Hot topics in cholangiocarcinoma

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Cholangiocarcinoma (CC) comprises a heterogeneous group of epithelial cancers emerging at any level from the biliary tree. CC is classified into intrahepatic (iCC) and extrahepatic (eCC), based on anatomical tumor location (1). The main points of interest of this topic include the changes in epidemiological assessment, alternative therapeutic options and the advent of new target treatments that may modify the therapeutic algorithm of CC patients.

In recent decades, we have witnessed an increasing specific incidence of CC worldwide, as shown by recent epidemiological reports conducted in the United States, United Kingdom, Japan, and Europe (2,3). However, the rising incidence of CC shows a significant geographical variation, reflecting the exposure to different risk factors and most likely different genetic backgrounds (2,3).

Liver flukes, primary sclerosing cholangitis, HCV and HBV-related liver diseases, and environmental exposure are the most prominent risk factors for CC (4-6), but about two thirds of Western patients develop disease without any known risk factor. Asbestos has been implicated as a hidden risk factor for CC, as investigated by our 2013 case-control study that suggested iCC could be associated with asbestos exposure (7). A recent population-based case-control study confirmed an increased risk of iCC with cumulative exposure to asbestos. In particular, the cumulative exposure index was highly correlated to the maximum intensity of exposure to asbestos and moderately correlated to the duration of exposure (8).

In recent years, the rising incidence of obesity and associated NAFLD/NASH may also account for the increased incidence of CC, mainly in the Western world (9,10). These findings were confirmed by our preliminary data. NASH seems to be an independent prognostic factor for iCC and impacted on long-term outcomes in iCC patients who underwent surgical resection, both in terms of overall survival (OS) and disease-free survival. Further studies are needed to clarify both the strength of this association and the underlying mechanisms responsible.

CC is usually asymptomatic in the early stages. Surgical resection is the only potentially curative therapy in patients with resectable disease, but fewer than one third of patients with potentially operable CC are offered surgical resection (11). Overall, reported 5-year survival rates after resection are in the range 22–44% for iCC, 11–41% for peri-hilar and 27–37% for distal CC (12). However, more than 50% of patients experience tumor recurrence within the second-year post resection. Risk factors associated with an increased disease recurrence include no radical resection (R >0), lymph node metastases, satellite nodules, and lymphovascular and perineural invasion (12).

Intensive follow-up will promptly disclose disease recurrence, allowing a second radical surgical treatment in a selected group of patients. A recent analysis by our group (still unpublished) showed that the OS (calculated from the date of second surgery) of patients undergoing surgical resection for relapse substantially overlaps the OS of patients undergoing primary tumor surgery. This suggests that further resection should be performed when feasible.

The high rate of distant and local CC recurrence provides a rationale for exploring adjuvant systemic therapy. A Japanese study analyzed data from 599 iCC patients who underwent adjuvant treatment after surgical resection. Adjuvant concomitant chemoradiotherapy improved the OS rate compared with both adjuvant sequential chemoradiotherapy and adjuvant chemotherapy alone in resected iCC at advanced stages (III and IV). Instead, no significant differences were identified between the three groups at early pathologic stages (I and II) (13). A recent

multicenter randomized phase III trial (BILCAP) on the role of adjuvant capecitabine in bile duct or gallbladder cancers showed that capecitabine improves median OS in resected biliary tract cancer compared to surveillance (53 *vs.* 36 months, respectively) (14). These data suggest that capecitabine could become the standard of care for patients after curative resection of biliary tract cancer.

Locoregional treatments may offer an alternative for CC patients who are not candidates for radical surgery. A recent study by Tao *et al.* demonstrated a correlation between the biological equivalent dose and survival in patients with unresectable iCC who underwent ablative radiotherapy. In particular, OS was significantly superior in patients with higher dose *vs.* lower dose radiation, with 3-year OS rates of 73% and 38% (P=0.02), respectively (15). Therefore, ablative radiation could be considered a therapeutic option in iCC patients unsuitable for surgical resection.

Considering the relative radiosensitivity of iCC, yttrium 90 radioembolization (90Y TARE) also represents a promising alternative treatment for iCC, as observed in our case-series in which 90Y TARE proved safe and showed a survival benefit with a median OS of 17.9 months in patients with unresectable primary or recurrent iCC (16).

For the last decade, systemic chemotherapy has been the standard approach for patients presenting with advanced or metastatic CC. The Advanced Biliary Cancer phase III trial (ABC-02) evaluated the use of gemcitabine with or without cisplatin. The addition of cisplatin significantly improved both progression-free survival (PFS) and OS (17) so that the combination of gemcitabine plus cisplatin is now the current standard of care for first-line therapy. If cisplatin is contraindicated (for instance, in renal insufficiency), the safety and efficacy of the gemcitabine plus oxaliplatin combination have been demonstrated in several phase II studies (18,19). In Japan, oral fluoropyrimidine S-1 is considered a likely drug for the treatment of CC with a recent phase III study demonstrating the non-inferiority of the gembitabine plus S-1 combination compared to gemcitabine plus cisplatin in term of OS with good tolerability (median OS was 15.1 *vs.* 13.4 months, respectively; P=0.046) (20). This treatment may be considered a new standard of care option for advanced CC, at least in Asiatic patients.

There is no standard option for patients who progress on gemcitabine and platinum-based therapy. Several trials evaluating regimens in the second-line setting are ongoing, including the recent phase III trial comparing the combination of 5-fluorouracil plus oxaliplatin (FOLFOX) *vs.* best supportive care alone.

Performance status plays a key role in response to both first- and second-line chemotherapy. Some studies demonstrated that performance status (ECOG-PS) was an independent prognostic factor for the survival of patients with advanced CC undergoing first-line chemotherapy. A recent retrospective study treated a subgroup of 357 CC patients with various second-line chemotherapy regimens after progression to a first-line platinum regimen at different Italian institutions. At multivariate analysis, ECOG-PS was found to be the main prognostic factor associated with survival even in this patient setting (21).

Recently, there has been a surge of interest in targeted therapies for CC. Next-generation sequencing studies have revealed some driver mutations in patients with iCC, including fibroblast growth factor receptor (FGFR) fusions, isocitrate dehydrogenase 1 (IDH1), BAP-1, KRAS and p53. A phase II trial on an oral selective pan-FGFR kinase inhibitor (BGJ398) demonstrated preliminary clinical activity against tumors with FGFR alterations, with an overall response rate of 15% and median PFS of 5.8 months (22). Clinical trials are currently evaluating other FGFR kinase inhibitors, such as ARQ087 (NCT 03230318). Considering the subgroup of 17 patients with iCC treated with ARQ087, a radiological response was observed in six patients, with a partial response in 2 (11.8%) and stable disease in 2 (11.8%) (23). IDH1 mutations have been reported in 7–36% of iCC cases (24,25). A recent phase I basket trial tested an oral inhibitor of IDH1 (AG-120) in several solid tumors, including iCC. An IDH1 mutation was detected in 72 patients with iCC whose best tumor response was partial response in four patients (6%) and stable disease in 40 (56%). The PFS rate at 6 months was 40% (26). The phase III trial of AG-120 *vs.* placebo for IDH1-mutated CC patients is ongoing (NCT 02989857). Other genomic alterations are being tested and we await the definitive data of ongoing trials.

In conclusion, CC is becoming a major oncologic emergency, with a high incidence rate and a change in epidemiology that must be investigated by additional studies. The treatment of CC is still evolving thanks to the emerging data from next-generation sequencing analyses and the new targeted therapies entering clinical development with encouraging results.

Footnote

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