder in eight (42%), and ampulla in one

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Table 1 Parameters in this study

Age	73(54–83)y/o
Sex	
men/women	11/8
CEA	4(1.4–976) ng/mL
CA19–9	153(14.9–66453.1) U/mL
ECOG Performance Status	
0/1/2	13/4/2
Primary tumor location	
Intrahepatic bile duct	5(26%)
Perihilar bile duct	2(10%)
Common bile duct	3(16%)
Gallbladder	8(42%)
Papilla	1(5%)
Tumor condition	
Unresectable	10(53%)
Postoperative recurrence	9(47%)
Disease stage	
Distant metastasis	18(94%)
Local recurrence	1(6%)
Timing of GCD therapy	
First-line	14(74%)
Second-line	5(26%)
Post-GCD therapy course	
Conversion to Durvalumab monotherapy	10(53%)
Treatment discontinued	4(21%)
Treatment modification	5(26%)
Best overall response (RECIST)	
Partial Response	9(47%)
Stable Disease	9(47%)
Progressive Disease	1(6%)
Adverse events (CTCAE grade3 or 4)	
Neutropenia	3(16%) Discontinued in 2 cases
Anemia	3(16%)
Thrombocytopenia	3(16%) Discontinued in 2 cases
Stomatitis	1(6%)

*CEA denotes carcinoembryonic antigen, CA19–9 carbohydrate antigen 19–9, ECOG Eastern Cooperative Oncology Group, GCD gemcitabine, cisplatin, and durvalumab, RECIST Response Evaluation Criteria in Solid Tumors, CTCAE Common Terminology Criteria for Adverse Events.

Table 2 the association between the best overall response and the primary tumor locations

Best overall response by Primary tumor location	
Partial Response	
Intrahepatic bile duct	3(33%)
Perihilar bile duct	1(11%)
Common bile duct	2(22%)
Gallbladder	3(33%)
Stable Disease	
Intrahepatic bile duct	1(11%)
Perihilar bile duct	1(11%)
Common bile duct	1(11%)
Gallbladder	5(55%)
Papilla	1(11%)
Progressive Disease	
Intrahepatic bile duct	1(100%)

(6%). The tumor was unresectable in 10 patients (53%) and a postoperative recurrence in nine (47%). Disease progression was distant metastasis in 18 patients (94%) and locally advanced disease in one (6%). GCD therapy was administered as first-line treatment in 14 patients (74%) and as second-line or later in five (26%). Following GCD therapy, 10 patients (53%) switched to durvalumab monotherapy, whereas four (21%) discontinued and five (26%) transitioned to other treatments. The best overall response was partial response in nine patients (47%; intrahepatic bile duct in three, perihilar bile duct in one, common bile duct in two, gallbladder in three), stable disease in nine (47%; intrahepatic bile duct in one, perihilar bile duct in one, common bile duct in one, gallbladder in five, papilla in one), and progressive disease in one (6%; intrahepatic bile duct in one). Adverse events of CTCAE grade 3 or higher included neutropenia in three patients (16%), anemia in three (16%), thrombocytopenia in three (16%), and stomatitis in one (6%). Treatment was discontinued in two patients with neutropenia and two with thrombocytopenia (Table 1, 2).

The median overall survival was 13.7 months (95% confidence interval, 9.7–not reached), and the median progression-free survival was 7.3 months (95% confidence interval, 4.2–12.8) (Fig. 1). These results were comparable to those reported in the TOPAZ-1 trial.

DISCUSSION

Biliary tract cancer is relatively common in Asia, including Japan, and has a five-year survival rate of less than 20%, making it the second most lethal cancer after pancreatic cancer. Statistics from the National Cancer Center Japan show 22,159 new cases and 17,773 deaths from biliary tract cancer in 2020. Although it ranks 14th in incidence among all cancer types, it ranks sixth in mortality - following lung, colon, stomach, pancreatic, and liver cancers - and the number of deaths has continued to rise in recent years [3].

As with other solid tumors, biliary tract cancer is staged according to tumor extent and the presence or absence of lymph node or distant organ metastasis [4]. Chemotherapy is administered when the disease is considered unresectable. Since the approval of gemcitabine as a cytotoxic anticancer agent in Japan in 2000, GC

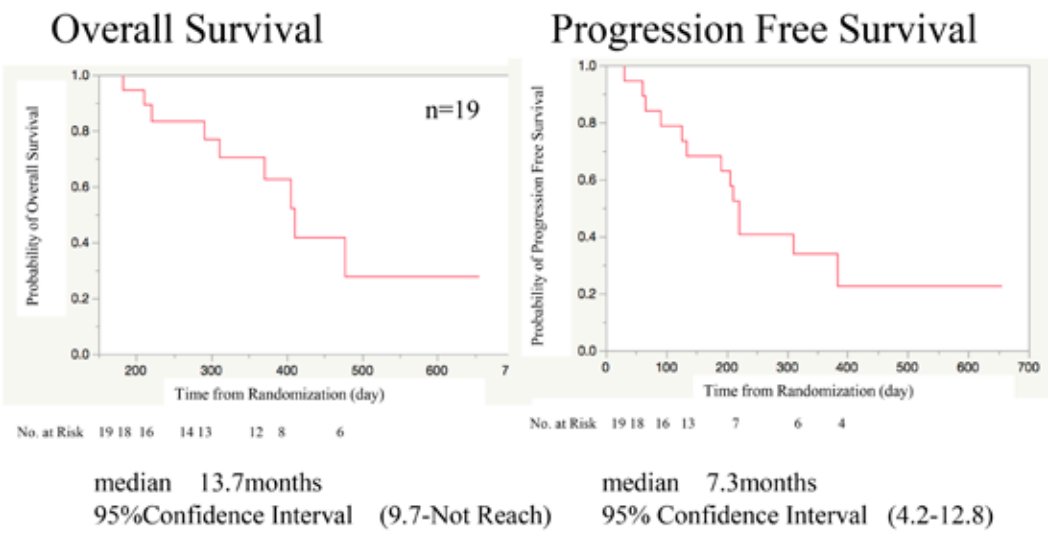

Fig. 1 The median overall survival and the median progression-free survival in this study

therapy and other combination regimens have been developed and widely adopted [5, 6].

In recent years, advances in understanding tumor immune responses have led to the development of ICIs, which harness the immune system to treat various cancers. The immune checkpoint pathway is a natural regulatory mechanism that prevents excessive immune activation by suppressing T cell activity through ligand - receptor interactions involving programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on T cells. ICIs block these interactions, thereby inhibiting immunosuppressive signaling and enhancing antitumor immune activity, producing therapeutic effects distinct from those of cytotoxic agents [7].

Treatment development for unresectable biliary tract cancer has progressed with the introduction of ICIs, used either alone or in combination with conventional chemotherapy. In 2022, the results of the Phase III TOPAZ-1 trial, which compared GCD therapy with GC therapy for unresectable biliary tract cancer, were reported [2]. The primary endpoint of overall survival was significantly longer in the GCD group (12.8 months) than in the GC group (11.5 months). Similarly, the secondary endpoint of progression-free survival showed improvement in the GCD group (7.2 months) compared with the GC group (5.7 months). The outcomes of GCD therapy in patients treated at our hospital were comparable to those of the TOPAZ-1 trial, with a median overall survival of 13.7 months and a median progression-free survival of 7.3 months. In the TOPAZ-1 trial, the most common adverse events were anemia (48.2%), nausea (40.2%), diarrhea (32.0%), and neutropenia (31.7%). In contrast, the incidence of adverse events in this study was lower, with anemia, neutropenia, and thrombocytopenia each occurring in 16% of patients, and stomatitis in 6%. Gastrointestinal symptoms, which are frequently reported as adverse events, were not observed. Furthermore, immune-related adverse events specific to ICIs, such as hypothyroidism (5.9%), dermatitis (3.6%), liver injury (1.2%), and adrenal insufficiency (1.2%), were reported in the TOPAZ-1 trial but were not observed in this study. The reason of adverse events less frequent than in the Phase III TOPAZ-1 trial, dosage adjustments, including initial dose reductions and interruptions, were determined at the discretion of each physician, and the incidence of adverse events, particularly non-hematological events, may have been underestimated.

ICIs have the advantage of producing a long-tail effect, maintaining durable therapeutic responses in a subset of patients [8]. In addition, GCD therapy allows patients to transition to durvalumab monotherapy after eight cycles, administered once every four weeks, thereby reducing treatment burden. However, in our study, four of the 10 patients who transitioned to durvalumab monotherapy died within a few cycles, coinciding with tumor progression, suggesting that monotherapy alone may not provide sufficient anticancer activity. Recently, gemcitabine, cisplatin, and pembrolizumab (GCP) combination therapy, an ICI-based regimen with a modified treatment schedule after the initial eight cycles, has become available [9]. Pembrolizumab, a PD-1 inhibitor, blocks both PD-L1 and PD-L2, potentially offering a distinct anticancer mechanism compared with durvalumab [10]. Therefore, when disease control appears inadequate after transitioning to durvalumab monotherapy, continuing GCD therapy or switching to GCP therapy should be considered.

This study has a few limitations, including its retrospective nature, single institution setting, small sample size, and shorter observation period compared with earlier studies. These limitations may affect the findings' generalizability and robustness, highlighting the need for further research with extended follow-up periods and larger, more diverse patient cohorts.

In conclusion, the efficacy and safety of GCD therapy in this study were comparable to those reported in the TOPAZ-1 trial. When disease control appears inadequate after transitioning to durvalumab monotherapy, continuing GCD therapy or switching to GCP therapy

should be considered.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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