

## Consolidating the Treatment Guidelines of Chemotherapy for Cholangiocarcinoma between the East and West

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### Abstract

Purpose of chemotherapy in cholangiocarcinoma (CC): Chemotherapy is applied not only for the treatment of unresectable CC, but also as adjuvant therapy after surgery. The prognosis of CC remains poor, and chemotherapy plays an important role in the treatment of CC. However, the chemotherapeutic agents available are limited, and effective chemotherapy regimens are yet to be established to improve the prognosis. Although there are some discrepancies in the standard chemotherapy regimens used between Asian countries and Western countries, global clinical trials of various molecular-targeted agents are increasing.

**Keywords:** Cholangiocarcinoma; Chemotherapy; Adjuvant Therapy; Guidelines

### Adjuvant therapy after surgery for CC

Recently, several phase III trials of adjuvant treatment after surgery have been conducted. However, to date, no agent or regimen has been shown to yield definitive benefit on the overall survival in the postoperative adjuvant setting in CC patients. Although gemcitabine (GEM) was investigated in a phase III trial for extrahepatic CC in Japan, there was no difference in the overall survival or relapse-free survival between the gemcitabine arm and the observation arm [1]. A study of GEM plus oxaliplatin (GEMOX) was conducted in France, but it also failed to demonstrate any benefit in terms of the overall or relapse-free survival [2]. The BILCAP study, which compared capecitabine with observation, was the largest trial of adjuvant therapy for biliary tract cancer, conducted in 447 patients. Although the primary endpoint of overall survival was met in the per-protocol analysis, no statistically significant superiority of the treatment over observation alone could be demonstrated in the intention-to-treat analysis [3]. S-1, which is an oral fluoropyrimidine, like capecitabine, is currently under investigation in a phase III trial (JCOG1202) [4]. Subject enrolment was completed in June 2018, and the results of an analysis of the 3-year overall survival will be reported in 2021. Pooled analysis of the BILCAP and JCOG1202 is proposed in the future.

### Chemotherapy for unresectable cholangiocarcinoma

Systemic chemotherapy is the standard of care for patients with advanced-stage cholangiocarcinoma. GEM plus cisplatin (GC) is recognized as the global standard chemotherapy (ESMO guidelines and NCCN guidelines), based on the results of the ABC-02 study comparing GC with gemcitabine alone [5]. The BT22 study conducted in Japan also demonstrated the survival benefit of GC [6]. Therefore, GC is also recommended as the standard of care in the Japanese guidelines. In 2018, two positive phases III studies were reported from Japan. The JCOG1113 study, comparing GEM plus S-1 (GS) with GC, demonstrated the non-inferiority of GS to GC in terms of the overall survival [7]. The KHBO1401 study, comparing GC plus S-1 (GCS) with GC, demonstrated the superiority of GCS over GC in terms of overall survival [8]. As a result, GS and GCS are recognized as alternative treatments for advanced CC in Japan.

There are still various unmet medical about CC. There are some discrepancies in the recommendations in guidelines because of the limited number of international clinical trials. There are no established second-line treatments. There are no established systemic treatments with targeted agents based on biomarkers in advanced CC, including immune therapies. Regarding targeted therapies, FGFR-2, IDH-1 and HER-2 are key biomarkers for CC [9]. Various FGFR inhibitors are currently under investigation for CCs harboring FGFR2 gene fusions [10,11]. Phase II trials of FGFR inhibitors are being conducted as global trials with the participation of Western countries and Asian countries. International clinical trials of immune checkpoint inhibitors are either ongoing or are being planned, not only as a second-line treatment, but also as first-line treatment, in combination with GC [12-14].

### Conclusion

Recently, microsatellite instability-high (MSI-H) tumors have been shown to benefit from PD-1 blockades, such as with pembrolizumab. Pembrolizumab has been approved for the treatment of MSI-H tumors, including CC. Treatment strategies using precision medicines such as MSI-H, FGFR2, and HER2 are expected to be established in the near future. It is important to conduct international clinical trials to establish a global standard of care for CC.

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