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Adjuvant treatment for biliary tract tumours: lost in a maze?

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Single agent capecitabine was stablished as the standard adjuvant treatment for biliary tract cancers (BTC) based on the BILCAP study (1–4). Two clinical trials exploring gemcitabine-based chemotherapy (5) (either gemcitabine alone in the BCAT study (6) or gemcitabine and oxaliplatin in the PRODIGE-12 study (7)) showed no significant activity over observation. The only recent positive adjuvant clinical trial was the ASCOT study, a randomised phase III study in Asian population that confirmed activity of single agent fluoropyrimidine-based therapy (S-1) in this setting (8). Despite the urgent need, it has become challenging to improve adjuvant strategies for BTC (9). Therefore, the results of studies exploring alternative adjuvant treatment such as cisplatin and gemcitabine (CisGem) in the STAMP (10) and ACTICCA-1 (NCT02170090; results awaited) trials were eagerly awaited.

The STAMP clinical trial represents an important step in the development of adjuvant strategies for BTC (10). This investigator-led, randomised phase II clinical trial recruited a total of 101 patients over a period of 3.5 years in South Korea and explored the role of adjuvant CisGem (experimental arm) over capecitabine (control arm) in patients with resected extrahepatic cholangiocarcinoma (eCCA) at high risk of recurrence. Unfortunately, the study did not show an improved outcome with CisGem; thus, capecitabine remains current standard of care in this setting. Despite these negative results, the design, and delivery of this study, are on their own, reasons for which to congratulate the investigators and highlight very interesting topics for discussion.

The trial focused on a specific group of patients with BTC: patients diagnosed with eCCA (both hilar (hCCA) and distal (dCCA)), who had undergone curative surgery with R0 or R1 resection, and who had lymph node positive disease in the surgical specimen. Most of these are known factors for higher risk of recurrence thus enriching the study for patients with high risk of recurrence. Interestingly, patients with Ca 19.9 ≥100 U/mL were excluded, which could somehow help identifying patients with better outcome within this “high risk” population selected.

Within the 101 patients recruited, 44.6% were hCCA and 55.4% dCCA, with R1 margin status in 31.7% of patients. Baseline characteristics were well balanced between study arms. Patients started treatment within 7 weeks from surgery in both study arms, which may feel short, taking into account the time that patients usually need to recover from surgery in standard clinical practice and also experience from prior studies (i.e. 10 weeks from time of surgery to randomisation in the BILCAP trial (1)). Unfortunately, the study did not show any benefit in favour of CisGem either in disease-free survival (DFS) (Hazard Ratio (HR) 0.96 (one sided 90% confidence interval (CI) 0.71-1.3); p-value 0.430) or overall survival (OS) (HR 1.08 (one sided 90% CI 0.71-1.64); p-value 0.404) in the intention to treat (ITT); with very similar findings in the per-protocol population. Worth also noticing that data were mature (with >70% of events for DFS in both arms) at the time of analysis, thus further follow-up is unlikely to change these findings.

In terms of the study design, patients were 1:1 randomised to each arm. Selected stratification factors (primary site and resection margin status) seem appropriate and should probably be adopted in future studies also (9). We are now aware that BTC represents an heterogeneous group of malignancies, with different surgical strategies, biology and natural history. The fact that authors chose to focus on one subgroup of BTC (eCCA) rather than recruiting all BTC

patients is worth mentioning, since this represents an ongoing topic of discussion for the design of future trials in this setting. Within the BILCAP trial, the hCCA derived the least benefit from capecitabine, thus highlighting the importance of this issue (2). While performing BTC-subgroup specific trials provides a more homogeneous population, the main caveat comes in the form of challenges at time of recruitment. The open-label design was also appropriate taking into account the way of administration of the treatment options being explored.

The fact that it took 3 and a half years to recruit these 101 patients reflects the challenge of delivering on adjuvant studies in BTC, especially when being performed in one single country. In order to have a feasible and deliverable estimated sample size, unrealistic HRs are often assumed at the time of the sample size calculation (7). The STAMP trial was powered to identify a HR of 0.6 (equivalent to 18% increase in DFS rate at 2 years between arms, estimated 40% with CisGem and 22% with capecitabine) in DFS with a power of 80% and a one-sided type I error of 10%. This HR might be seen as quite optimistic, in view of the achieved HR of 0.81 by capecitabine vs observation in the BILCAP trial (2). In addition, studies (STAMP being an example) are sometimes designed accounting with a one-sided (rather than two-sided) type I error (8), with the aim of bringing the sample size estimation down. Aiming for a deliverable sample size, these strategies at time of study design are, in many occasions, the reason why studies in this setting have been somehow "underpowered" (9), something to be avoided in future and likely to be overcome by joined efforts and international collaborations.

Despite the potential above-mentioned pitfalls identified in the sample size calculation, these may not be the explanation to the negative results in this occasion. The fact that there is no trend in favour of the experimental arm at all, is pointing in the direction of a real lack of activity of CisGem in the adjuvant setting, not just an "underpowered" trial. How can we make sense of this, with CisGem being the standard backbone chemotherapy (11,12) in the first-line palliative setting? How did we get into this maze and how can we find the exit?

One could wonder whether the absence of benefit from adjuvant CisGem could be due to how this is impacting on the treatment given at time of recurrence in the first-line palliative setting. In the STAMP trial, 81% of the patients with recurrence in the CisGem arm received systemic chemotherapy (43% CisGem-based, 47% 5-fluorouracil (5-FU) and platinum-based combinations). In the capecitabine arm, a similar proportion received systemic treatment (90%), but all received this in the form of CisGem-based schedules (100%). Whether this could impact on OS findings could be hypothesised and has been suggested for GEMOX in the PRODIGE-12 trial (7); it would not, however, change DFS outcome data.

Patterns of recurrence are of interest, especially when looking into the future and when planning new studies to come. In the STAMP trial, the pattern of recurrence was predominantly systemic (59% distant recurrence only, 17% combination of both distant and local recurrence). This is clearly supporting the use of systemic therapy-based approaches for future studies. Recent guidelines are now incorporating recommendation for pre-surgical ^{18}F-18 fluoro-2-deoxyglucose positron emission tomography (^{18}FDG-PET) to identify occult metastases prior to surgery and maybe future studies should take this into account for adequate patient selection for surgical and adjuvant studies (3,13).

Interestingly, recurrence was local-only in 24% of occasions. For patients with local recurrence, radiotherapy-based strategies were utilised in 8% (CisGem arm) and 5% (capecitabine arm) of patients. In order to reduce risk of local recurrence, whether consolidation radiotherapy should be incorporated at the time of completion of the systemic adjuvant treatment should be further explored in clinical trials. In order to do so, identifying the patients at higher risk of local recurrence would be of much relevance, so these could be recruited into such trials. One of the pitfalls we could highlight of this study is the fact that some of the patients with R1 resection did actually receive additional adjuvant radiotherapy after completion of CisGem or capecitabine (in the absence of recurrence, thus before the primary end-point associated event was reached). Authors report that once the adjuvant treatment was completed, 3 out of 16 patients with R1 resection in the CisGem and 5 out of the 16 patients with R1 in the capecitabine arm were treated with radiotherapy. Even though numbers are small, this could impact on interpretation of findings and administration of additional treatments outside the research question should be avoided in coming studies, with specific trials to assess the impact of radiotherapy being design. Albeit cross-trial comparisons are always at risk, 2-years DFS in the adjuvant SWOG S0809 trial was 54% for extra-hepatic cholangiocarcinoma, quite higher than that shown in the STAMP trial, while 2-years OS rates appear similar (14).

Toxicity profile was as expected with these treatments and did not impact negatively on quality of life. It is, however, worth highlighting the fact that despite a high rate of dose modifications occurring in 92% and 82% of patients in the CisGem and the capecitabine arm, respectively, rate of patients completing the 8 planned cycles of treatment was high (78% for CisGem and 80% for capecitabine arms). This was much higher than for the BILCAP study (only 55% of patients completed the planned treatment). In addition, treatment interruption due to toxicity in the STAMP trial was lower (3/50 (6%) with CisGem) and 5/50 (10%) with capecitabine) than in BILCAP (32% in the capecitabine arm). This could maybe be explained by a better management of toxicity (investigators had more experience with adjuvant capecitabine at the time of the STAMP trial being performed) and a higher incentive to continue on treatment in the STAMP trial (patients already knew that adjuvant therapy was of benefit) than in BILCAP (at the time of the study being performed, no evidence was available supporting adjuvant treatment and observation was the standard of care at the time). Lower interruption rate for CisGem over capecitabine in the STAMP trial could be explained by similar arguments and the open label design.

Capecitabine remains the standard of care for resected BTC. Unfortunately, the relapse rate remains high and better treatment options are urgently needed. Whether the combination of CisGem will be the answer may seem unlikely based on the STAMP trial results, but we probably should wait for the ACTICCA-1 study before making a final statement on this regard. Main arguments for this are the fact that ACTICCA-1 is a larger (over 400 patients) and international study, targeting a wider population of patients (all cholangiocarcinoma and gallbladder cancer). Unanswered questions in the adjuvant setting for BTC are the role of targeted therapies and immunotherapy as adjuvant strategies, since these two strategies are already incorporated in the treatment algorithms for advanced setting (3) but their role in the adjuvant scenario are not known. International collaboration in the delivery of adequately powered and well-designed clinical trials in the adjuvant setting in BTC will be the key to exist this maze. We will for sure succeed, we must just “keep going”.

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