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Systemic Therapy of Cholangiocarcinoma

Ruben R. Plentz Nisar P. Malek

Department of Internal Medicine I, Medical University Hospital, Tübingen, Germany

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Chemotherapy · Cholangiocarcinoma · Survival

Summary
Background: Cholangiocarcinoma (CC) is the second most common primary malignant liver disease. During the last decades, various novel therapies have been introduced in the field of oncology; nevertheless, the number of treatment options for CC is still limited. **Methods:** In this article, current palliative chemotherapy concepts as well as new drug therapies are outlined. **Results:** Gemcitabine and cisplatin are the standard treatment of care for patients with inoperable CC. Second-line chemotherapy is not standardized yet and is dependent on the first-line compounds. Antibodies against VEGFR and EGFR showed mixed or negative results. New molecular systemic treatments are not established yet. **Conclusion:** Many clinical trials are still ongoing and new therapeutic strategies, including immunotherapies, are under active investigation.

Introduction

Cholangiocarcinoma (CC) is a rare but increasing tumor disease, and many patients (80%) present with unresectable intra- and extrahepatic metastases or advanced tumor stage at diagnosis [1–5]. The median survival of untreated patients with unresectable CC is approximately 3–6 months [6]. Therefore, the majority of patients are undergoing palliative systemic chemotherapy. Even though large phase III trials are missing, the role of chemotherapy is evidence-based and has a fixed place in the palliative setting.

Adjuvant Chemotherapy

The role of adjuvant chemotherapy or chemoradiation after complete resection is not clear yet (fig. 1). The local recurrence, especially of extrahepatic CC, is high, and the European (European Society for Medical Oncology (ESMO)) as well as the US (National Comprehensive Cancer Network (NCCN)) guidelines mention adjuvant therapy as an option [7, 8]. After R0 resection without lymph node involvement, both guidelines recommend chemotherapy with gemcitabine or 5-fluorouracil (5-FU). In contrast, patients with R1 resection or positive lymph nodes could be treated by chemoradiotherapy. The SWOG-S0809 study recently showed that sequential chemotherapy with gemcitabine and capecitabine for 12 weeks followed by radiochemotherapy led to promising results [9]. The further role of adjuvant chemotherapy will be evaluated in three large, currently ongoing phase III studies (BILCAP, PRODIGE-12, ACTICCA-1) in three different European countries (France, Germany, UK).

Palliative Chemotherapy

Retrospectively, systemic chemotherapy with a combination of 5-FU as well as leucovorin with and without etoposide improved survival [10]. Phase II trials with 5-FU demonstrated response rates between 10 and 34% [11, 12]. However, the combination of 5-FU/capecitabine and platinum (cisplatin/oxaliplatin) compounds did not improve the tumor response rates significantly [13–17]. So far, different chemotherapeutic drugs have been tested: Gemcitabine as a monotherapy showed response rates between 17.5 and 36% [18, 19]. Gemcitabine and capecitabine showed response rates of 25% [20–24], and oxaliplatin and gemcitabine showed response rates of 50% [25–27]. Since 2010, a combination therapy with gemcitabine and cisplatin is considered as the standard first-line chemotherapy for non-resectable CC [28]. In this ABC-02 phase III trial, a significantly longer median survival in the combination group compared to gemcitabine monotherapy (11.7 vs. 8.1 months) was achieved (fig. 1). However, patients with impairment of renal function can

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Prof. Dr. Ruben R. Plentz
Abteilung Innere Medizin 1
Medizinische Universitätsklinik
Otfried-Müller-Straße 10, 72076 Tübingen, Germany
Ruben.Plentz@med.uni-tuebingen.de

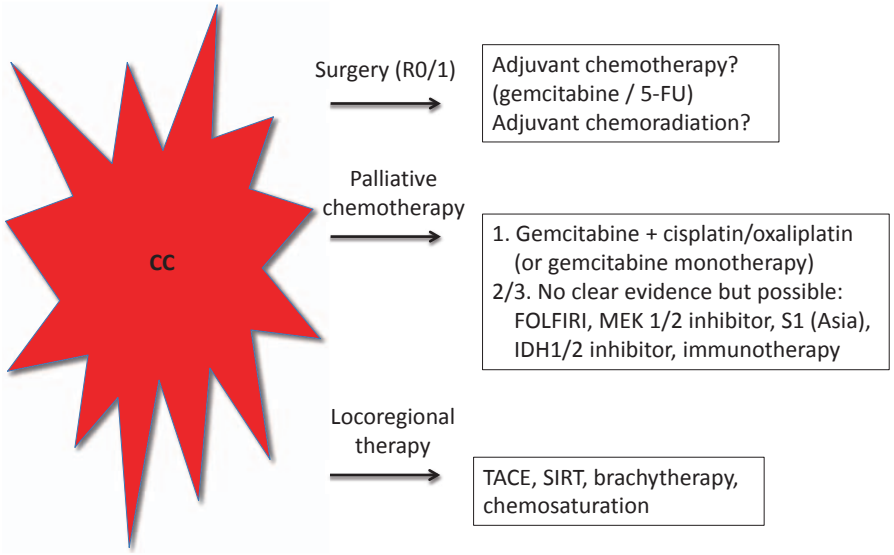

Fig. 1. Treatment options for inoperable cholangiocarcinoma.

also be treated with oxaliplatin. Monotherapy with gemcitabine is mainly recommended for elderly patients or patients with impaired ECOG (Eastern Cooperative Oncology Group) performance status or significant additional diseases.

Second-Line Chemotherapy

For the use of second-line chemotherapy, there is currently no clear evidence, while large studies are missing. Thus, the median survival in both a Japanese phase II study as well as in the larger ABC-02 phase III study with gemcitabine and cisplatin was 11.7 and 11.2 months, respectively [29]. Interestingly, in the Japanese study, 75% of the patients received a subsequent therapy, while second-line treatment was only applied in 15% of all patients in the ABC-02 trial. One of the biggest retrospective analyses examined the use of various chemotherapeutic drugs after failure of gemcitabine and showed a better survival compared to best supportive care [30]. A systematic review of second-line chemotherapies in CC analyzed data of 761 patients [31]. The median progression-free survival (PFS) and overall survival (OS) was 3.2 and 7.2 months, respectively. The response rates and the tumor control rates were low with 7.7 and 48%, respectively. However, in daily practice it is not uncommon and probably justified to offer patients with good performance status a second-line chemotherapy.

New Targets and Therapies

New clinical targeted and immunotherapeutic trials with peptide-based vaccines, dendritic cell-based vaccines, and antibodies have been initiated. In more detail, immunotherapeutic approaches are divided into passive and active immunotherapies. For passive immunotherapy, antibodies against epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) were investigated. Currently, the most studied aspect is EGFR inhibition. EGFR expression is frequently observed in intrahepatic CC but only 5–32% of cancers show true overexpression of the EGFR compared to normal tissues. Interestingly, KRAS mutations occur significantly less often in CC compared to other types of cancer [32–35]. In a single-arm study by Gruenberger et al. [36], the chimeric EGFR antibody cetuximab in combination with GEMOX achieved response rates of 63%. However, the data of the randomized phase II BINGO study were disappointing. This trial did not show an advantage for the combination of cetuximab with GEMOX [37]. It is possible that KRAS mutations are causing resistance to EGFR-targeted therapy. However, a phase II study from Asia found no benefit of EGFR targeting in patients with CC and KRAS wildtype [38]. The German PICCA study also showed no benefit for the treatment with panitumumab [39]. Regarding patients with CC, gallbladder carcinoma, or papillary cancer, another study has tested the combination of GEMOX and the tyrosine kinase inhibitor erlotinib; adding erlotinib showed no benefit in patients with CC, though [40]. In the subgroup analysis, patients treated with erlotinib showed a prolonged PFS; however, it is not yet clear whether overexpression of EGFR is a prerequisite for the efficacy of erlotinib treatment. Erlotinib was also tested in combination with the VEGFR antibody bevacizumab. A tolerable toxicity with response rates of 12% has been demonstrated [41]. The PFS was 4.4 months and the OS 9.9 months. A combination of gemcitabine, oxaliplatin, and bevacizumab (antibody against VEGFR) showed a tumor response measured by fluorodeoxyglucose-positron emission tomography [42].

The multikinase inhibitor sorafenib approved for the treatment of hepatocelluar and kidney cancer showed no significant anti-tumor activity [43, 44]. Moreover, the combination of sorafenib and gemcitabine showed no improvement of survival in patients with CC [45, 46]. The same is true for the combination of sorafenib and erlotinib which did not show a benefit in patients with CC [47]. Another tyrosine kinase inhibitor, cediranib, which was tested in a

phase II study in combination with gemcitabine and cisplatin, did not show an advantage [48]. Sunitinib, another multikinase inhibitor tested in the second-line setting, demonstrated a PFS of 1.7 months, while the response rate was 8.9% [49]. Furthermore, the multi-targeted tyrosine kinase inhibitor vandetanib (inhibition of EGFR and VEGFR) in combination with gemcitabine showed no survival benefit [50]. Recently, the MEK 1/2 inhibitor selumetinib was tested in patients with CC and showed response rates of 12%, a PFS of 3.7 months, and an OS of 9.8 months [51]. In addition, the oral prodrug of 5-FU (S1), which is used mainly in Asia, was tested in combination with gemcitabine and cisplatin [52, 53]. The combination therapy with gemcitabine resulted in a response rate of 20%, but the combination did not differ from monotherapies. Yet another therapeutic approach, i.e. the combination of a c-MET inhibitor (tivantinib) and gemcitabine, was evaluated and achieved a partial response in 1 patient [54]. In a second study, unselected patients were treated with cabozantinib (inhibitor of c-MET) but did not result in a meaningful response [55]. The incidence of mutations of isocitrate dehydrogenase 1 and 2 (IDH1/2), which is essential for the cellular response to oxidative stress, is approximately 20% for intrahepatic CC [56, 57]. IDH inhibitors are also currently being evaluated in clinical trials (fig. 1).

As an active immunotherapeutic approach, Aruga et al. [58] combined different peptides in a palliative setting. Here, the median PFS was 156 days and the OS 380 days. It was also shown that programmed cell death ligand 1 (PD-L1) and human leukocyte antigen (HLA) class I is expressed in human intrahepatic CC [59]. The authors confirmed that positive HLA class I expression in combination with negative/low PD-L1 expression was associated with better clinical disease and that their findings support the usage of immunotherapeutic checkpoint inhibitors. Besides, Gani et al. [60] showed that PD-L1 was expressed in the majority of intrahepatic CC and that PD-L1 expression was associated with decreased survival. However, the role of immune checkpoint inhibitors against CC is not fully investigated yet. Different studies with non-colorectal cancers, including CC, treated with pembrolizumab are not published. Also, the role of defects in mismatch repair genes for CC carcinogenesis is not completely understood. Further immune checkpoint blockade therapies are warranted, and immunotherapeutic approaches for CC are not the standard of care yet.

Disclosure Statement

No conflicts of interest.

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