

Second-line therapy in advanced upper gastrointestinal cancers: current status and new prospects

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Abstract: The prognosis of patients with advanced upper gastrointestinal cancers (UGC) remains poor. Current available systemic armamentarium is limited, and little progress has been made over the last decades. Main achievements have been obtained in first-line setting, however an increasingly proportion of patients are considered for second-line therapy, although data from randomized trials are scarce or even lacking. In this comprehensive review we examine the literature to summarize the efficacy and limitations of second-line systemic options in patients with advanced UGC, with a glimpse into the innovations.

Keywords: Upper gastrointestinal tract cancers; second line; systemic therapy

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Introduction

Gastrointestinal malignancies are the most common cause of cancer worldwide (1). Upper gastrointestinal cancers (UGC) arise from the esophagus, stomach, pancreas and hepatobiliary system. Often, patients with UGC present with advanced incurable disease or relapse after initial surgery. For these patients, prognosis is dismal, and the goal of therapy is to palliate symptoms, improve quality of life (QoL) and prolong survival. Patient- and tumor-related factors, such as performance status (PS), comorbidities, organ function, tumor-related symptoms, tumor burden, histologic-molecular subtypes and doctor-patient preference, influence the therapeutic choice (2-4). Fewer than half of patients with UGC receive any additional treatment after progressing on frontline therapy (5-7). Hereafter, we provide an overview on second-line therapies for these patients and examine emerging strategies.

Second-line therapy: achievements and limitations

Esophagogastric cancer (EGC)

Chemotherapy

Fluoropyrimidines (FP), platinum compounds, taxanes, topoisomerase inhibitors and anthracyclines form the platform for treatment of patients with advanced OGC. Platinum and FP-based doublets (either alone or in combination with trastuzumab in HER2-overexpressing adenocarcinoma) or triplets are commonly used as first-line therapies (8,9). Three phase III trials support the use of chemotherapy as second-line treatment. The AIO trial compared irinotecan with best supportive care (BSC). Unfortunately, the study closed prematurely after randomization of 40 patients due to poor accrual (10). Overall survival (OS) was improved in the irinotecan arm (4.0 vs. 2.4 months; HR 0.48, P=0.012). In a larger Korean

trial, patients (n=202) were assigned to receive either single-agent docetaxel or irinotecan plus BSC *vs.* BSC alone (11). OS was significantly improved in the chemotherapy arm (5.3 *vs.* 3.8 months; HR 0.65, P=0.009), and no difference has emerged between agents. With a similar design, in the COUGAR-2 study, patients (n=168) received docetaxel plus BSC *vs.* BSC alone (12). OS was superior in the docetaxel arm (5.2 *vs.* 3.6 months; HR 0.67, P=0.01). In a meta-analysis of these 3 trials, the risk of death was reduced in those treated with chemotherapy compared with BSC (HR 0.63, P<0.0001), and the benefit was observed regardless the chemotherapeutic agent (13). In a further phase III trial (n=223), paclitaxel was compared with irinotecan, and no difference in OS (9.5 *vs.* 8.4 months; HR 1.13, P=0.38) emerged between agents (14). Two additional phase III trials have been conducted in Japanese patients. In the first study, patients (n=130) refractory to S-1-based chemotherapy received irinotecan plus cisplatin or irinotecan alone (15). Progression-free survival (PFS), which served as the primary endpoint, was marginally improved in the doublet arm (3.8 *vs.* 2.8 months; HR 0.68, P=0.0398). However, this improvement did not translate into OS benefit. In the second trial, platinum-naïve patients (n=163) progressing on single-agent S-1 for metastatic disease or relapsing within 6 months after completion of S-1 adjuvant therapy were randomized to receive irinotecan plus cisplatin or irinotecan alone (16), and no difference in OS (13.9 *vs.* 12.7 months; HR 0.834, P=0.288) was detected. In a recent phase III trial (n=741), nab-paclitaxel was not inferior in terms of OS compared with standard paclitaxel (HR 0.97, non-inferiority one-sided P=0.0085). The response rate (RR) was in favor of nab-paclitaxel, and QoL was similar between the two arms (17). In a phase II trial with cabazitaxel for previously treated patients, the reported DCR was 20% in second-line and 30% in all lines in patients without prior taxane use. The median PFS was 2.01 months for patients not previously treated with taxanes (18).

Targeted agents

Vascular endothelial growth factor (VEGF)

In a phase III trial of first-line therapy, no survival benefit was observed with bevacizumab in addition to chemotherapy (19). Signals of the efficacy of VEGF blockade emerged with ramucirumab, a recombinant IgG1 monoclonal antibody class that binds to VEGF-2. Two phase III trials support the use of ramucirumab as second-line therapy. In the first study, patients (n=355) progressing on FP or platinum-based therapy were assigned to BSC plus either

ramucirumab or placebo (20). OS, which served as the primary endpoint, modestly improved in the ramucirumab arm (5.2 *vs.* 3.8 months; HR 0.77, P=0.047). In addition, PFS (2.1 *vs.* 1.3 months; HR 0.48, P<0.05), and duration of disease control (4.2 *vs.* 2.9 months) improved. Symptom control and QoL were not significantly improved. In the second trial, patients (n=665) with disease progression on or within 4 months after platinum-based chemotherapy were assigned to paclitaxel alone or in combination with ramucirumab (21). OS (9.6 *vs.* 7.4 months; HR 0.807, P=0.017), PFS (HR 0.635, P<0.0001) and the disease control rate (DCR; 80 *vs.* 64%, P<0.0001) were significantly improved in the ramucirumab-containing arm at the cost of more grade 3 adverse events (AEs; neutropenia, hypertension, fatigue, anemia and abdominal pain). Given that ramucirumab alone confers an OS improvement of only 6 weeks, the combination with a taxane should be preferred in patients with PS 0–1. In a phase III study, patients (n=267) who failed ≥ 2 lines were assigned to receive apatinib, an oral VEGF-2 tyrosine kinase inhibitor (TKI), or placebo (22). Both OS (6.5 *vs.* 4.7 months; HR 0.71, P<0.016) and PFS (2.6 *vs.* 1.8 months; HR 0.44, P<0.001) were significantly improved in the experimental arm. However, apatinib resulted in a not negligible rate of grade 3–4 hand-foot syndrome (8.5%) with approximately half of the patients experiencing proteinuria (mainly grade 1–2) and 5.7% having grade 3–4 neutropenia. In addition, no significant improvement in QoL was observed in the apatinib arm. The small molecule inhibitor regorafenib inhibits endothelial cells by targeting VEGF-2 and TIE. Regorafenib was evaluated in a randomized phase II trial over BSC in 152 refractory patients up to a maximum of two lines (23). Regorafenib significantly prolonged PFS (2.6 *vs.* 0.9 months; HR 0.40, P<0.001) with a trend in OS, and the toxicity profile was consistent with that observed in other malignancies.

Human epidermal growth factor receptor 2 (HER2)

In first-line treatment, the addition of trastuzumab to platinum-based chemotherapy significantly prolongs OS in HER2+ metastatic gastric/esophagogastric junction cancer patients (9). Lapatinib is a dual HER2 and epidermal growth factor receptor TKI. In a phase III trial as a second-line therapy, no survival advantage was reported with lapatinib plus paclitaxel compared with paclitaxel alone in patients with HER2-amplified gastric cancer (24).

Mammalian target of rapamycin (mTOR)

In a phase III trial, everolimus was evaluated in patients who progressed after 1–2 lines of therapy, but no survival benefit

emerged compared with the placebo arm (25).

Epidermal growth factor receptor (EGFR)

In phase III trials for previously untreated patients, the addition of cetuximab or panitumumab to platinum-based doublets did not improve survival compared with chemotherapy alone (26,27). In a phase III trial of second-line therapy, the TKI gefitinib was evaluated in patients with esophageal cancer, but no OS benefit was noted in the experimental arm compared with the placebo arm (28).

Poly ADP ribose polymerase (PARP)

PARP inhibition might be an effective strategy, particularly in cases exhibiting the coexistence of ataxia-telangiectasia mutated (ATM)-deficient cells and TP53 mutations (29). In a randomized phase II study of second-line therapy comparing paclitaxel either with olaparib or placebo (30), OS was significantly improved in both the overall (13.1 *vs.* 8.3 months; HR 0.56, $P=0.005$) and ATM low population (median OS not reached *vs.* 8.2 months; HR 0.35, $P=0.002$). Despite these promising data, the experimental arm in the follow-up phase III trial did not exhibit a significant improvement in OS in both the overall and ATM low populations (31).

Signal transducer and activator of transcription (STAT)

STAT3 is a transcription factor that when overactivated becomes an oncogenic signaling hub that promotes the stemness of cancer stem cells (CSCs), which is associated with resistance to conventional therapeutic agents. Napabucasin, an oral specific cancer CSCs inhibitor, was evaluated in combination with paclitaxel in a phase Ib/II study in pretreated patients. In total, 78% of these patients were previously administered ≥ 2 lines. In 20 patients who had not received a taxane, encouraging outcomes in terms of RR (31%), DCR (75%) and PFS (20.6 weeks) were reported (32). A phase III trial is ongoing comparing paclitaxel either plus napabucasin or placebo as a second-line therapy.

Phosphatidylinositol 3-kinase (PI3K)

Buparlisib (or BKM120) is an oral PI3K inhibitor evaluated in a phase II study in previously treated patients with platinum-based chemotherapy for esophageal squamous cell cancer. The reported DCR, PFS and OS were 51.2%, 2.0 and 9.0 months, respectively (33).

Immunotherapy

Cancer cells can evade detection and eradication by the immune system by reducing antigen expression, secreting immune-suppressive cytokines, or upregulating inhibitory signals (34). The modern immunotherapies block specific

immune checkpoints such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein (PD-1) and its ligand (PD-L1). Nivolumab is the first agent demonstrating a survival benefit in pretreated gastric cancer patients. In the ONO-4538-12 phase III trial, patients refractory or intolerant to standard therapy were randomized to receive 3 mg/kg nivolumab every 2 weeks or placebo. PD-1 positivity was not required for study enrollment. Median OS, which served as the primary endpoint, was in favor of the nivolumab arm (5.32 *vs.* 4.14 months; HR 0.63, $P<0.0001$). In addition, PFS (1.61 *vs.* 1.45 months; HR 0.60, $P<0.0001$) and RR (11 *vs.* 0%, $P<0.0001$) were improved in the experimental arm. Nivolumab was well tolerated with a safety profile comparable to the placebo group (35). The anti-PD-1 agent pembrolizumab was evaluated in pretreated patients in 2 phase Ib trials with an RR ranging from 22% to 30% and grade 3–4 AEs that occurred in 13% and 17% of patients (36,37). Results consistent with pembrolizumab emerged in a recent large phase II trial ($n=259$) for patients treated with ≥ 2 lines. An overall RR of 11.2% was reported that was more pronounced in those exhibiting PD-L1+ tumors as assessed immunohistochemistry and defined as $\geq 1\%$ tumor or stromal cells (38). Three phase III trials involving pembrolizumab in OGC are currently in progress; both trials are assessing first- and second-line therapies (39–41). In a phase Ib trial (42), the fully human anti-PD-L1 IgG1 antibody avelumab has demonstrated modest activity as first- (as a maintenance agent, RR 9%) and second-line (RR 10%) therapy. On the other hand, no activity has been observed with the anti-CTLA-4 antibody ipilimumab (43).

Pancreatic adenocarcinoma

Chemotherapy

Three systemic options can be considered in first-line treatment for patients with locally advanced unresectable or metastatic disease, i.e., gemcitabine alone or in combination with nab-paclitaxel (Gem-P) and the FOLFIRINOX regimen (44–46). As a consequence of better results obtained with combination regimens, approximately 40% of patients are considered for second-line treatments (47) given that a standard sequence is not established. In patients who progressed on gemcitabine, oxaliplatin-based regimens have been evaluated in 2 phase III trials. The CONKO-003 trial evaluated oxaliplatin added to 5-FU in the so-called OFF regimen in 160 patients (48). OS significantly improved in the oxaliplatin-containing arm

compared with 5-FU alone (5.9 *vs.* 3.3 months; HR 0.66, $P=0.010$). The AEs were similar between the two groups except for increased neurotoxicity in the OFF arm (38.2% *vs.* 7.1%, $P<0.001$). In contrast, disappointing results were noted in the PANCREOX trial, in which patients ($n=108$) who progressed within 4 weeks of randomization either during or following prior gemcitabine were assigned to receive modified FOLFOX6 or infusional 5FU/LV (49). OS was reduced in the experimental arm with a surprisingly high outcome in the reference arm (6.1 *vs.* 9.9 months; $P=0.02$). In addition, more grade 3–4 AEs occurred in the FOLFOX6 arm (63% *vs.* 11%). The conflicting results of these two trials can be possibly explained by the reduced dose of oxaliplatin in the OFF regimen resulting in enhanced tolerability, and different eligibility criteria at progression status. Of note, the PANCREOX trial was closed prematurely due to slow accrual. A new formulation of irinotecan encapsulated into liposome-based nanoparticles was evaluated in a phase III trial in patients ($n=417$) who failed gemcitabine-containing therapy (50). Patients were assigned either to nanoliposomal irinotecan monotherapy, 5FU/folinic acid or the combination of both. Median OS was 6.1 months for nanoliposomal irinotecan monotherapy plus 5FU/LV and 4.2 months for 5FU/LV (HR 0.67, $P=0.012$). No significant difference in OS was noted between nanoliposomal irinotecan monotherapy and 5FU/LV. Nevertheless, the significant incidence of grade 3–4 AEs (diarrhea 13%, vomiting 11%, fatigue 14%, neutropenia 27%) in the experimental arm warrants caution in the systematic use of this regimen that is approved by the FDA. Indeed, ECOG PS 0–1, a relatively favorable comorbidity profile, an adequate supportive medical therapy and a port device are essential conditions for the application of this regimen. The optimal treatment for patients who progress on FOLFIRINOX is not established. In the PRODIGE4/ACCORD1 trial, approximately 50% of patients underwent second-line therapy. In those treated with FOLFIRINOX, gemcitabine was more often used as a single agent (82.5%) or in combination (12.5%), whereas FOLFOX (49.4%) or gemcitabine plus oxaliplatin (17.6%) were chosen in patients assigned to the gemcitabine arm. In a prospective multicenter cohort of 57 patients, encouraging PFS and OS (5.1 and 8.8 months, respectively) were reported using second-line Gem-P (51). This combination appeared to provide some clinical activity in retrospective single institution experiences (52,53). No standard options are available after failure of the Gem-P regimen. In the MPACT trial, 77% of patients received a

FP-based regimen (54). The median OS for patients treated with a FP-containing second-line treatment after Gem-P was 13.5 months (*vs.* 9.5 for those treated with gemcitabine alone, $P=0.012$). Finally, some phase II trials evaluating single agents (i.e., docetaxel, paclitaxel or irinotecan) or combinations (i.e., oxaliplatin either plus raltitrexed or gemcitabine, FOLFIRI, XELOX or FOLFIRINOX) have reported OS values ranging from 4 to 8.5 months (55–63).

Targeted agents

With the exception of erlotinib, which confers a clinically negligible benefit when added to gemcitabine (64), first-line efforts to integrate a number of targeted agents have been disappointing. By inhibiting inflammation-promoted cancer progression, the JAK-STAT inhibitor ruxolitinib achieved promising outcomes in preclinical and phase II trials (65), but the subsequent phase III trial was terminated prematurely after demonstration of insufficient efficacy at a planned interim analysis of the JANUS1 trial. Additional strategies involved inhibitors of EGFR, HER2, IGF-1, VEGF, NOTCH, WNT and farnesyl-transferase pathways mainly in combination with gemcitabine (66). Early trials indicate that patients carrying BRCA mutations may benefit from platinum agents and PARP inhibitors. Promising activity of olaparib has been reported in a variety of different tumors associated with germline BRCA1/2 mutations (67), including PC (RR 21%, PFS 4.6 months and OS 9.8 months). A phase III trial of olaparib maintenance is currently enrolling patients with germline BRCA mutations who have not progressed on first-line platinum chemotherapy (68). Hyaluronidase over-accumulation in the extracellular matrix of many solid tumors is associated with tumor progression and poor prognosis (69). PEGPH20 has been developed to deplete tumor-associated hyaluronan in the extracellular matrix. In a phase Ib trial, twenty-eight patients were treated with escalating intravenous doses of PEGPH20 plus gemcitabine. Overall, PFS and OS were 5.0 months and 6.6 months, respectively. In 17 patients evaluated for pretreatment tissue hyaluronan levels, encouraging PFS and OS rates were 7.2 and 13.0 months, respectively, in those with high hyaluronan levels (70). A phase III trial of Gem-P +/- PEGPH20 is currently recruiting previously untreated patients who overexpress hyaluronan as assessed by immunohistochemistry (71). Abemaciclib is a selective ATP-competitive inhibitor of CDK4 and CDK6 kinases, preventing the phosphorylation and inactivation of the Rb tumor suppressor protein and subsequently inducing

G1 cell cycle arrest and inhibition of cell proliferation. This compound is under evaluation in a randomized phase II trial as a single agent or in combination with either LY3023414 (PI3K/mTOR dual inhibitor) or galunisertib (TGF- β R1 inhibitor) versus chemotherapy in previously treated patients with metastatic disease (72). The vitamin D receptor is expressed in stroma from PC, and calcipotriol significantly reduces markers of inflammation and fibrosis in both in pancreatitis and the tumor stroma. Interestingly, targeting the vitamin D receptor leads to transcriptional reprogramming of pancreatic cancer stroma and improves the response to gemcitabine, which might have implications for therapeutic purposes (73).

Immunotherapy

Two vaccines have been evaluated in patients with advanced disease, namely, GV1001 (phase III as first-line therapy in combination with chemotherapy *vs.* chemotherapy alone) and GVAX (phase IIB after 2 prior lines in a 3-arm study in combination with the live-attenuated *Listeria monocytogenes* vaccine CRS-207, *vs.* either CRS-207 alone or chemotherapy). Unfortunately, in both trials the vaccine-containing arms failed to improve OS compared to chemotherapy alone (74,75). Other vaccines have been tested in randomized phase II trials in combination with gemcitabine, in particular the Wilms' tumor (WT1) vaccine and IMM-101, a heat-killed *Mycobacterium obuense* (76,77). In the first trial, WT1 plus gemcitabine resulted in superior PFS compared with gemcitabine (133 *vs.* 76 days; HR 0.48, $P=0.008$). In the second trial, IMM-101 plus gemcitabine correlated with improved OS in a preplanned subgroup of metastatic patients (7.0 *vs.* 4.4 months; HR 0.54, $P=0.01$) compared with gemcitabine. Other therapeutic strategies in development include checkpoint inhibition combined with vaccines or combined immune checkpoint blockade.

Hepatobiliary cancers

Hepatocellular cancer (HCC)

HCC usually typically develops from a background of chronic liver diseases. Hepatitis B and C viruses, alcohol consumption, and non-alcoholic steatohepatitis represent frequent predisposing etiologies. The TKI sorafenib is the first agent that produced a survival benefit reported in two phase III trials over placebo (78,79). After sorafenib, a number of phase III trials evaluating other targeted agents (namely, brivanib, everolimus and ramucirumab) in first-

and second-line settings have failed to improve OS as a consequence of marginal antitumor efficacy in this disease, risk of toxicity related to underlying liver dysfunction, lack of understanding of critical drivers of tumor progression/dissemination, imbalances in disease status (liver-only *vs.* metastatic), and different patient characteristics according to etiology of cirrhosis, Child-Pugh class and ethnicity (80).

Targeted agents

Encouraging results of second-line treatment emerged from the phase III RESORCE trial, in which 573 patients who failed sorafenib (given at ≥ 400 mg/day for ≥ 20 of last 28 days of treatment) were assigned to BSC plus either regorafenib or placebo (81). The majority of patients were Child-Pugh class A (98%). Approximately one-third of patients had macrovascular invasion, 70% had extrahepatic disease and 75% were cirrhotic. Regorafenib improved OS compared with BSC alone (10.6 *vs.* 7.8 months; HR 0.60, $P<0.0001$). The most relevant grade 3–4 AEs included hypertension (15%), hand-foot syndrome (13%), fatigue (9%), and diarrhea (3%). Extended knowledge is required in order to better clarify whether this agent can be used in patients who could not tolerate sorafenib and the optimal dose in this setting of patients at increased risk for toxicity. Cabozantinib blocks MET, RET and VEGF-2 receptors. This compound has been evaluated within a randomized placebo-controlled phase II trial in patients with Child-Pugh A class and ≤ 1 prior systemic therapy (82). A non-significant trend for PFS was observed in the experimental arm (2.5 *vs.* 1.4 months in the placebo arm). PFS and OS calculated from day 1 in all patients were 5.2 and 11.5 months, respectively. The phase III CELESTIAL trial comparing cabozantinib *vs.* placebo is ongoing in patients who progressed on sorafenib (83). Other potential therapeutic targets are the include EGFR/RAS/MAPK, IGF, PI3K/Akt/mTOR, Wnt- β -catenin, hedgehog, apoptotic, c-MET and antiangiogenic signaling pathways. The anti-angiogenic ramucirumab and c-MET inhibitor tivantinib, which were both evaluated as second-line therapies in 2 phase III trials, did not meet the primary endpoint of improving OS compared with placebo (84,85).

Immunotherapy

Immunological mechanisms are also assumed to play a crucial role in HCC proliferation (86). The rationale to target immune checkpoints is based on evidence that HCC may evade the immune system by expressing PD-1, CTLA-4, TIM-3, LAG-3 and others. Preclinical and clinical studies have demonstrated the potential benefit of modulating immunogenicity, and relevant approaches are

currently being tested. Tremelimumab, an anti-CTLA-4 antibody, was evaluated in a pilot study involving 20 patients with HCC and chronic HCV infection. Of 17 assessable patients, the RR, DCR and time to progression were 17.6%, 76.4% and 6.5 months, respectively. In addition, a significant reduction of viral load was observed, and no major safety issues emerged (87). The results of a phase I/II study with the anti-PD-1 nivolumab were recently published. Patients (n=262) with advanced HCC and Child-Pugh score ≤ 7 who previously failed, refused or were intolerant to sorafenib were enrolled in three parallel cohorts based on the underlying disease etiology (no active hepatitis virus infection, HBV-infected, and HCV-infected). The reported RR was 20% in patients treated with 3 mg/kg nivolumab in the dose-expansion phase, and grade 3/4 AEs occurred in 25% of patients (88). Based on these data, nivolumab is currently being evaluated as a first-line agent compared with sorafenib in a phase III study (89). In addition, vaccines have been tested in clinical trials. The oncolytic vaccine virus Pexa-Vec delivered by intratumoral injection was evaluated in a randomized dose-finding phase II trial in patients with advanced disease (90). OS survival was significantly improved in the high-dose arm compared with the low-dose arm (14.1 *vs.* 6.7 months; HR 0.39, $P=0.02$) with an acceptable toxicity profile. Encouraging results from a phase II trial have been reported with another oral vaccine, hepcortespenlisimut-L. A drop of alpha fetoprotein was observed in 66.7% of patients, and OS was not reported given that 90.7% of patients were alive after a median follow-up of 12 months (91). Both vaccines are currently under evaluation in phase III trials (92).

Biliary tract cancer (BTC)

Chemotherapy

As first-line therapies, various non-randomized phase II trials evaluating gemcitabine and platinum-based regimens have been published, with reported OS ranging from 8 to 15 months (93). In the large phase III ABC-02 trial, previously untreated patients (n=410) with intra- or extrahepatic cholangiocarcinoma, gallbladder cancer or ampullary cancer were randomized to receive either cisplatin plus gemcitabine for 8 cycles or gemcitabine alone. Median OS (11.7 *vs.* 8.1 months; HR 0.64, $P<0.001$), PFS (8.0 *vs.* 5.0 months, $P<0.001$) and DCR (81.4% *vs.* 71.8%, $P=0.049$) were increased for the doublet (94). Based on these results, cisplatin plus gemcitabine is a recognized first-line standard of care in advanced BTC. Only limited data of second-line therapy are available, and no randomized

trials comparing systemic therapy versus BSC are published. Accordingly, the choice of second-line regimen is currently empiric. Experiences with single-agent FP or in combination with oxaliplatin have been reported in patients who failed cisplatin plus gemcitabine, with RR ranging from 1% for FP alone to 8% to 22% for FP plus oxaliplatin (95,96).

Targeted agents

As first-line agents, targeted agents have been incorporated in phase II trials (either single arm or randomized), including bevacizumab (plus erlotinib) or erlotinib alone, cetuximab, or panitumumab (plus gemcitabine and oxaliplatin). Modest or even absent significant clinical activity was noted at the cost of relevant toxicities (97-99). In a meta-analysis of 6 trials involving 855 patients treated either with erlotinib, cetuximab, panitumumab, cediranib or sorafenib, no OS advantage was observed in the experimental arms despite enhanced or a trend for enhanced RR and PFS (100). As second-line agents, in a very small retrospective analysis of 13 patients refractory to GEMOX, FOLFIRI plus bevacizumab achieved a RR of 41% with a median PFS and OS of 7.6 and 14.2 months, respectively (101). In a phase II trial for both chemo-naïve and pretreated (one prior line permitted) patients, some signals of activity have been observed with erlotinib given that 17% of patients were progression-free at 6 months (102). In a phase II study, patients (n=26) who failed ≥ 1 chemotherapy line and harbored fusions or other FGFR alterations were treated with BGJ398, a selective pan-FGFR inhibitor (103). Among 22 evaluable patients, three achieved partial response, and 15 had stable disease (including 10 experiencing some tumor reduction) for an overall DCR of 82%. In a phase II study with selumetinib, an inhibitor of MEK1/2, 12% of patients experienced a response with PFS and OS of 3.7 of 9.8 months, respectively (104). The TKI regorafenib has been evaluated as a second-line therapy in a phase II trial, and data have been recently presented (105). The primary endpoint was met with a reported PFS of 3.55 months. OS was 5.55 months, and grade 3-4 AEs occurred in 40.5% of cases. Phase I trials targeting isocitrate dehydrogenase in enriched populations, including BTC patients, are underway. CAP7.1 is a compound that releases etoposide in the presence of carboxylesterases, leading to increased intra-tumor etoposide concentration. Patients with BTC were assigned to either CAP7.1 or BSC in a randomized phase II trial allowing crossover at progression (106). Some antitumor activity emerged (DCR 59%, PFS 3.5 months in the experimental arm) with overall

Table 1 Positive randomized phase III for second-line therapy in UGC

Ref.	Treatment arms	Patients (n)	PS (ECOG)	OS (months)	PFS (months)	RR (%)
Esophagogastric cancer						
(17)	IRI vs. BSC	40 (evaluable 19/17)	0–2	4.0 vs. 2.4, HR 0.48	2.5 months (only for irinotecan)	0% (IRI arm)
(18)	Docetaxel or IRI vs. BSC	202 (evaluable 126/62)	0–1	5.3 vs. 3.8, HR 0.657	NR	13% (only for IRI)
(19)	Docetaxel vs. BSC	168	0–2	5.2 vs. 3.6, HR 0.67	29% at 24 weeks (only for docetaxel)	7% (docetaxel arm)
(25)	RAMU vs. Placebo	355	0–2	5.2 vs. 3.8, HR 0.776	2.1 vs. 3.1	3.4 vs. 3.0
(26)	RAMU/PACLI vs. PACLI	665	0–1	9.6 vs. 7.4, HR 0.807	4.4 vs. 2.9	27 vs. 16
Pancreatic cancer						
(42)	OFF vs. 5FU/LV	160	0–2	5.9 vs. 3.4, HR 0.66	2.9 vs. 2.0, HR 0.68	NR
(44)	nal-IRI/5FU/LV vs. 5FU/LV	417	0–2	6.1 vs. 4.2, HR 0.67	3.1 vs. 1.5, HR 0.56	16 vs. 1
Hepatocellular cancer						
(63)	Regorafenib vs. BSC	573	0–1	10.6 vs. 7.8; HR 0.60	3.1 vs. 1.5, HR 0.46	11 vs. 4

IRI, irinotecan; BSC, best supportive care; RAMU, ramucirumab; PACLI, paclitaxel; OFF, oxaliplatin, 5-fluorouracil, folinic acid; 5FU/LV, 5-fluorouracil, folinic acid; nal-IRI, liposomal irinotecan.

manageable toxicity (mainly hematological).

Miscellanea

In a retrospective study of 603 patients who failed gemcitabine and platinum therapy, second-line therapy (including irinotecan- or oxaliplatin-based chemotherapy, single agent FP, sunitinib or other regimens) was administered to 196 patients. Among 186 evaluable patients, reported PFS and OS were 3.2 and 6.7 months, respectively. In addition, FP-based doublets were not superior to FP alone (107). Similar survival results were reported in another retrospective analysis of 174 patients, achieving a PFS and OS of 3 and 6.6 months, respectively. These results have been substantiated in a pooled analysis of 5 additional studies (n=499), reporting a median OS of 6.3 months (108). Both studies identified potentially favorable prognostic factors, i.e., good PS, low Ca19.9 levels, absence of distant metastases and duration of disease control on first-line therapy. Once again, in a systematic review including 14 phase II trials, 9 retrospective analyses and 2 case reports (n=761), the mean OS was 7.2 months (109).

Immunotherapy

Chronic inflammation plays a crucial role in the development of BTC. Cholelithiasis, parasites, HCV infection, primary biliary cirrhosis and sclerosing cholangitis are well known risk factors. This knowledge

represents the platform to implement immunotherapeutic strategies in BTC, and a number of clinical trials involving either peptide-based vaccines or dendritic cell-based vaccines have been conducted. Promising results have been reported that warrant further confirmation (110). Single agent pembrolizumab has been evaluated in patients with PD-L1-positive gallbladder or biliary tree adenocarcinomas as a part of the KEYNOTE-028 phase Ib trial (111). Twenty-four out of 37 identified patients were enrolled, and all received at least 1 prior line of therapy (38% of them ≥ 3 regimens). The RR was 17.4%, and pembrolizumab was generally well tolerated (grade 3 AEs reported in 17% of patients).

Conclusions

Advanced UGC are highly fatal malignancies characterized by marked genetic complexity. The development of second-line systemic therapies for these patients has been met with only few successes over recent decades (*Table 1*). Based on better understanding of molecular drivers and the advent of new targeted agents, UGC are increasingly entering into the era of personalized medicine. Research on immunotherapies in these malignancies is vibrant, aiming to identify predictive and prognostic biomarkers to define

subgroups of patients who are most likely to benefit from these agents. In this regard, an important achievement has been the proof of clinical activity of PD-1 blockade in MSI-high colorectal and non-colorectal cancers, which lead FDA to approve approval of pembrolizumab for all MSI-H/MMR-deficient cancers (112). Of interest, a high tumor mutational burden seems to predict favorable outcome to PD-1/PD-L1 blockade across various cancers (113). In addition, other biomarkers, including serum proteins, tumor-specific receptor expression patterns, factors in the tumor microenvironment, circulating immune and tumor cells, and host genomic factors, are potential candidates in predicting response to immunotherapy (114). Finally, distinct molecular subtypes of gastric, esophageal cancer and PC have been identified, providing a guide to targeted strategies that should be evaluated in clinical trials (115-117). Global collaborative efforts are essential to give a decisive boost to further improve survival in these patients.

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Footnote

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